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 ( )

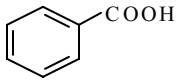
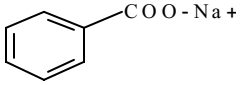
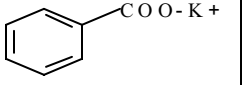
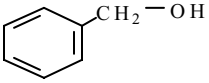
COMMENTS:
The Benzoates were already discussed in other frameworks such as the WHO. Therefore the original data were not again evaluated. The conclusions of other frameworks are discussed in the SIAR. This SIAR can be considered as a state of the art report on benzoates.

Deadline for circulation:

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

SIDS INITIAL ASSESSMENT PROFILE

Benzoates Category

CAS No.	65-85-0	532-32-1	582-25-2	100-51-6
Chemical Name	Benzoic acid	Sodium benzoate	Potassium benzoate	Benzyl alcohol
Structural Formula				

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 histopatology 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 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 $Pa*m^3/mol$; 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.

SIDS Initial Assessme nt Report (SIAR)

1. IDENTITY

Category name: Benzoates

Chemicals:	CAS#:	Molecular Weight
Benzoic acid	65-85-0	122.12
Sodium benzoate	532-32-1	144.11
Potassium benzoate	582-25-2	160.21
Benzylalcohol	100-51-6	108.4

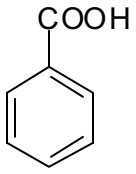
Physico-chemical properties:

Chemical	Appearance	Melting point	Boiling point @ 1013 hPa	Vapor pressure (at 20ºC)	octanol/water partition coefficient (LogP)	Water Solubility (at 20ºC)	Henry's law constant	pKa
Benzoic acid	White solid	122.4ºC	249.2ºC	0.0011 hPa	1.88	2.9 g/l	.0046 - .022 $Pa*m^3/mol$	4.19
Sodium benzoate	White solid	330.6ºC	464.9ºC	< 0.001 hPa	-2.269	556 g/l		
Potassium benzoate *	White solid	330.6ºC	464.9ºC	< 0.001 hPa	-2.269	556 g/l		
Benzyl alcohol	Clear liquid	-15ºC	205.3ºC	0.13 hPa	1.1	40 g/l		

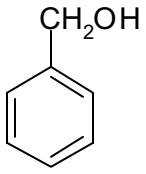
*) No data for Potassium benzoate were available, but they are expected to be the same as for sodium benzoate.

Category Justification:

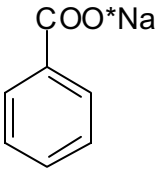
The proposed category of this ICCA HPV Benzoates submission consists of the following chemicals:



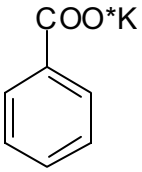
Benzoic Acid
CAS# 65-85-0



Benzyl Alcohol
CAS# 100-51-6

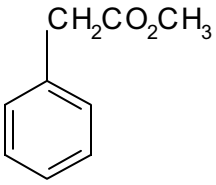


Sodium Benzoate
CAS# 532-32-1



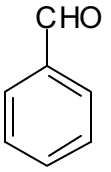
Potassium Benzoate
CAS# 582-25-2

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

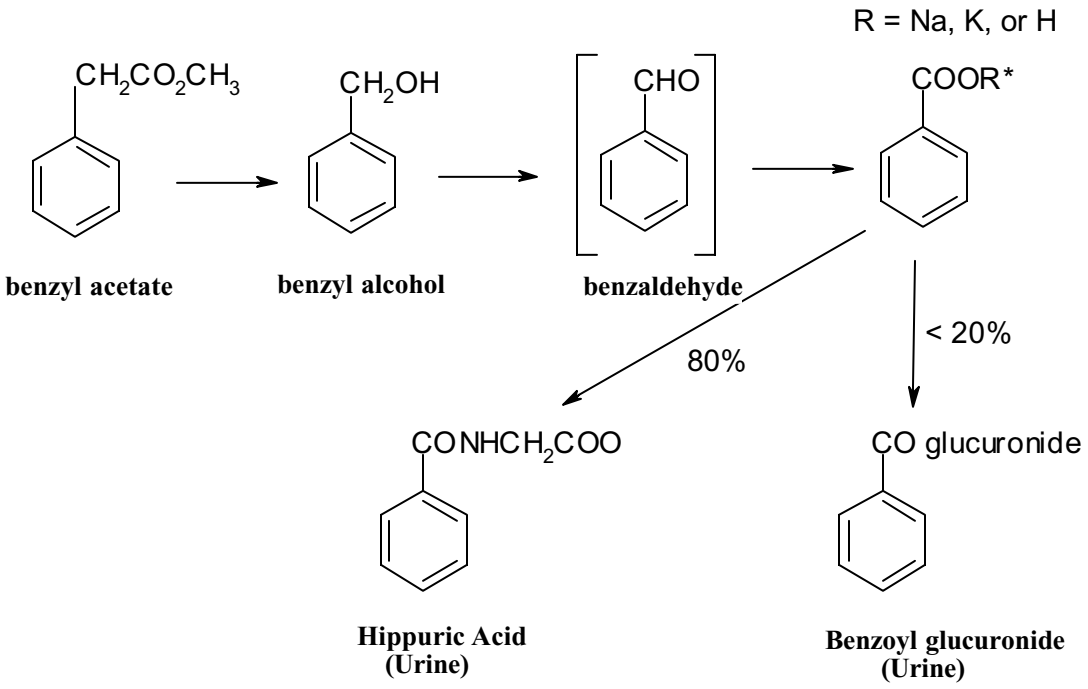
Sponsored in the US EPA HPV Program by the Flavor and Fragrance High Production Volume Consortia (FFHPVC)



Benzaldehyde
CAS# 100-52-7

Completed SIDS/SIAR

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):



The sodium and potassium salts of benzoic acid are expected to immediately dissociate and form benzoic acid in an aqueous environment.
The benzylacetate, 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 benzylacetate (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 radiolabel 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

Chemical	CAS#	Air	Water	Soil	Sediment
Benzoic acid	65-85-0	0.911	34.8	64.2	0.093
Sodium benzoate	532-32-1	1.45e-007	45.3	54.6	0.0755
Potassium benzoate	582-25-2	1.61 e-007	45.3	54.6	0.0755
Benzyl alcohol	100-51-6	1.51	50.0	48.4	0.0923

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.

Chemical	Species	Protocol	Result	Reference
Benzoic acid	rat	Directive 84/449/EEC	LD50 =2565 mg/kg	IRDC#163-282, 1974
	mouse	OPPTS 870.1100	LD50 =2250 mg/kg	BRL#9348, 1979
Sodium benzoate	rat	Directive 84/449/EEC	LD50 =3140 mg/kg	Loeser, 1977-A; Deuel et al., 1954
	rat	other	LD50 =4070 mg/kg	Smyth & Carpenter, 1948
Benzyl alcohol	rat	Directive 84/449/EEC	LD50 =1610 mg/kg	Loeser, 1978
	rat	other	LD50 =2080 mg/kg	Graham & Kuizenga, 1945; Opdyke, 1973
	mouse	other	LD50 =1580 mg/kg	Jenner, 1964; Opdyke, 1973
Potassium benzoate	rat	other	LD50 = >10,000 mg/kg	Kravets-Bekker & Ivanova, 1970
	mouse		LD50 = >10,000 mg/kg	Kravets-Bekker & Ivanova, 1970
	guinea pig		LD50 = >10,000 mg/kg	Kravets-Bekker & Ivanova, 1970

3.1.2 Acute Dermal Toxicity

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

Chemical	Species	Protocol	Result	Reference
Benzoic acid	rabbit	EPA OTS 798.1100	LD50= > 2000 mg/kg	IRDC#163-282, 1974; Opdyke, 1973
Benzyl alcohol	Rabbit	Other	LD_{50} = 2000 mg/kg	NPIRI,1974
	guinea pig	Other	LD_{50} = < 5 ml/kg	Jones, 1967; Opdyke, 1973

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.

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

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.

Chemical	Species	Protocol	Result	Reference
Benzoic acid	Rabbit	EPA OTS 798.4470	not irritating	IRDC # 163-282
	rabbit	Directive 84/449/EEC	slightly irritating	RCC NOTOX - study no. 0847/1083, 1988.
Sodium benzoate	Rabbit	OECD Guide-line 404	not irritating	RCC NOTOX - study no. 014658
	rabbit	Directive 84/449/EEC	not irritating	Loeser, E., 1977-B
Benzyl alcohol	rabbit	OECD Guide-line 404	not irritating	Bayer AG data, Report No. 19232, 1990
	rabbit	Other	slightly irritating	Smyth, H. F. et al., 1951; reported in US NTP: TR 343, 1989.

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.

Chemical	Species	Protocol	Result	Reference
Benzoic acid	Rabbit	Directive 84/449/EEC	highly irritating	RCC NOTOX - study no. 0847/1084, 1988
	rabbit	EPA OTS 798.4500	severely irritating	IRDC #163-282
Sodium benzoate	Rabbit	Directive 84/449/EEC	not irritating	Loeser, E., 1977-B
	rabbit	OECD Guide-line 405	slightly irritating	RCC NOTOX - study no. 014669, 1988
Benzyl alcohol	Rabbit	OECD Guide-line 405	moderately irritating	Bayer AG data, Report No. 19232, 1990
	rabbit	Other: limited data	highly irritating	Smyth, H. F. et al., 1951; reported in US NTP: TR 343, 1989

In conclusion: Benzoic acid and benzylalcohol 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 $\geq$ 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/m^3 (analytical concentration; MMAD 4.7 µm) for 6 hours/day and 5 days/week over 4 weeks. At $\geq$ 25 mg/m^3 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 $\geq$ 250 mg/m^3 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/m^3 (However no clear dose-response was observed).
NOAEC (systemic) = 25 mg/m^3
(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 chlolesterol 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 $\approx$ 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 benzo ate** continuously in feed showed no adverse effects at $\leq$ 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)

(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)

(US NTP Technical Report No. TR 343, 1989)

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).

(US NTP Technical Report No. TR 343, 1989)

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 $\geq$ 400 mg/kg bw/d for rats and $\geq$ 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 subtilus* 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 subtilus* H17 and M45 was positive (reported with minimal documentation in an abstract, Nonaka, 1989).

Potassium benzoate tested positive in a recombination assay using *Bacillus subtilus* 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 subtilus* H17 and M45 was positive (reported with minimal documentation, Kuroda et al., 1984).

Summary of (non-Ames) *in vitro* results:

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

? = 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 subtilus 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 cerevesiae* 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 (Foureman, et al., 1994)

Summary of genetic toxicity *in vivo* results:

Species (test system)	End-point	Results	Remarks
Sodium benzoate			
male Sprague Dawley rats	Cytogenetic Assay (bone marrow)	Negative	
male ICR mice	Host-Mediated Assay (tester strains Salmonella typhimurium TA 1530, G 46 and Saccharomyces cerevisiae D3)	Negative	elevated mutant frequency with TA 1530 in the intermediate single gavage dosing only (clear negative after multiple gavage dosing)
male random bred rats	Dominant Lethal Assay	Negative	
Benzyl alcohol			
male mice	Mouse Micronucleus Assay	Negative	
male Fischer 344 rats	Replicative DNA Synthesis	Negative	
male B6C3F1	Replicative DNA Synthesis	Negative	
Drosophila melanogaster	SLR assay	Negative	

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 *in vivo* results:

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

In conclusion: The compounds exhibit no genotoxicity in several *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) **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*. 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% **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 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. 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 a 2-year carcinogenicity study , **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.

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.

(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 menopauze.
NOAEL (Parental) $\geq$ 750 mg/kg/day
NOAEL (F1 Offspring) $\geq$ 750 mg/kg/day
NOAEL (F2 Offspring) $\geq$ 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 no compound related effects on reproductive organs (gross and histopatology 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: $\geq$ 750 mg/kg/day
NOAEL Teratogenicity: $\geq$ 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
(US National Institute of Occupational Safety and Health, 1983; Hardin et al., 1987).

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 >= 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

Chemical	Species	Protocol	Result	Reference
Benzoic acid	*Lepomis macrochirus*	EPA-660/3-75-009	LC_{50} (96 h) =44.6 mg/l LC0 = 180 mg/l (pH control)	UCES#11506-03-85, 1979
	Salmo gairdneri	EPA-660/3-75-009	LC_{50} (96 h) =47.3 mg/l	Buzzel et al 1968 UCES#11506-03-84, 1979
	Leuciscus idus	other	LC_{50} (48 h) =460 mg/l (pH 7 –8)	Juhnke & Luedemann, 1978
Sodium benzoate	*Pimephales promelas*	EPA OPP 72-1	LC_{50} (96 h) =484 mg/l (pH 7.4, flow-through, measured concentrations)	Geiger et al., 1985
	Pimephales promelas		LC50 (96 h) > 100 mg/l	Ewell et al 1986
Benzyl alcohol	*Pimephales promelas*	EPA OPP 72-1	LC_{50} (96 h) =460 mg/l	Mattson, V.R. et al., EPA-600 /3-76-097, PB-262897, 1976
	Leuciscus idus	DIN 38412 Teil 15	LC_{50} (48 h) =646 mg/l	Knie et al., 1983
Benzyl alcohol		Specific acute spill testing (*)	LC50 (96 h) 10 and 15 mg/l	Dawson et al 1975/1977

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

Chemical	Species	Protocol	Result	Reference
Benzoic acid	*Daphnia magna*	EPA-660/3-75-009	EC_{50} (48 h) => 100 mg/l (pH 8.4)	UCES#11506-03-80, 1979
		other	EC_{50} (24 h) = 500 mg/l (with neutralization)	Bringmann, & Kuehn, 1982
		other	EC_{50} is 102 mg/l (without neutralization)	Bringmann, & Kuehn, 1982
Sodium benzoate	*Daphnia magna*	other	EC_{50} (48 h) => 100 mg/l	Ewell et al., 1986
Benzyl alcohol	*Daphnia magna*	DIN 38412 Teil 11	EC_{50} (24 h) =400 mg/l	Knie et al., 1983
	Daphnia magna	other	EC_{50} (48 h) = 360 mg/l	Bringmann & Kuehn, 1959

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

Acute toxicity to aquatic plants (algae)

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

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)

Chemical	Species	Protocol	Result	Reference
Benzoic acid	activated sludge	OECD 209 (respiration inhibition)	EC_{50} (3 h) > 1000 mg/l (pH 7.5)	Klecka et al., 1985
	Photobacterium phosphoreum	Static	EC_{50} (30 min) = 16.85 mg/l	Kaiser, 1987
	Pseudomonas putida	Static	Inhibition starts at 480 mg/l (16 h) (pH neutral)	Cicad 2000
Sodium benzoate	*Achromobacter liquefaciens*	other: static	EC_{50} (24 h) = > 3000 mg/l	Nikkilae, 1955
	Micrococcus flavus	other: static	EC_{50} (24 h)= >500 mg/l	Nikkilae, 1955
Benzyl alcohol	*Escherichia coli*	cell multiplication inhibition test	EC_0 (48 h) = 1000 mg/l	Bringmann & Kuhn, 1959
	Pseudomonas putida	cell multiplication inhibition test	EC_{10} (16-18 h) = 658 mg/l	Knie et al., 1983

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 terrestial 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 $\geq$ 400 mg/kg bw/d for rats and $\geq$ 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 genotoxicty *in vivo*.

While some mixed and/or equivocal in vitro chromasomal/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.

Carcinogencity 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 histopatology 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 potassiumbenzoate 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 benzylalcohol is as 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.

Benzylalcohol, 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*m^3/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:	
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Flags (profile):	
Flags:	without flag, confidential, non confidential, WGK(DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: American Chemistry Council (formerly Chemical Manufacturers Association, HPV Benzoates Panel
Street: 1300 Wilson Boulevard
Town: 22209 Arlington, VA
Country: United States
14-AUG-2001

Type: cooperating company
Name: ATOFINA Chemicals, Inc.
Country: United States
14AUG-2001

Type: cooperating company
Name: Bayer Corporation
Country: United States
14-AUG-2001

Type: cooperating company
Name: DSM Special Products
Country: Netherlands
13-DEC-2000

Type: cooperating company
Name: Noveon, Inc.
Country: United States
14-AUG-2001

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

21-MAY-2001

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

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
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
14-AUG-2001 (1) (2)

Value: = 122 degree C
15-JAN-2001 (3)

Value: = 121.7 degree C
15-JAN-2001 (4)

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
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
14-AUG-2001 (1) (5)

Value: = 250 degree C at 1013 hPa

Reliability: (2) valid with restrictions
15-JAN-2001 (2)

Value: = 249 degree C at 1013 hPa

15-JAN-2001 (4)

2.3 Density

Type: density
Value: = 1.2659 at 15 degree C

Method: other:

Reliability: (2) valid with restrictions
Data from Handbookor collection of data
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
Data from Handbook or collection of data
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
Meets generally accepted scientific method and is described in sufficient detail

Flag: Critical study for SIDS endpoint
14-AUG-2001 (9)

log Pow: = 1.9

Method: other (calculated): CLOGP-3.63 (1991)
Year: 1991

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
26-JAN-2001 (10)

log Pow: = 1.93

Method: other (measured): gemessen, Schuettelmethode, spektralphotometrischeKonzentrationsbestimmung
15-JAN-2001 (11)
log Pow: 1.81 - 1.88

Method: other (measured): gemessen, Schuettelmethode, spektralphotometrischeKonzentrationsbestimmung
14-AUG-2001 (12)

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)

Method: According to Pal, A., Maity, S.K., & Lahiri, S.C. J. Indian Chem. Soc. (1983) 60:475.
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
14-FEB-2002 (13)

Solubility in: Water
Value: = 2.91 g/l at 20 degree C

Remark: pH-value: no data
14-FEB-2002 (14)

2.6.2 Surface Tension

2.7 Flash Point

Value: = 121 degree C

Method: other: no data

Remark: nicht angegeben
15-JAN-2001 (2)

2.8 Auto Flammability

Value: = 574 degree C at 1013 hPa

Method: other
Year: 1990
GLP: no
15-JAN-2001 (15)

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 (16)

Remark: Dissociation-constant (20 degree C): pKa = 4.21
Flag: Critical study for SIDS endpoint
14-AUG-2001 (17)

Remark: Dissociation-constant pKa (25 degree C): 3.99-4.205 (various methods; summarized values)
14-AUG-2001 (18)

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 (2)

Remark: pH-value: 3,1 at 1 g/l water(roomtemperature)
14-AUG-2001 (19)

Remark: pH-value: 2.8(saturated solution, 25 degree C)
14-AUG-2001 (2)

3.1.1 Photodegradation

```
Type:              other:mineralization in aqueous TiO2
Light source:      other:20W NEC blacklight blue flourescent 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:            othermeasured):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                                                (20)

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
```

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
14-AUG-2001 (21)

Remark: UV-Spectrum lambda max (nm):
227.5 (Methanol; lg epsilon: 4.27)
222 (Methanol/KOH; lg epsilon: 4.07)
15-JAN-2001 (22)

Remark: photochemical dissociation of benzoic acid by UV-irradiation if fixed on solid carriers (SiO_2):-10.2 % mineralization after 17 h irradiation with light(lambda > 290 nm)(no data concerning concentration)
15-JAN-2001 (23)

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 (24)

Remark: Formation of a small amount of photochemical aerosols after irradiation of some cristalls of benzoic acid with a deuterium lamp (180 < lamda < 400 nm) in a laboratory reactor.
15-JAN-2001 (25)

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 (26)

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.

Result:	Distribution (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	0.911	207	1000	2.3 e-011
Water	34.8	360	1000	6.11e-013
Soil	64.2	360	1000	1.22e-011
Sediment	0.093	1.44e+003	0	4.73e-013

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
14-FEB-2002 (21)

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 (27)

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 (28)

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 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
Meets generally accepted scientific standards, Well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-AUG-2001 (29)
Type: aerobic
Inoculum: 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 (30)

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
14-FEB-2002 (31)

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
14-FEB-2002 (32)

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)

15-JAN-2001 (33)

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 (34)

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 (35)

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 (36)

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 (37)

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 (38)

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 (39)

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 (40)

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 (41)

Inoculum: other bacteria: anaerobic sludge, domestic, washed
Concentration: 50 mg/l related to Test substance

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 (41)

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, 37degree C

15-JAN-2001 (42)

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 (19)

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 (43)

3.6 BOD5, COD or BOD5/COD Ratio

Method:
Year:
Method:
Remark: BOD5/COD ratio is 0.72, indicating readily biodegradation.
14-AUG-2001 (15)

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
Accepted calculation method
Flag: Critical study for SIDS endpoint
14-AUG-2001 (21)

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 (44)

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 (45)

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 (50)

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, Hansenulaanomala). No information about test conditions.

23-OCT-1995 (50)

Remark: Elimination in rainwater:
Inoculum: rainwater
Methode: 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 (51)

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 (52)

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 (36)

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 (44)

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.

14-AUG-2001 (53)

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 Analytical monitoring: no
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 ater 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
Guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
14-FEB-2002 (54)

Type: static
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
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 (55)

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 (56)

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

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

15-JAN-2001 (31)

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

Method: other: no data

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 EC0 : 77 mg/l
EC50 : 102 mg/l
EC100: 136 mg/l
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
Guideline study
Flag: Critical study for SIDS endpoint
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 (62)

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 (63)

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 94.9ml 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: 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 (62)

Species: Chlorella pyrenoidosa (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) wasdetermined 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 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 (64)

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 (62)

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 94.9ml 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

06-SEP-2000 (62)

Species: Anabaena inaequalis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
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 9.9ml 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

14-AUG-2001 (62)

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

14-AUG-2001 (62)

4.4 Toxicity to Microorganisms e.g. Bacteria

Species: activated sludge
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
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
Guideline study
Flag: Critical study for SIDS endpoint
14-AUG-2001 (62)

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

Method: other: static at 15 degree C; Microtox-Test
Test substance: other TS: benzoic acid; 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
14-AUG-2001 (66)

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

Method: other: static; 25 degree C; pH 7
Test substance: other TS: benzoic acid; 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

14-AUG-2001 (63)

Species: Pseudomonas fluorescens (Bacteria)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC0: 1000

Method: other: Bestimmung der biologischen Schadwirkung toxischer Abwaessergegen Bakterien. DEV, L 8 (1968) modifiziert

14-AUG-2001 (19)

Species: other bacteria: Pseudomonas Stamm Berlin
Exposure period: 1 hour(s)

Unit: mg/l Analytical monitoring:
EC10: 50

Method: other: Oxygen consumption test acc. to Robra, GWF-Wasser/Abwasser 117,80-86 (1976)

14-AUG-2001 (61)

Species: other bacteria: population of microorganisms from communal sewage
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
Tlm : 500

Method: other: static, inhibition of cell multiplication; 37 degree C; pH 6.9

14-AUG-2001 (31)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Remark: No data available.
14-AUG-2001

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Remark: No data available.
14-AUG-2001

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)

23-OCT-1995 (69)

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 ludwigii	650	300
-Schizosaccharomyces pombe	567	325
-Zygosaccharomyces bailii	1250	600

23-OCT-1995 (70)

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 %

23-OCT-1995 (71)

Remark: Antimicrobial effects (pH 6):

	minimal microbizide Conc. (MMC)	minimal inhib. 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

23-OCT-1995 (72)

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.

Dose level (mg/kg)	Mortality
500	0/5
1250	0/5
1984	0/5
3150	4/5
5000	5/5

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

14-FEB-2002 (73)

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
Guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002 (74)

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

26-JAN-2001 (75)

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

26-JAN-2001 (4)

Type: LD50
Species: rat
Value: = 2530 mg/kg bw

26-JAN-2001 (76)

Type: LD50
Species: mouse
Value: = 1940 mg/kg bw

26-JAN-2001 (77)

Type: LD50
Species: mouse
Value: = 2370 mg/kg bw

26-JAN-2001 (78)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex: male/female
No. of Animals: 10
Exposure time: 4 hour(s)
Value: > 12.2 mg/l

Method: EPA OTS 798.1150
Year: 1974
GLP: no data
Test substance: other TS: technical grade benzoic acid

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 (73)

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 (4)

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 (73)

Type: LD50

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 classificat.: 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
Guideline study
Flag: Critical study for SIDS endpoint
14-AUG-2001 (81)

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
23-MAR-2001 (4)

Species: rabbit

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
13-MAR-2001 (82)

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
Guideline study
Flag: 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
Guideline study
Flag: Critical study for SIDS endpoint
14-AUG-2001 (89)

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
23-MAR-2001 (4)

Species: rabbit
Result: slightly irritating

Method: other: OECD Guideline 405

23-MAR-2001 (90)

Species: rabbit
Result: moderately irritating

Method: other: see remark

Remark: 2 animals; instillation of 50 mg/animal into The conjunctical sac
23-MAR-2001 (82)

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                                                  (91)

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                                                  (92)

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                                                  (92)

Type:             Mouse local lymphnode assay
```

Species: mouse
Result: not sensitizing

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

Remark: test concentrations: 5, 10 or 20 %
14-AUG-2001 (93)

Type: Mouse ear swelling test
Species: mouse
Result: not sensitizing

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

Remark: test concentrations: induction 20 %, challenge 20 %
14-AUG-2001 (92)

Type: other: see remarks
Species: guinea pig
Result: sensitizing

Method: other: ear swelling test

Remark: 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).
14-AUG-2001 (94)

Type: other: see remarks
Species: human

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

Remark: 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.

The time course of the responses to benzoic acid and sodium benzoate was similar in controls and workers.
The potential of sodium benzoate to elicite 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.
14-AUG-2001 (98)

Type: other: see remark
Species: human

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)

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 histo-pathological 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
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-FEB-2002 (105)

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
14-FEB-2002 (4)

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

14-AUG-2001 (106)

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 histopathlogic evaluations were conducted.

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/3: 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 4.7um.
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 (107)

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 (108)

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 (109)

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 (110)

Species: rat Sex: male
Strain: Wistar
Route of administration: oral feed
Exposure period: 7 - 35 days
Frequency of treatment: continuously in diet
Post exposure period: no
Doses: 1.1 % in diet (approx. 825 mg/kg/day)
Control Group: yes

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 (109)

Species: rat Sex: male
Strain: Wistar
Route of administration: oral feed
Exposure period: 5 days
Frequency of treatment: continuously in diet
Post exposure period: no
Doses: 3 % in diet (approx. 2250 mg/kg/day)
Control Group: yes

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 (109)

Species: rat Sex: male/female
Strain: Wistar
Route of administration: oral unspecified
Exposure period: 72 weeks
Frequency of treatment: once daily
Post exposure period: no
Doses: 40 mg benzoic acid/kg/day and 80 mg sodium bisulphite/kg/day
Control Group: yes

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 Sex: male/female
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 Sex: male/female
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 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/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)
(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)

Species: cat Sex: male
Strain: no data

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 Sex: male
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, 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

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

Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-FEB-2002 (115)

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
06-JUN-2001 (116)
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
12-JAN-2001 (117)

Type: other: Salmonella microsome assay
System of testing: S. typhimurium TA 97, TA 98, TA 100, TA 1535, TA 1537
Metabolic activation: with and without
Result: negative

12-JAN-2001 (118)
Type: other: Salmonella microsome assay
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Metabolic activation: with and without
Result: negative

11-JAN-2001 (119)

Type: other: Mitotic recombination
System of testing: Saccharomyces cerevisiae D3
Metabolic activation: with and without
Result: negative

Remark: insufficient documentation
11-JAN-2001 (117)
Type: other: Chromosomal aberration test
System of testing: Chinese hamster fibroblast cell line (CHL)
Metabolic activation: without
Result: ambiguous

11-JAN-2001 (120)

Type: other: umu test
System of testing: S. typhimurium TA 1535/pSK1002
Metabolic activation: with and without
Result: negative

11-JAN-2001 (121)

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 isindicated.
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 ("Aufzugt 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 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
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-AUG-2001 (105)

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

Flag: Critical study for SIDS endpoint

14-AUG-2001 (122)

Species:	rat Sex: male/female
Strain:	no data
Route of administration:	other: oral feed (first 8 weekspaired 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,

well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
14-FEB-2002 (105)

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 (123)

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 (124)

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 (125)

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 (126)

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 (127)

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 (128)

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 (129)

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/cmE+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/cmE+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 8^{th} 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 (137)

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 glucuro- nide, is excreted in the urine of some species (no further information available).

14-AUG-2001 (138)

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 (143)

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 (144)

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 (111)

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.

14-AUG-2001 (145)

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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10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment

I U C L I D Data Set

(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
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

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	(1) (2)

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	(3)

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	(3)

2.3 Density

Type:	relative density
Value:	= 1.44 g/cm3
Flag:	Critical study for SIDS endpoint
26-JAN-2001	(4) (5)

Type: bulk density
Value: 650 kg/m3
Remark: thickened
Source: DSM Special Products B.V. GeleenECB - Existing Chemicals Ispra (VA)
26-MAY-2000 (6)

Type: bulk density
Value: 350 kg/m3
Remark: not thickened
Source: DSM Special Products B.V. GeleenECB - Existing Chemicals Ispra (VA)
26-MAY-2000 (6)

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
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2001 (3)

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
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2001 (7)

log Pow: = -2.13
Method: other (calculated): CLogP
Year:
Testsubstance: other TS: molecular structure

Remark: Calculated according to C. Hansch et al 1985.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-MAR-2001

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
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
09-AUG-2001 (8) (9)

Value: 630 g/l at 20 degree C
pH: 7
26-JAN-2001 (6) (6)

Remark: concentrated solutions react neutral
diluted solutions react weakly alkaline (pH 8)
26-JAN-2001 (10)

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 (6)

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

Result:
Remark: Can form explosive mixtures with air.
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: .0000000000017775 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 (3)

Type:
Method:
  Year: GLP:
Test substance:
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:	Distribution (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	1.45e-007	144	1000	4.83e-019
Water	45.3	360	1000	1.38e-020
Soil	54.6	360	1000	6.16e-019
Sediment	0.0755	1.44e+003	0	1.15e-020

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 (12)

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 GLP: no data
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
Guideline study
Flag: Critical study for SIDS endpoint
09-AUG-2001 (13) (14)

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 (15)

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
Testsubstance:

2 day	20 %
4 day	45 %
6 day	55 %
8 day	70 %
20 day	85 %

Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year: 1981 GLP:
Test substance:
Method: Guideline adapted to use seawater as test medium and inoculum
Reliability: (1) valid without restriction
03-JAN-2001 (16)

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:gasproduction
Year: GLP:
Test substance:
Remark: concentration: 50/60/90 mg/l
degradation : 47/49/28 d = 60.5/82.7/74 %

26-JAN-2001 (17)

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

Testsubstance: 14 day 84 %
28 day 92 %
Method: Directive 84/449/EEC, C.7 "Biotic degradation - modified MITI test"
Year: 1982 GLP:
Test substance: other TS: purchased from Sigma Chemicals
Reliability: (1) valid without restriction
19-MAY-2000 (17)

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
Testsubstance: 5 day 57.4 %
10 day 72.8 %
30 day 83.4 %
50 day 91.7 %
61 day 96.4 %
Method: OECD Guide-line 301 A (new version) "Ready Biodegradability: DOC Die Away Test"
Year:
GLP:
Test substance: no data
09-MAY-2000 (19)

Type: aerobic
Inoculum:
Degradation: 100 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: GLP:
Test substance: no data
09-MAY-2000 (20)

Type:
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:
GLP:
Test substance:

```
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
Testsubstance:         60 day      95 %
Method:            OECD Guide-line 301 A (new version)  "Ready
Biodegradability:
                   DOC Die Away Test"
  Year:                                      GLP:
Test substance:    no data
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:                                      GLP:
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:                                      GLP:
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:                                      GLP:
Test substance:
```

Remark: concentration: 60/60 mg/l
degradation : 35/56 d = 95.3/96.5 %
26-JAN-2001 (17)

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 (24)

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:
Remark: Original data of concentration: 2.13 mM
Test condition: 37 degree C
26-JAN-2001 (24)

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 (25)

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 GLP:
Test substance: other TS: molecular structure
Remark: Based on the log P and its rapid metabolization and excretion in many species no bioaccumulation is indicated.
Result: Estimated Log BCF = 0.500 (BCF = 3.162)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2001 (3)

Species:
Exposure period:
Concentration:
BCF:
Elimination:
Method:
Year: GLP:
Test substance:
Remark: Based on the log P and its rapid metabolization and excretion in many species no bioaccumulation is indicated.
09-AUG-2001

3.8 Additional Remarks

Remark: Aerobic degradation in sea water:
Inoculum: sea water; salinity 18,6 %,
20 degree C
Method: Modified OECD Screening Test, OECD Guideline 301 E adopted 12 May 81, EG-Richtlinie 84/449/EWG, part C.3 im EG-Amtsblatt L 251, ISO 7824 (1984)
Concentration: 20 mg/l DOC
degradation after 28d: 100 %
degradation after 12d: 95 %
23-OCT-1995 (26)

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:
Inokulum: 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-Xylol; 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 Suprior 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
Guideline study
Flag: Critical study for SIDS endpoint
09-AUG-2001 (30) (31)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
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.) pps 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 (32)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (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).
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 (33) (32)

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 (32)

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:
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

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 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 (32)

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
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 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.
09-AUG-2001 (32)

Type: static
Species: other aquatic worm: Lumbriculus variegatus
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 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
09-AUG-2001 (32)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: other algae: green algae
Endpoint:
Exposure period: 96 hour(s)
Unit: g/l Analytical monitoring: no
EC50: 430
Method: other: (calculated) ECOSAR Program (v0.99e)
Year: 1999 GLP: no

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

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (12)

4.4 Toxicity to Microorganisms e.g. Bacteria

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

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

Type:
Species: other bacteria: Sarcina flava
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: < 100
Method: other: static, 22 degree C, pH 7
Year: GLP:
Test substance: other TS
Remark: 7 d-EC0 >= 3000 mg/l

Test substance: sodium benzoate; purity not noted
Flag: Critical study for SIDS endpoint
10-AUG-2001 (35)

Type:
Species: other bacteria: Micrococcus luteus
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 500
Method: other: static, 22 degree C, pH 7
Year: GLP:
Test substance:
Remark: 7 d-EC0 500 mg/l
10-AUG-2001 (35)

Type:
Species: other bacteria: Sarcina lutea
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: < 100
Method: other: static, 22 degree C, pH 7
Year: GLP:
Test substance:
Remark: 7 d-EC0 1000 mg/l
10-AUG-2001 (35)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species:
Endpoint:
Exposure period:
Unit: Analytical monitoring:
Method:
Year: GLP:
Test substance:
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: Analytical monitoring:
Method:
Year: GLP:
Test substance:
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 absorbtion and metabolisation and excretion. Conjugation with glycine and excreted in urine as hippuric acid.
10-AUG-2001

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 (36)

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 (37)

Remark: Toxicity to fungi: MIC (at room temperature):
100 mg/l (Byssochlamys fulva, 16 d, pH 3.5)
23-OCT-1995 (38)

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 Byssochlamys nivea was reduced in apple- and grapefruit juice up to an exposure period of 105 days.
23-OCT-1995 (39) (40)

Remark: Toxicity to fungi:
no visible growth of:

	Saccharomyces cerevisae	Willia anomala	Penicillium glaucum
pH 2.6	200 mg/l	120 mg/l	600 mg/l
5	2000 mg/l	1000 mg/l	4000 mg/l
7	30000 mg/l	20000 mg/l	60000 mg/l

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

23-OCT-1995 (41)

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 (42)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	rat
Strain:	no data
Sex:	male/female
Number of Animals:	5
Vehicle:	water
Value:	= 3450 mg/kg bw
Method:	other: see below
Year:	GLP: no data
Test substance:	other TS: USP Sodium benzoate, purchased from Merck
Method:	5 animals/sex/group; animals did not fast prior to treatment; animals observed for 14 days.
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	(43)

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
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 Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag:	Critical study for SIDS endpoint
10-AUG-2001	(44)

Type:	LD50

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:
Year: GLP: no data
Test substance: other TS: USP Sodium benzoate, purchased from Merck
Method: Animals fasted 18 h prior to treatment; dosed by gavage; observed for 5 days.
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: 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

5.1.4 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: GLP:
Test substance:
10-AUG-2001 (46)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: not irritating
EC classificat.:
Method: OECD Guide-line 404 "Acute Dermal
Irritation/Corrosion"
Year: 1981 GLP: yes
Test substance: other TS: sodium benzoate; purity not noted
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint

10-AUG-2001 (47)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: not irritating
EC classificat.:
Method: other: see remarks
Year: GLP:
Test substance: other TS: sodium benzoate; purity not noted
Remark: application of dry powder (500 mg/animal) for
24 h; responses were scored at end of
treatment and after 48 h
Flag: Critical study for SIDS endpoint
10-AUG-2001 (48)

Species: rat
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: irritating
EC classificat.:

Method: other: intradermal; see remark
Year: GLP:
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 (49)

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 GLP: yes
Test substance: other TS: sodium benzoate; purity not noted
Remark: according to EEC Directive 84/449/EEC, Annex V of the EEC Directive 67/548/EEC no labelling as eye irritant
Draize score: 9.3
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (50)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating

EC classificat.:
Method: Directive 84/449/EEC, B.5 "Acute toxicity (eye irritation)"
Year: GLP:
Test substance: other TS: sodium benzoate; purity not noted
Remark: application of dry powder (50 mg/animal) for 24 h; responses were scored at 24 h, 48 h and 72 h; postexposure observation time: 7 d
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (48)

5.3 Sensitization

Type: Patch-Test
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method: other: patch-test
Year: GLP:
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: GLP:
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.

	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 elicite nonimmunologic contact urticaria may be due to the formation of benzoic acid at skin contact.
Flag:	Critical study for SIDS endpoint
10-AUG-2001	(52)

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			
Year:			GLP: no	
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			
10-AUG-2001	(53) (54)			

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 challange 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:
Remark: 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 excerbations 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:

Result:
Classification:
Method: other: oral challenge test
Year: GLP:
Test substance:
Remark: 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).
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 (61)

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 dermatits resp.
10-AUG-2001 (62)

5.4 Repeated Dose Toxicity

Species: rat Sex: male/female
Strain: Sherman
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: GLP: no data
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
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
10-AUG-2001 (43)

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: GLP: no data
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.

Result:	No adverse effects were observed.
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	(63) (44)

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 %
Method:	other: Toth, B. (1984)
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 Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag:	Critical study for SIDS endpoint
10-AUG-2001	(64)

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:
Year: GLP:
Test substance: other TS: sodium benzoate, purity not noted
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 chlolesterol 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
10-AUG-2001 (65)

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

Flag: Critical study for SIDS endpoint

10-AUG-2001 (65)

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 (66)

Species: rat Sex: male/female
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: 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
Significant methodological deficiencies
10-AUG-2001 (67)

Species: rat Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 42 d

Frequency of treatment: continuously in diet
Post. obs. period: no data
Doses: 0.5; 1; 2; 4 or 8 % in diet (approx. 375-6000 mg/kg/day)
Control Group: yes
Method: other: see below
Year: GLP:
Test substance: other TS: sodium benzoate, purity not noted; supplied by National Institute of Hygienic Sciences pellets in the basal diet
Method: 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.
Result: 2 % in diet (approx. 1500 mg/kg/day): maximum tolerated dose;
>= 4 % in diet (approx. >= 3000 mg/kg/day): mortality 10/11 or 10/10; atrophy of the spleen and lymph nodes at autopsy.
10-AUG-2001 (66)

Species: rat Sex: no data
Strain: no data
Route of admin.: oral feed
Exposure period: until death (see below)
Frequency of treatment: continuously in diet
Post. obs. period: no
Doses: 5 % in diet (approx. 3750 mg/kg/day)
Control Group: yes
Method:
Year: 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: 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.

10-AUG-2001 (68)

Species:	rat	Sex: no data
Strain:	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:		
Year:	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	

10-AUG-2001 (68)

Species:	rat	Sex: male
Strain:	no data	
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:		
Year:	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 "long-term" 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	

10-AUG-2001 (69)

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:		GLP:
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)	

26-JAN-2001 (70)

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	GLP: no data
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 (71) (72)

Type:	Cytogenetic assay	
System of testing:	cultured human embryonic lung cells	

Concentration: 2.0, 20.0, 200.0 ug/ml
Cytotoxic Conc.:
Metabolic activation: without
Result: negative
Method: other: anaphase preparations
Year: GLP: no data
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
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
10-AUG-2001 (73) (74)

Type: other: Chromosomal aberration test
System of testing: Chinese hamster fibroblast cell line (CHL)
Concentration: 0 - 2 mg/plate
Cytotoxic Conc.:
Metabolic activation: without
Result: positive
Method: other: similar to OECD Guideline 473
Year: 1983 GLP: no data
Test substance: other TS: samples obtained from Japan Food Additives Association; purity = 99% analysed at Ministry of Health and Welfare of Japan

Reliability: (2) valid with restrictions
Comparable to Guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
10-AUG-2001 (75) (72)

Type: other: 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: GLP: no data
Test substance: other TS: sodium benzoate, purchased from Baker; purity not noted

Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (76)

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 (fluorecence 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 (77)

Type: other: Sister chromatid exchange
System of testing: human lymphocytes
Concentration:
Cytotoxic Conc.:
Metabolic activation: without
Result: positive
Method:
Year: GLP:
Test substance:
Remark: only one concentration (10E-2 M) tested

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
10-AUG-2001 (80)

Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis H17, M45
Concentration: 6-20 mg/disk, in water
Cytotoxic Conc.:
Metabolic activation: with and without
Result: ambiguous
Method:
Year: GLP:
Test substance:
10-AUG-2001 (81)

Type: Ames test

System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method:
Year: GLP:
Test substance:
11-JAN-2001 (76)

Type: Ames test
System of testing: Salmonella typhimurium, TA 98, TA100, TA1537
Concentration:
Cytotoxic Conc.:
Metabolic activation: with and without
Result: negative
Method:
Year: GLP:
Test substance:
01-SEP-2000 (82)
Type: other: Chromosomal aberration test
System of testing: Chinese hamster cell line (Don)
Concentration:

Cytotoxic Conc.:
Metabolic
activation: without
Result: positive
Method:
Year: GLP:
Test substance:
11-JAN-2001 (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: GLP:
Test substance: other TS: purity not given
Method: other: Ishidate M. and Odashima S. Mutation Res. 48: 337-354(1977) and Matsuoka A. et al. Mutation Res. 66: 277-290 (1979)
01-SEP-2000 (82)

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

Method: EPA OTS 798.5385
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 metaphase chromosomes
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (74)

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
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
Year: GLP: yes
Test substance: other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (74)

Type: Dominant lethal 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 870.5450
Year: GLP: yes
Test substance: other TS: compound FDA 71-37, sodium benzoate, as supplied by the Food and Drug Administration

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (74)

Type: other: Host mediated assay
Species: mouse Sex: male
Strain: no data
Route of admin.: gavage
Exposure period: single application
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 and no increase in recombinant frequencies in Saccharomyces cerevesiae D3
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (74)

Type: other: Host mediated assay
Species: mouse Sex: male
Strain: no data
Route of admin.: gavage
Exposure period: single application
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: 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
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (74)

Type: other: Host mediated assay
Species: mouse 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: 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
GLP guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (74)

5.7 Carcinogenicity

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 (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 (66)

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
10-AUG-2001 (64)

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

Year:	GLP:
Test substance:	
Remark:	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

26-JAN-2001 (83)

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
Year:	GLP: no data
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 (66)

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 (84) (85)

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

10-AUG-2001 (86)

Species:	mouse	Sex:	female
Strain:	CD-1		
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		
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 Guideline study		
Flag:	Critical study for SIDS endpoint		

10-AUG-2001 (85)

Species:	rabbit	Sex:	female
Strain:	other: Dutch-belted		
Route of admin.:	gavage		
Exposure period:	Day 6-18 of gestation		
Frequency of treatment:	once daily		
Duration of test:			
Doses:	2.5; 12; 54 or 250 mg/kg/d		
Control Group:	yes		
NOAEL Maternalt.:	250 mg/kg bw		
NOAEL Teratogen.:	250 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
Guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (85)

Species: hamster Sex: female
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
Guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (85)

Species: rat Sex: female
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:
Year: GLP:

Test substance:
Remark: no further information available
Result: 1000 mg/kg: increased rate of in utero deaths, reduced fetal body weight
26-JAN-2001 (87)

Species: rat Sex: female
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 (87)

Species: hen Sex:
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 (88)

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

synthetase activity, protein content or aggregate size; or increasing trend in aggregate number and at least one concentration group that was significantly different (p<0.05) from the control.
Result: Sodium benzoate was classified as inactive in the CERC assay with LOEL at >34.7mM.
19-MAY-2000 (90)

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 (91)

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 (92)

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 (93)

Type: Metabolism

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.
23-OCT-1995 (94)

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.
23-OCT-1995 (95)

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.
23-OCT-1995 (62)

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.
23-OCT-1995 (96)

Type:
Remark: Toxicity:
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.
10-AUG-2001 (97)

Type:
Remark: Effect on ammonia levels:
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:
Remark: Liver perfusion:
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 (57)

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7.1 End Point Summary

7.2 Hazard Summary

7.3 Risk Assessment

I U C L I D Data Set

(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
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SID

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 (1)

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 (1)

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 (1)

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
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (1)

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
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
10-AUG-2001 (2)

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
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (1)

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: .0000000000017775 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:
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

Year:

Result:	Distribution (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	1.61e-007	144	1000	4.83e-019
Water	45.3	360	1000	1.38e-020
Soil	54.6	360	1000	6.16e-019
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 (1)

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum:
Degradation: 80.9 % after 22 day
Method: other: (calculated) Fugacity Level III
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)

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 GLP: no data
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
Guideline study
Flag: Critical study for SIDS endpoint
10-AUG-2001 (3)

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 (4)

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 (1)

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 (Baseline Toxicity)	14-day	LC50	1.13e+006
	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
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (1)

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

4.2 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
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (1)

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.
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
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (1)

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
Original reference in foreign language
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
Original reference in foreign language
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
Original reference in foreign language
Flag: Critical study for SIDS endpoint
10-AUG-2001 (5)

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: GLP:
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: GLP:
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 (6)

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:
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

5.8 Toxicity to Reproduction

Type:
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 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: Sex:
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Duration of test:
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

5.10 Other Relevant Information

5.11 Experience with Human Exposure

(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

(2) Budavari, S. (ed.), The Merck Index. An encyclopedia of chemicals, drugs, and biologicals. 11th ed., Rahway, New Jersey, 1357 (1989)

(3) Salanitro, J.P. et al., Water Sci. Technol. 20, 125-130 (1988)

(4) Battersby, N.S. & Wilson, V., Appl. Environ. Microbiol. 55: 433-439 (1989)

(5) Kravets-Bekker A.A. & Ivanova O.P. 1970. Faktory Vnesh. Sredy Ikh Znachenie Zdorov'ya Naseleniya No.2, 125: in BIBRA Toxicity Profiles, BIBRA International, Great Britain.

(6) Ishizaki, M. & Ueno, S., J. Food Hyg. Soc. Japan 30, 447-451 (1989)

7.1 End Point Summary

7.2 Hazard Summary

7.3 Risk Assessment

I U C L I D 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

1.0.1 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
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
14-FEB-2002 (1)

Value: -15.3 degree C

Test substance: other TS: benzyl alcohol, purity not noted

12-FEB-2002 (2)

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
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
14-FEB-2002 (1)

Value: 205.4 degree C at 1013 hPa

19-JAN-2001 (2)

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
Data from Handbook or collection of data

Flag: Critical study for SIDS endpoint
14-FEB-2002 (1)

Type: density
Value: 1.0442 g/cm³ at 22.5 degree C

19-JAN-2001 (2)

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 (2)

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 (2)

Value: .67 hPa at 50 degree C

Flag: Critical study for SIDS endpoint
19-JAN-2001 (2)

2.5 Partition Coefficient

log Pow: 1.1

Method: other (calculated): Leo, A.: CLOGP-3.54 MedChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 91711, USA

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 (6)

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.

Result:

	Distribution (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	1.51	11.2	1000	2.95e-011
Water	50.0	360	1000	6.71e-012
Soil	48.4	360	1000	1.7 e-010
Sediment	0.0923	1440	0	5.52e-012

Persistence Time: 287 hr
Reaction Time: 353 hr
Advection Time: 1.54e+003 hr
Percent Reacted: 81.3
Percent Advected:

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-FEB-2002 (6)

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: slugde conc.: 30 mg/l

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-FEB-2002 (7)

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 (8)

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)

Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
GLP: no

Remark: related to ThOD
19-JAN-2001 (11)

Type: aerobic
Degradation: 77 % after 20 day(s)

Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
GLP: no

Remark: related to ThOD
19-JAN-2001 (11)

Type: aerobic
Inoculum: activated sludge, adapted
Degradation: 95 % after 28 day(s)

Method: other: Closed bottle test

Remark: Test concentration: 2 - 5 mg/l
Degradation related to ThOD
19-JAN-2001 (12)

Type: aerobic
Inoculum: domestic sewage
Degradation: 89.2 % after 5 day(s)

Method: other: respirometric diluting method
GLP: no

Remark: related to ThOD
19-JAN-2001 (13)

Type: aerobic
Inoculum: activated sludge, industrial
Degradation: 88.9 % after 5 day(s)

Test substance: other TS

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.
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 (14)

Type: aerobic
Degradation: 85 % after 5 day(s)

GLP: no

Remark: related to ThOD
19-JAN-2001 (15)

Remark: The activity of degradation is at a concentration of 100 mg/l not hindered in a model plant (Ascomat)
19-JAN-2001 (8)

Remark: Biodegradation characteristics: biodegraded completely in a short time by general microorganisms.
19-JAN-2001 (16)

3.6 BOD5, COD or BOD5/COD Ratio

Method:
Year:
Method:
Remark: ThOD: 2515.1 mg/l
19-JAN-2001 (13)

3.7 Bioaccumulation

BCF: .31

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
Accepted calculation method
Flag: Critical study for SIDS endpoint
14-FEB-2002 (6)

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 (17)

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 Reserach 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 Analytical monitoring: no
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 (19)

Type: static
Species: Petromyzon marinus
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: >= 5

GLP: no

Remark: larvae; screening test
17-JAN-2001 (20)

Species: Carassius auratus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
LC0: >= 5

17-JAN-2001 (21)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: Analytical monitoring: no
LC0: 136

GLP: no

Remark: Testing of acute oral toxicity
Unit: mg/kg

17-JAN-2001 (22)

Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
LC0: >= 5

17-JAN-2001 (21)

Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring:
LC50: 10

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 (23)

Species: Menidia beryllina (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring:
LC50: 15

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 (23)

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 Wasserinhaltsstoffen 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

GLP: no

Reliability: (2) valid with restrictions
16-JAN-2001 (25)

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 Analytical monitoring: no data
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+E5 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 (26)

Species: Haematococcus pluvialis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 4 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: 2600

Method: other: according to Tuempling v.W. (Fortschritte Der Wasserchemie. 14 S: 205-213 (1972) using a Warburg apparatus
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 (19)

Species: Scenedesmus quadricauda (Algae)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring:
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 (24)

Species: Anabaena cylindrica (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 90

Remark: blue-green algae
17-JAN-2001 (26)

Species: Anabaena inaequalis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC0: 30

Remark: blue-green algae
17-JAN-2001 (26)

Species: Anabaena variabilis (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 35

Remark: blue-green algae
17-JAN-2001 (26)

Species: Scenedesmus quadricauda (Algae)
Endpoint: other: Inhibition of photosynthesis
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 79

GLP: no

Remark: green algae
17-JAN-2001 (26)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Escherichia coli (Bacteria)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: 1000

Method: other: cell multiplication test
GLP: no

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
06-JUN-2001 (24)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Unit: mg/l Analytical monitoring: no
EC10: 658

Method: other: Test according to Bringmann and Kuehn (cell multiplication inhibition test)

GLP: no

Remark: Exposure period: 16-18 h
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
06-JUN-2001 (19)

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

19-JAN-2001 (27)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mg/l Analytical monitoring: no
EC50: 50

GLP: no

19-JAN-2001 (28)

Type: aquatic
Species: other bacteria: Aerobic heterotrophic
Exposure period: 49 hour(s)
Unit: mg/l Analytical monitoring:
IC50 : 2100

GLP: no

Remark: Inhibition of respiration;
prolonged incubation compared with ISO 8192
19-JAN-2001 (29)

Type: aquatic
Species: other bacteria: Nitrosomonas
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
IC50 : 390

Method: other: Inhibition of nitrification, comparable with ISO/DIS 9509
GLP: no

Remark: Inhibition of N-oxidation
19-JAN-2001 (29)

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 (30)

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)

Type: LD50
Species: rat
Strain: other: Osborne-Mendel
Sex: male/female
No. of Animals: 10
Vehicle: other: neat
Value: = 1230 mg/kg bw

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 (32)

Type: LD50
Species: rat
Value: = 2080 mg/kg bw

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 (34) (33)

Type: LD50
Species: rabbit
Value: = 1040 mg/kg bw

12-FEB-2002 (34) (35)

Type: LD50

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

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 (36)

Type: LC50
Species: rat
Exposure time: 4 hour(s)
Value: > .9 mg/l

Remark: LC33 (4h) = 200 ppm.
19-JAN-2001 (40)

Type: LC50
Species: rat
Sex: no data
No. of Animals: 6
Vehicle: other: neat
Exposure time: 4 hour(s)
Value: 8.9 mg/l

Test substance: no data

Result: Exposure to 2000 ppm kills either 2/6, 3/6 or 4/6 rats.
Therefore benzyl alcohol is considered to be of moderate toxicity.
07-SEP-2000 (41)

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 (42)

Type: LD50
Species: guinea pig
Value: < 5 ml/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 (43) (35)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: > 400 - 800 mg/kg bw

19-JAN-2001 (44)

Type: LD50
Species: mouse
Strain: CD-1
Sex: male
Route of admin.: i.p.
Value: = 1000 mg/kg bw

Remark: Acute toxicity after 4 h.
14-FEB-2002 (45)

Type: LD50
Species: mouse
Strain: CD-1
Sex: male
Route of admin.: i.p.
Value: = 650 mg/kg bw

Test substance: other TS: benzyl alcohol, purity not noted

Remark: Acute delayed toxicity after 7 d.
14-FEB-2002 (45)

Type: LD50
Species: guinea pig
Route of admin.: i.p.
Value: > 400 - 800 mg/kg bw

19-JAN-2001 (44)

Type: LD50
Species: rat
Route of admin.: s.c.
Value: = 1700 mg/kg bw

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (46)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 950 mg/kg bw

19-JAN-2001 (38)

Type: other: LDLO
Species: rabbit
Route of admin.: s.c.
Value: ca. 2080 mg/kg bw

19-JAN-2001 (37)

Type: LD50
Species: rat
Route of admin.: i.v.
Value: = 314 mg/kg bw

19-JAN-2001 (47)

Type: LD50
Species: rat
Route of admin.: i.v.
Value: = 53 mg/kg bw

Remark: Rapid injection
19-JAN-2001 (47)

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 324 mg/kg bw

19-JAN-2001 (48)
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 (49)

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

19-JAN-2001 (47)

Type: other: LDLO
Species: mouse
Strain: CD-1
Sex: male
Route of admin.: i.v.
Value: ca. 135 mg/kg bw

14-FEB-2002 (50)

Type: other: LDLO
Species: dog
Route of admin.: i.v.
Value: ca. 50 mg/kg bw

19-JAN-2001 (47)

Type: LD50
Species: rat
Route of admin.: other
Value: = 410 mg/kg bw

Remark: Application: intra-arterial.
19-JAN-2001 (47)

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 (49)

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 (51) (36)

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 (52)

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 (53)

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 (44)

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 (54)

Species: guinea pig
Result: slightly irritating

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

Remark: Exposure time: 24 h, 10 % in purified water, occlusive, observation time: no data.
19-JAN-2001 (58)

Species: other: mini-pig
Result: not irritating

Method: other: Patch Test

Remark: Exposure time: 48 h, clipped skin, 50 mg/animal, observation time: no data.
19-JAN-2001 (52)

5.2.2 Eye Irritation

Species: rabbit
Result: moderately irritating

Method: OECD Guide-line 405 "Acute Eye 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 (49)

Species: rabbit
Result: highly irritating

Method: other: see remarks
GLP: no data
Test substance: other TS: benzyl alcohol, purity not noted

Remark: Exposure time: 24 h, dose: 750 microg., no other data.
Flag: Critical study for SIDS endpoint
14-FEB-2002 (51) (36)

Species: rabbit
Concentration: 4 %
Result: not irritating

Method: other: see remarks
Test substance: other TS: benzyl alcohol, purity not noted

Remark: 4 % aqueous solution, tested for stability, no other data.
Flag: Critical study for SIDS endpoint
14-FEB-2002 (59)

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 (38)

Species: rabbit
Result: moderately irritating

Method: other: see remarks

Remark: ca. 100 mg/animal, observation time: 7 d.

19-JAN-2001 (53)

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 (54)

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 (54)

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
(54)

Type: Open epicutaneous test
Species: guinea pig
Result: sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

Flag: Critical study for SIDS endpoint
14-FEB-2002 (54)

Type: Patch-Test
Species: human
Result: sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

Remark: Maximum incidence of sensitization: 1 %.
Flag: Critical study for SIDS endpoint
14-FEB-2002 (60) (61) (62)

Type: Patch-Test
Species: human
Result: sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (63) (64)

Type: Patch-Test
Species: human
Result: ambiguous

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (57)

Type: Patch-Test
Species: human

Test substance: other TS: benzyl alcohol, purity not noted

Remark: Two patients with contact dermatitis were found to be sensitised by benzyl alcohol: 1 per cent in petrolatum
14-FEB-2002 (65)

Type: Patch-Test
Species: human

Test substance: other TS: benzyl alcohol, purity not noted

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 (66)

Type: other
Species: laboratory animal

Method: other: additional animal studies are reported

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (68) (69) (70) (67)

Type: other
Species: human

Method: other: additional data
Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (71) (72) (73) (74) (75) (76) (77) (78) (79) (80)
(81) (82) (83) (84) (85) (86) (87) (88) (89) (90)
(91) (92) (93) (94) (95) (96)

Type: other: Application to shaved skin
Species: guinea pig
Result: not sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (38)

Type: other: Intradermal application
Species: guinea pig
Result: not sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (38)

Type: other: Maximization Test
Species: human
Result: not sensitizing

Test substance: other TS: benzyl alcohol, purity not noted

14-FEB-2002 (97)

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; histolgic 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 thelower 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 (98)

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%)
Method: 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; histolgic 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

14-FEB-2002 (98)

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

Year: 1981
GLP: yes
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 (98)

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 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
GLP guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002 (98)

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 histlogical 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 (99)

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 (98)

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.
14-FEB-2002 (98)

Species: rat Sex: male
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.
14-FEB-2002 (40)

Species: rat Sex: male/female
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.
14-FEB-2002 (38)

Species: mouse Sex: no data
Strain: no data
Route of administration: gavage
Exposure period: 8 d
Frequency of treatment: daily
Post exposure period: no data specified
Doses: 325, 645, 1300, 2595 mg/kg/d
Control Group: no data specified

Test substance: other TS: benzyl alcohol, purity not noted

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.
14-FEB-2002 (100)

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

GLP: yes
Test substance: other TS: technical grade benzyl alcohol (purity = 99%)

Method: Separate trials were done using metabolic activation with Aroclor 1254-induced S9 from male Syrian hamster liver and male Sprague-Dawley rat liver.
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002 (98)

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 (101) (102)

Type: Cytogenetic assay
System of testing: CHO cells
Concentration: up to 5000 ug/ml

Cytotoxic Concentration: none noted
Metabolic activation: without
Result: negative

Method: other: similar to OECD 473; Galloway S.M. et al., Environ. Mutagen. 7, 1-52 (1985)
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 (103) (98) (104)

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 Galloway S.M. et al. Environm. Mutagen.7, 1-52 (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 (103) (98) (104)

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 (98)

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 (105)

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 (98)

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

Method: other: Matthews E.J.,J. Tissue Culture Methods 10, 157-164 (1986),Matthewy E.J. et al., Environm. Health Perspect. 101 [Suppl 2], 319-345 (1993)
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 cytotoxity or abnormal positive control). The number of type I-III transformed foci were identified microscopically considering their various different phenotypic properties.
REFERENCES:
Matthews E.J.,J. Tissue Culture Methods 10, 157-164 (1986),
Matthews E.J. et al., Environm. Health Perspect. 101 [Suppl 2], 319-345 (1993)

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: 7.36foci/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

Metabolic activation: with and without
Result: negative

Remark: Rat and hamster liver S-9 mix.
16-JAN-2001 (109) (104)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Metabolic activation: without
Result: negative

16-JAN-2001 (110)

Type: Ames test
System of testing: S. typhimurium TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537
Metabolic activation: with
Result: negative

16-JAN-2001 (111)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1535
Metabolic activation: no data
Result: negative

16-JAN-2001 (112)

Type: other: Point-mutation
System of testing: E. coli WP2 uvrA
Metabolic activation: no data
Result: negative

16-JAN-2001 (105)

Type: Bacillus subtilis recombination assay
System of testing: B. subtilis M 45, H 17
Result: positive

16-JAN-2001
(113)

Type: other: Point-mutation
System of testing: E. coli WP2 uvrA
Metabolic activation: without
Result: negative

16-JAN-2001 (113)

Type: Cytogenetic assay

System of testing: CHL cells

Result: negative

16-JAN-2001 (111) (114)

Type: Mouse lymphoma assay
System of testing: L5178Y tk+/tk- cells
Metabolic activation: with and without
Result: ambiguous

16-JAN-2001 (115) (116) (104)

Type: Ames test
System of testing: S. typhimurium TA 100
Metabolic activation: without
Result: negative

16-JAN-2001 (117)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Metabolic activation: with and without
Result: positive

16-JAN-2001 (104)

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.

1 Dose (mg/kg)	MNPCE (%)	PCE (%) Mortality
0	0.23 +/-0.18	48.8 +/-6.2 0/6
50	0.23 +/-0.15	55.5 +/-4.0 0/6
100	0.27 +/-0.12	51.8 +/-9.5 0/6
200	0.12 +/-0.10	48.7 +/-5.2 0/6
(4 doses)		
100	0.20 +/-0.14	63.1 +/-4.1 0/6
Mitomycin C		
2.0	2.63 +/-0.32*	43.8 +/-1.1 0/6

MNPCE = Micronucleated polychromatic erythrocyte

PCE = polychromatic erythrocyte
* = (P < 0.01)
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002 (120)

Type: other: replicative DNA synthesis
Species: rat Sex: male
Strain: Fischer 344
Route of admin.: gavage
Exposure period: once
Doses: 0, 300, 600 mg/kg bw
Result: negative

Method: other: according to Uno Y. et al., Toxicol. Lett. 63, 191-199, 201-209 (1992)
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 (121)

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

Method: other: according to Uno Y. et al., Toxicol.Lett.63,191-199,201-209 (1992),
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 (122)

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 (123)

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)

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

GLP guideline study

Flag: Critical study for SIDS endpoint

14-FEB-2002 (124) (98)

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	
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
GLP guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002 (124) (98)

Species: mouse Sex: male
Strain: B6C3F1
Route of administration: i.p.
Exposure period: 22 d

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
GLP guideline study
Flag: Critical study for SIDS endpoint
14-FEB-2002 (98)

Type: other: 2 year gavage study
Species: mouse
Sex: male/female
Strain: B6C3F1
Route of administration: gavage

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 (126)

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 (127) (128)

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 afer 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
14-FEB-2002 (129) (130) (131)

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 Toxity: 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

14-FEB-2002 (132) (133)

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 Toxity:	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.

Flag: Critical study for SIDS endpoint
06-JUN-2001 (126)

Species: other: chicken embryo Sex:
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.
no post observation
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
15-JUL-1993 (144) (145) (146) (147) (148) (149) (150) (151) (152) (153) (154) (155)

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 requirering 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 voluteers: Benzyl alcohol is itself an effective anesthetic and can reduce the pain of injection for lidocain without adversely affecting its anesthetic properties.
Source: Bayer AG Leverkusen
24-FEB-1998 (161)

Remark: Benzyl alkohol 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 (176)

Type: other

Remark: yeast test: according to the author an a 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 (177) (178)

Type: other

Remark: Benzylalkohol differencially 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 (179) (180) (181) (182)

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 (183)

Type: other

Remark: In vitro, benzyl alcohol relaxes airway smooth muscle, probably through the dercrease in intracellular Ca2+ release by inhibiting agonist-mediated phosphatidylionositol 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

15-JUL-1993 (187)

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 (188) (189)

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 (190)

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

27-MAY-1993 (191)

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 oxido-reductase 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 (196)

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 (197)

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 (198)

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 (199)

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.

Source: Bayer AG Leverkusen

27-MAY-1993 (200)

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)-ATPaseactivity, higher concentrations inhibited enzyme activity to about 80 % of those activities found in resting parietal cells.

Source: Bayer AG Leverkusen

15-JUL-1993 (201)

Remark: Benzyl alcohol is a fairly efficient anesthetic for intact mucous membranes, greatly surpassing procain. Its action is not as lasting as that of cocain. It appears that 1 % does not produce satisfactory anesthesia of the tongue, even after 10 min. contact.

Source: Bayer AG Leverkusen

27-MAY-1993 (202)

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 (203)

Remark: It was demonstrated that benzyl alcohol, a neutral local anesthetic, inhibits the uptake and degradation of lowdensity 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 appearence 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 mortility 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 (211)

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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10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment