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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR BENZOIC ACID

Prepared for

OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval, for example, one that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. A carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided instead. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer-based RQs are defined in U.S. EPA, 1983 and 1986, respectively.

EXECUTIVE SUMMARY

Benzoic acid is a white solid at ambient temperatures with an odor characteristic of benzoin or benzaldehyde. It is soluble in most common organic solvents but is only slightly soluble in water (Hawley, 1981). As of January, 1986, three U.S. companies at five sites manufactured this chemical (SRI, 1986; USITC, 1986). The reported U.S. production of benzoic acid in 1984 was 165 million pounds and the projected demand for 1988 is 179 millions pounds (CMR, 1984). Benzoic acid can be manufactured by decarboxylation of phthalic anhydride; hydrolysis of benzotrichloride; oxidation of toluene; or from benzoin resin (Hawley, 1981). Some of the uses for benzoic acid in the United States are in the manufacture of phenol, plasticizers, benzoyl chloride and alkyd resins (CMR, 1984).

Few studies are available on the fate of benzoic acid as a result of chemical reactions. Since it contains no hydrolyzable functional groups, it has been predicted that hydrolysis will not be a significant process in aquatic media. Reaction with OH radicals in aquatic media is also not likely to be significant (Dorfman and Adams, 1973). From the UV absorption spectrum of this compound at wavelength >290 nm (Sadtler, n.d.) and the study of Draper and Crosby (1983), it has been concluded that this compound will not undergo significant photodegradation in natural waters. Both pure culture and mixed microorganisms studies indicate that this compound is readily biodegradable (Banerjee et al., 1984; Freitag et al., 1985; Rubin et al., 1982). The biodegradation half-life of benzoic acid in most natural waters is expected to be 1-4 days (Banerjee et al., 1984; Rubin et al., 1982). It has also been shown that the mineralization rate of benzoate is not usually affected by the presence of suspended solids or sediments in

water (Subba-Rao and Alexander, 1982; Subba-Rao et al., 1982). Benzoic acid is also susceptible to anaerobic biodegradation, although such biodegradation may require a longer acclimation period (Horowitz et al., 1982; Suflita et al., 1982; Grbic-Galic and Young, 1985). The anaerobic process has practical significance in that it can be used for industrial wastewater treatment (Speece, 1983), and it indicates that biodegradation of benzoic acid may occur in bottom sediments.

Based on an estimated Henry's Law constant, it has been concluded that this compound will not volatilize significantly from water. Neither adsorption nor bioconcentration in aquatic organisms are expected to be significant for benzoic acid (Freitag et al., 1985; Loekke, 1984; Bailey and White, 1970).

Based on its expected photolytic behavior in water, it has been concluded that significant photolysis in air is unlikely. Based on the rate constant in water, the estimated half-life for its reaction with OH radicals in the atmosphere is ~1 day. No information about the reaction of benzoic acid with atmospheric bases was available in the literature. Removal of atmospheric benzoic acid by rainwater and snow has been observed (Lunde et al., 1977).

On the basis of its expected reactivity in water, neither hydrolysis nor photolysis will be significant in soils. Isolated microorganism, mixed soil microorganism and soil biodegradation studies show that benzoic acid is easily biodegradable in soils (Kilpi et al., 1980; Tabak et al., 1964; Alexander and Lustigman, 1966; Ward, 1985). In a subsurface sand, the half-life for biodegradation was 7 hours under aerobic conditions (Ward, 1985). This compound is also susceptible to anaerobic biodegradation. The half-life for anaerobic biodegradation in a subsurface soil was 17 hours (Ward,

1985). Based on its estimated volatility in water, it probably will not volatilize significantly from soils. Benzoic acid will show medium to high mobility in soils (Bailey and White, 1970; Loekke, 1984). Therefore, it is likely to leach from most soils to groundwater.

Benzoic acid was reported to be present in the exhaust from gasoline and diesel-powered vehicles (Hampton et al., 1982; Kawamura et al., 1985). A mean concentration of 0.010 ppb was detected in the Los Angeles atmosphere (Kawamura et al., 1985). Human exposure to benzoic acid in the United States from inhalation of air cannot be estimated until more monitoring data are available. Benzoic acid was detected in industrial and municipal effluents, leachates from waste disposal sites, raw surface water and drinking water (Ellis et al., 1982; Lindstrom and Osterberg, 1986; Francis et al., 1980; Reinhard et al., 1984; Stuermer et al., 1982; Goerlitz et al., 1985; Stepan et al., 1981; Fielding et al., 1981). Benzoic acid at a concentration of 15 ppb was reported in the drinking water from Ottumwa, IA (U.S. EPA, 1975). Human exposure to this compound from ingestion of drinking water in the United States cannot be estimated until more drinking water monitoring data are available. Benzoic acid is present naturally in some foods. Benzoic acid and sodium benzoate are also added to food as preservatives. Based on production data, estimated per capita daily intakes are 0.9 mg for benzoic acid and 34 mg for sodium benzoate (FASEB, 1973).

The data concerning aquatic toxicity of benzoic acid were limited. The lowest reported toxic concentration was 31 mg/ℓ, a threshold for inhibition of cell multiplication in the protozoan, Uronema parduczi (Bringmann and Kuehn, 1981).

Gastrointestinal absorption of benzoic acid appears to be virtually complete and fairly rapid in humans (Bridges et al., 1970; Riihmaki, 1979; Amsel and Levy, 1969), rats (Bridges et al., 1970; Hall and James, 1980; Jones, 1982), hamsters and dogs (Bridges et al., 1970); urinary excretion products account for ≥90% of the dose within 24 hours of treatment. In situ studies using rats indicate that increasing intestinal pH above 4.2 decreases the rate of absorption (Hoegerle and Winne, 1983) and increasing or decreasing the net flux of water from the intestine by altering the tonicity of the perfusion solution (Ochsenfahrt and Winne, 1974) increases or decreases, respectively, the rate of uptake of benzoic acid. Data were not located regarding inhalation absorption; however, in an in situ nasal cavity perfusion study using rats, absorption of benzoic acid occurred and the rate depended on the pH of the perfusing solution (Huang et al., 1985).

The dermal absorption of 31.4% of a 4 $\mu g/cm^2$ dose has been demonstrated in guinea pigs (Andersen et al., 1980). With in vitro preparations of human and rat skin, Bronaugh and Stewart (1985) showed that scarification increased percutaneous absorption ~2-fold.

Data were not located regarding the distribution or retention of benzoic acid or its metabolites, but the rapidity and extent of benzoic acid elimination suggests that retention is probably not important in the pharmacokinetics and toxicity of the compound (FASEB, 1973).

In humans and common laboratory species (Bridges et al., 1970; Riihmaki, 1979; Amsel and Levy, 1969; Hall and James, 1980; Jones, 1982; Huckle et al., 1981; Thabrew et al., 1980) hippuric acid, formed by conjugation with the amino acid glycine, is the predominant metabolite (up to 100% of the dose) and benzoyl glucuronide, formed by conjugation with glucuronic acid,

is a lesser metabolite (0-22% of the dose). The rate and extent of conversion of benzoic acid to hippuric acid is dependent upon the availability of glycine, and can be increased by the administration of exogenous glycine (Quick, 1931; Riihmaki, 1979; Amsel and Levy, 1969). The proportion excreted as hippuric acid by humans and rats is reduced in the very young (Green et al., 1983; Edwards and Voegeli, 1984; Baines et al., 1978; Hall and James, 1980). The liver and kidney appear to be the major sites of conversion to hippuric acid and benzoyl glucuronide, but there are marked species differences in the rate, extent and products of metabolism at each site (Kao et al., 1978). CO_2 resulting from decarboxylation is a minor metabolite in rats (Jones, 1982), but its importance has not been investigated in other species. In vitro studies suggest that hydroxylation of the benzene ring, probably followed by conjugation, may also occur (Sato et al., 1956; Daly et al., 1968).

For humans, rats and dogs, excretion appears to occur rapidly and nearly completely in the urine (Bridges et al., 1970; Riihmaki, 1979, Amsel and Levy, 1969; Hall and James, 1980). Renal excretion of the metabolites hippuric acid and benzoyl glucuronide is rapid. In rats, ~3% of an oral dose was expired as CO_2 (Jones, 1982). This mode of elimination may be more significant in other species or if preferential routes of elimination become saturated. Biliary and intestinal excretion has not been adequately studied in those species in which urinary excretion accounted for a smaller portion of the dose. In many species, fecal excretion of radioactivity following an intraperitoneal dose of [carboxy-^{14}C]-benzoic acid is <5% (Huckle et al., 1981).

Inhalation of benzoic acid was irritating to the lungs of rats and resulted in histologically detectable signs of inflammation (IRDC, 1981).

Inflammatory changes were noted in all treated groups of rats exposed to 25, 250 or 1200 mg/m^3, 6 hours/day, 5 days/week for 4 weeks.

Several investigators studied the subchronic toxicity of orally administered benzoic acid and sodium benzoate in laboratory animals and humans. A subchronic study reported a reduced rate of body weight gain in mice with benzoic acid at 80 mg/kg/day (Shtenberg and Ignat'ev, 1970). Cats, on the other hand, tolerated a 130-160 mg/kg/day dosage of benzoic acid for 23 days without clinical signs or clinicopathologic evidence of liver or kidney impairment (Bedford and Clarke, 1972).

A number of subchronic dietary studies were performed with rats using benzoic acid (Kreis et al., 1967) and sodium benzoate (Smyth and Carpenter, 1948; Griffith, 1929; White, 1941; Harshbarger, 1942; Fanelli and Halliday, 1963; Deuel et al., 1954). In the study with benzoic acid, reduced growth rate and impaired efficiency of feed conversion were observed at 1.1% of the diet, the only concentration tested. With sodium benzoate, mortality occurred at dietary levels $\geq$3.0% (Griffith, 1929; Harshbarger, 1942; Fanelli and Halliday, 1963; Deuel et al., 1954). Depression of body weight gain, but no mortality was reported for a dietary level of sodium benzoate of 2% (Fanelli and Halliday, 1963).

In 20- to 92-day oral studies using humans, no externally visible adverse effects were noted at 7 or 14 mg/kg/day (Gerlach, 1909), but irritation, discomfort, weakness and malaise were observed at 25 mg/kg/day (Wiley and Bigelow, 1908). In hypersensitive humans, oral (Clemmensen and Hjorth, 1982; Ros et al., 1976; Michaelsson and Juhlin, 1973) or occupational exposure (Nethercott et al., 1984) to benzoic acid or sodium benzoate may lead to urticaria.

Long-term oral studies using rats and mice were performed with benzoic acid. Shtenberg and Ignat'ev (1970) reported that mice treated with 40 mg/kg/day for 17 months followed by a 5-day fast had reduced ability to cope with stress, manifested as an increased incidence of mortality and greater weight loss, compared with controls. In another report (Ignat'ev, 1965), 80 mg/kg/day in mice was associated with reduced viability and weight gain, and altered organ weights.

In rats exposed to benzoic acid for $\geq$18 months, decreased food intake and growth were observed at 1.5% in the diet (Marquardt, 1960), but not at $\leq$1.0% in the diet (Kieckebusch and Lang, 1960).

Data regarding the inhalation carcinogenicity of benzoic acid or its soluble alkali salts were not located. In a drinking water study, exposure to 2% sodium benzoate for the lifetime resulted in no increased incidence of tumors in mice (Toth, 1984). Benzoic acid and sodium benzoate have been consistently negative in mutagenicity tests in prokaryotes (McCann et al., 1975), eukaryotes (Litton Bionetics, Inc., 1974) and mammalian test systems (Litton Bionetics, Inc., 1974; Oikawa et al., 1980).

Oral administration of sodium benzoate appeared to cause no maternal toxicity, fetal toxicity or teratogenicity in mice, rats, hamsters or rabbits (FDRL, 1972). The highest dosages tested were 175.0, 175.0, 300.0 and 250.0 mg/kg/day, respectively, in these species. Intraperitoneal injection of 1000 mg/kg sodium benzoate in rats, however, was associated with fetal toxicity and gross anomalies (Minor and Becker, 1971).

An RfD of 4 mg/kg/day or 312 mg/day for a 70 kg human for subchronic and chronic oral exposure was estimated using the upper end of the range of the estimated daily intakes of 34 mg for benzoic acid and 328 mg for sodium benzoate. Correcting for molecular weight differences, 328 mg sodium

benzoate is equivalent to 278 mg benzoic acid, which when added to the upper end of the range of the daily intake of 34 mg for benzoic acid, yields a human NOEL of 312 mg/day, and hence an RfD of 312 mg/day. An uncertainty factor of 10 to protect sensitive individuals was not used. Data were insufficient to derive RfDs for inhalation exposure. An RQ of 100 based on chronic toxicity was derived from the IRDC (1981) data for lesions in the lungs of rats exposed by inhalation to benzoic acid. Data regarding the carcinogenicity of benzoic acid were inadequate, placing benzoic acid in EPA Group D.

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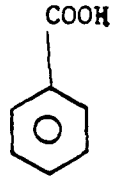
LIST OF ABBREVIATIONS

BODT	Biological oxygen demand theoretical
bw	Body weight
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
CNS	Central nervous system
COD	Chemical oxygen demand
CS	Composite score
EC_{50}	Concentration effective to 50% of recipients
GRAS	Generally recognized as safe
i.p.	Intraperitoneal
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
POTW	Publicly owned treatment works
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
UDP	Uridine diphosphate
UV	Ultraviolet
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly called benzoic acid is also known by the synonyms benzenecarboxylic acid, benzeneformic acid, benzenemethanoic acid and phenylcarboxylic acid. The structure, molecular weight, empirical formula and CAS Registry number are as follows:



Molecular weight: 122.12

Empirical formula: $C_7H_6O_2$

CAS Registry number: 65-85-0

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Benzoic acid is a white solid at ambient temperatures with an odor characteristic of benzoin or benzaldehyde. It is soluble in ethanol, ethyl ether, chloroform, benzene and carbon disulfide but is only slightly soluble in water (Hawley, 1981). The sodium salt, however, is readily soluble in water with a solubility of 660,000 mg/ℓ (Weast, 1980). Other physical properties are listed below:

Melting point:	122.13°C	Weast, 1980
Boiling point:	249.0°C	Weast, 1980
Density (15/4°C):	1.2659	Weast, 1980
Flash point (closed cup):	121.1°C	Hawley, 1981
Vapor pressure, mm Hg		
at 20°C:	3.36×10^{-4}	McEachern and Sandoval, 1973
at 25°C:	4.86×10^{-4}	Scala and Banerjee, 1982
at 30°C:	10.72×10^{-4}	McEachern and Sandoval, 1973
Water solubility		
at 18°C:	2700 mg/ℓ	Chiou et al., 1977
at 40°C:	9480 mg/ℓ	Volpi and Toffoli, 1979

Log K_{ow}:	1.87	Chiou et al., 1977
Henry's Law constant:	2.0×10^{-8} atm-m³/mol at 20°C (estimated)	
pK_a at		
25°C:	4.19	Ferber, 1961
ambient temperatures:	4.17	Cessna and Grover, 1978
40°C:	3.89	Volpi and Toffoli, 1979
Air conversion factor:	1 ppm = 5.077 mg/m³	

Chemically, benzoic acid can undergo electrophilic substitution reactions to form meta-substituted products. It can also react with phosphorus pentachloride to form the acid chloride (Gutsche and Pasto, 1975). Benzoic acid reacts with bases to form salts; however, it is a reasonably stable compound under most environmental conditions.

1.3. PRODUCTION DATA

According to the U.S. EPA TSCA production data base (U.S. EPA, 1977), ~11 companies in 13 locations in the United States produced between 112 and 571 million pounds of this chemical in 1977. Several companies also imported this chemical in the United States during the same year (U.S. EPA, 1977). Table 1-1 lists the manufacturers of benzoic acid in the United States as of January, 1986. CMR (1984) and USITC (1986) also listed the same U.S. manufacturers in 1984 and in 1985. In 1984, 165 million pounds was produced in the United States and the projected demand for benzoic acid is 179 million pounds in 1988 (CMR, 1984).

Benzoic acid can be manufactured by decarboxylation of phthalic anhydride in the presence of a catalyst; chlorination of toluene to benzotrichloride, followed by hydrolysis of the product; oxidation of toluene; or from benzoin resin (Hawley, 1981).

TABLE 1-1

Manufacturers of Benzoic Acid in the United States
as of January, 1986*

Manufacturer and Location	Annual Capacity (millions of pounds)
Velsicol Chem. Corp.	
Beaumont, TX	50
Chattanooga, TN	60
Kalama Chem. Inc.	
Garfield, NJ	15
Kalama, WA	140
Pfizer Inc.	
Terre Haute, IN	9
TOTAL	274

*Source: SRI, 1986

1.4. USE DATA

According to CMR (1984), benzoic acid has the following use pattern: phenol manufacture, 54%; plasticizers, 18%; benzoyl chloride, 13%; sodium benzoate, 8%; alkyd resins, 3%; butyl benzoate, 2%; others, 2%. This chemical is also used as a food preservative and antifungal agent, in seasoning tobacco, in flavors, perfumes, dentrifices, and as a standard in analytical chemistry (Hawley, 1981).

1.5. SUMMARY

Benzoic acid is a white solid at ambient temperatures with an odor characteristic of benzoin or benzaldehyde. It is soluble in most common organic solvents but is only slightly soluble in water (Hawley, 1981). As of January, 1986, three U.S. companies at five sites manufactured this chemical (SRI, 1986; USITC, 1986). The reported U.S. production of benzoic acid in 1984 was 165 million pounds and the projected demand for 1988 is 179 million pounds (CMR, 1984). Benzoic acid can be manufactured by decarboxylation of phthalic anhydride; hydrolysis of benzotrichloride; oxidation of toluene; or from benzoin resin (Hawley, 1981). Some of the uses for benzoic acid in the United States are in the manufacture of phenol, plasticizers, benzoyl chloride and alkyd resins (CMR, 1984).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. WATER

The fate of benzoic acid in water will depend on its ability to undergo microbial degradation, photochemical and chemical reactions, and to partition from the water column into air and sediment. Of these processes, the biodegradation process is the most thoroughly studied. The ready biodegradability of benzoic acid or its sodium salt by pure cultures of microorganisms was demonstrated by Neujahr and Varga (1970) and Banerjee et al. (1984). With Trichosporon cutaneum as pure culture, sodium benzoate showed a 10- to 30-minute lag period before initiation of degradation (Neujahr and Varga, 1970). Benzoic acid is also readily biodegraded by mixed microorganisms. Phenol-adapted mixed microorganisms biodegraded the equivalent of 64% of the BODT in 1.5 hours (Chambers et al., 1963). Thom and Agg (1975) reported that benzoic acid was easily biodegraded by microorganisms under biological sewage treatment conditions. Using adapted activated sludge as microorganisms, 99% of benzoic acid was removed in 5 days of incubation when the percent removal was based on COD (Pitter, 1976). Lund and Rodriguez (1984) reported ~98% degradation of benzoic acid in 20 days with phenol-acclimated sludge. About 66% of benzoic acid was completely mineralized to carbon dioxide with activated sludge in 5 days (Freitag et al., 1985). Rubin et al. (1982) and Mills and Stack (1954) reported the biodegradability of benzoic acid by mixed microorganisms from sewage. At an initial concentration of 59 mg/ℓ, 99.5% of benzoic acid mineralized in 7 days with sewage seed as microbial inoculum (Rubin et al., 1982).

Although the above studies demonstrate the easy biodegradability of benzoic acid, they cannot be used for predicting the biodegradation half-life of this compound in natural water. Lu and Metcalf (1975) studied the

biodegradation of benzoic acid in an aquatic ecosystem and concluded that this chemical is easily degradable in natural water. Benzoic acid at initial concentrations of 15-18 mg/ℓ was biodegraded with half-lives of 1-4 days by two natural surface waters (Banerjee et al., 1984). At initial concentrations of 59 µg/ℓ and 59 mg/ℓ, >94.5% of benzoate mineralized in 7 days with two lake waters (Rubin et al., 1982). Evidence was also provided that biodegradation at trace levels are different from biodegradation at higher concentrations and that mineralization of benzoate involves little or no incorporation of carbon into microbial cells. In other words, mineralization of benzoate is not usually affected by the presence of suspended solids and sediments in water (Subba-Rao and Alexander, 1982; Subba-Rao et al., 1982).

The anaerobic biodegradation of benzoate was studied by several investigators. A stable methanogenic bacterial mixture enriched from sludges or sediments was shown to mineralize benzoate into methane and carbon dioxide (Horowitz et al., 1982; Suflita et al., 1982; Grbic-Galic and Young, 1985; Shelton and Tiedje, 1984). Sleat and Robinson (1983) reported that long adaptation times were required before methanogenesis of benzoate occurred. Enriched methanogenic mixtures obtained from sewage sludge almost completely converted benzoate into methane and carbon dioxide in <4 days (Grbic-Galic and Young, 1985). Similarly, sludge from municipal digesters almost completely mineralized benzoate in 7 days under anaerobic conditions. Freshwater lake sediment also anaerobically mineralized benzoate in 7 days (Horowitz et al., 1982). This anaerobic process can be used for industrial wastewater treatment (Speece, 1983).

The suggested pathway for the methanogenesis of benzoic acid is as follows (Keith et al., 1978):

benzoic acid → 1-cyclohexene-1-carboxylic acid → cyclohexane carboxylic acid → heptanoic acid → valeric acid → acetic acid + propanoic acid → methane + carbon dioxide

Few studies are available on the fate of benzoic acid with respect to chemical reactions in aquatic media or any other media. Benzoic acid does not contain functional groups susceptible to hydrolysis. Therefore, this compound is unlikely to hydrolyze in most aquatic media. The rate constant for the oxidation of benzoic acid with hydroxyl radicals is 4.3×10^{9} M-sec (Dorfman and Adams, 1973). Given this rate constant and a value of 3×10^{-17} M as the concentration of OH radicals in eutrophic water (Mill and Mabey, 1985), the half-life for this reaction is estimated to be >60 days. Therefore, this reaction is not expected to be significant in water. Suzuki et al. (1982) reported detection of mutagenic compounds after irradiation of water containing nitrite and benzoic acid with long wavelength light; however, the significance of this reaction in natural water cannot be evaluated since the nitrite concentration used in this experiment was much higher (>16 ppm) than concentrations present in most natural waters.

Draper and Crosby (1983) studied the possibility of photochemical oxidation of benzoic acid by irradiating 1.0 mmol/ℓ of the compound in water in July sunlight (Davis, CA) for 5 hours; no oxidation products were detected. Freitag et al. (1985), on the other hand, irradiated this compound adsorbed to silica gel for 17 hours with light of wavelength >290 nm and observed ~10% mineralization of the compound to carbon dioxide. Although the intensity of light used by these investigators was greater than sunlight, it appears that some photodegradation of adsorbed benzoic acid is possible under sunlight. The UV absorption spectra of benzoic acid in both methanol

and potassium hydroxide show little absorption at wavelengths >290 nm (Sadtler, n.d.). Based on absorption spectra and the investigation of Draper and Crosby (1983) it has been concluded that this compound will not undergo significant photodegradation in natural waters.

Pertinent data regarding the rate of volatilization of benzoic acid from water could not be located in the available literature as cited in Appendix A. Based on the estimated Henry's Law constant of 2×10^{-8} atm-m³/mol and the volatility characteristics associated with various values of Henry's Law constant (Lyman et al., 1982), it has been concluded that significant volatilization of benzoic acid from water is unlikely. Data on the removal of benzoic acid from the aqueous phase by sorption onto suspended solids and sediments could not be located in the available literature as cited in Appendix A. Using the equation, $\log K_{oc} = -0.55 \log S + 3.54$ (Lyman et al., 1982) and the value of solubility given in Section 1.2., the K_{oc} for benzoic acid is estimated as 45. Based on this value and its K_{oc} capacity (Section 2.3.), it is concluded that it is unlikely that significant amounts of this compound may be removed through sorption by suspended solids and sediments.

The bioconcentration factor of benzoic acid in the fish, golden ide, Leuciscus idus melanotus, was reported to be <10 (Freitag et al., 1985). Therefore, this compound will not bioconcentrate significantly in aquatic organisms.

2.2. AIR

Information on the fate of benzoic acid in air is limited. Given the assumption that the first-order reaction rate constant should be about the same in the gas and liquid phases (Guesten et al., 1981), the rate constant for OH radical reaction with benzoic acid in the gas phase will be

7.14×10^{-12} cm^3/molecule-sec (Dorfman and Adams, 1973). Using this rate constant and a value of 10^6 radicals/cm^3 for the concentration of OH radicals in the atmosphere, the half-life of benzoic acid in the atmosphere is ~1 day. Based on photolysis data in aquatic media, it has been concluded that benzoic acid is not likely to undergo significant photolysis in the atmosphere. Benzoic acid is expected to behave like other acids and react with atmospheric bases, such as ammonia and amines to form salts; however, information about such reactions could not be located in the available literature as cited in Appendix A.

Since the vapor pressure of benzoic acid at ambient temperatures is $>10^{-4}$ mm Hg (see Section 1.2.), this compound is expected to exist predominantly in the vapor phase in the atmosphere (Eisenreich et al., 1981). Based on its aqueous solubility (see Section 1.2.), this compound is expected to be removed partially from the atmosphere by wet deposition. It has been detected in rainwater and in snow in three locations in Norway (Lunde et al., 1977).

2.3. SOIL

The biodegradability of benzoic acid by microorganisms isolated from soil was studied by several authors. A species of Pseudomonas bacterium isolated from soil was shown to degrade this compound (Kilpi et al., 1980). For example, Tabak et al. (1964) reported oxidation equivalent to ~41% of BODT with phenol-adapted mixed microorganisms in 3 hours, and Alexander and Lustigman (1966) reported almost complete degradation of benzoic acid in 1 day with mixed microorganisms derived from soil. In natural soils, Haller (1978) reported that the biodegradation of benzoic acid required a 0- to 1-day lag period. Ward (1985) reported that benzoic acid is rapidly biodegraded in surface soils by microorganisms under aerobic conditions and in

subsurface soils under both aerobic and anaerobic conditions. In a subsurface sand, the half-life for aerobic biodegradation was ~7 hours, and for anaerobic biodegradation was ~17 hours (Ward, 1985). The capability of heterotrophic bacteria in groundwaters to biodegrade benzoic acid was reported by Ventullo and Larson (1985). In a groundwater sample from Canada, the authors estimated that the complete mineralization half-life for benzoic acid was ~3 days.

Pertinent data regarding the fate of benzoic acid in soils as a result of chemical reactions or interaction with sunlight could not be located in the available literature as cited in Appendix A; however, based on its predicted fate in water, it is unlikely that either photolysis or hydrolysis will be significant in soils.

With montmorillonite clay, Bailey and White (1970) observed no adsorption of benzoic acid under acidic or neutral conditions. Loekke (1984) also reported no adsorption of this compound by sandy clay loam or sandy loam soils, but a sandy clay soil showed adsorption with a K_{oc} value of 230. Therefore, it is concluded that benzoic acid will show medium to very high mobility in most soils.

Based on its estimated volatility from aquatic media, it is predicted that benzoic acid will not significantly volatilize from soils.

2.4. SUMMARY

Few studies are available on the fate of benzoic acid as a result of chemical reactions. Since it does not contain any hydrolyzable functional groups, it has been predicted that hydrolysis will not be a significant process in aquatic media. Reaction with OH radicals in aquatic media is also not likely to be significant (Dorfman and Adams, 1973). From the UV absorption spectrum of this compound at wavelength >290 nm (Sadtler, n.d.)

and the study of Draper and Crosby (1983), it has been concluded that this compound will not undergo significant photodegradation in natural waters. Both pure culture and mixed microorganisms studies indicate that this compound is readily biodegradable (Banerjee et al., 1984; Freitag et al., 1985; Rubin et al., 1982). The biodegradation half-life of benzoic acid in most natural waters is expected to be 1-4 days (Banerjee et al., 1984; Rubin et al., 1982). It has also been shown that the mineralization rate of benzoate is not usually affected by the presence of suspended solids or sediments in water (Subba-Rao and Alexander, 1982; Subba-Rao et al., 1982). Benzoic acid is also susceptible to anaerobic biodegradation, although such biodegradation may require a longer acclimation period (Horowitz et al., 1982; Suflita et al., 1982; Grbic-Galic and Young, 1985). The anaerobic process has practical significance in that it can be used for industrial wastewater treatment (Speece, 1983) and it indicates that biodegradation of benzoic acid may occur in bottom sediments.

Based on an estimated Henry's Law constant, it has been concluded that this compound will not volatilize significantly from water. Neither adsorption nor bioconcentration in aquatic organisms are expected to be significant for benzoic acid (Freitag et al., 1985; Loekke, 1984; Bailey and White, 1970).

Based on its expected photolytic behavior in water, it has been concluded that significant photolysis in air is unlikely. Based on the rate constant in water, the estimated half-life for its reaction with OH radicals in the atmosphere is ~1 day. No information about the reaction of benzoic acid with atmospheric bases was available in the literature. Removal of atmospheric benzoic acid by rainwater and snow has been observed (Lunde et al., 1977).

On the basis of its expected reactivity in water, it is concluded that neither hydrolysis nor photolysis will be significant in soils. Isolated microorganism, mixed soil microorganism and soil biodegradation studies show that benzoic acid is easily biodegradable in soils (Kilpi et al., 1980; Tabak et al., 1964; Alexander and Lustigman, 1966; Ward, 1985). In a subsurface sand, the half-life for biodegradation was 7 hours under aerobic conditions (Ward, 1985). This compound is also susceptible to anaerobic biodegradation. The half-life for anaerobic biodegradation in a subsurface soil was 17 hours (Ward, 1985). Based on its estimated volatility in water, it is predicted that benzoic acid will not volatilize significantly from soils. Benzoic acid will show medium to high mobility in soils (Bailey and White, 1970; Loekke, 1984). Therefore, it is likely to leach from most soils to groundwater.

3. EXPOSURE

3.1. AIR

Benzoic acid was detected in the process exhaust from a phthalic anhydride manufacturing plant at concentrations of 5-40 ppm (v/v); however, application of pollution abatement devices is expected to reduce the pollutant level (Fawcett, 1970). Benzoic acid at a concentration of 0.164 ppb was also detected in the exhaust of gasoline-powered automobiles. Although a new engine oil showed no benzoic acid, used oil from a similar automobile engine contained 45.3 ppb of the compound (Kawamura et al., 1985). Similarly, other authors reported the detection of benzoic acid in the exhaust of diesel-powered vehicles (Hampton et al., 1982). Kawamura et al. (1985) reported benzoic acid at a mean concentration of 0.010 ppb in the Los Angeles atmosphere.

3.2. WATER

Benzoic acid was detected in industrial and municipal effluents, leachates from waste disposal sites, raw surface water and drinking water. The compound was tentatively identified in the primary and final effluents from POTWs (Ellis et al., 1982; U.S. EPA, 1975) and in the effluents from a pulp mill plant (Lindstrom and Osterberg, 1986). Francis et al. (1980) detected benzoic acid at a maximum concentration of 6.7 ppm from the leachates of two low level radioactive disposal sites in Maxey Flats, KY, and West Valley, NY. The maximum concentration of benzoic acid detected in leachates from two landfill sites in Ontario, Canada was >1 ppm (Reinhard et al., 1984). This compound was detected in the groundwater at concentrations as high as 0.86 ppm from an underground coal gasification site in northeastern Wyoming (Stuermer et al., 1982), and at 27.5 ppm from a wood-preserving facility in Pensacola, FL (Goerlitz et al., 1985). Stepan et al.

(1981) qualitatively detected benzoic acid in the groundwater from a chemical waste disposal site near Melbourne, Australia. Benzoic acid was also present in surface waters in England (Fielding et al., 1981) and in Norway (Schou et al., 1981). Benzoic acid at a concentration of 15 ppb was reported in the drinking water from Ottumwa, IA (U.S. EPA, 1975; Kopfler et al., 1977).

3.3. FOOD

Benzoic acid is present naturally in many foodstuffs. FEMA (1984) reported that levels ranged from a minimum of 0.239 ppm in apple wine to a maximum of 40 ppm in apple essence. The greater contribution to the human diet, however, results from the addition of benzoic acid and sodium benzoate to food as an antimicrobial preservative (Chapter 7). FASEB (1973) reported results of a comprehensive survey by the Subcommittee on Review of the GRAS List (1972) from which possible daily dietary intakes of benzoic acid and sodium benzoate were estimated (Table 3-1). The report acknowledged that these data probably represent a gross exaggeration of actual dietary intakes. Based on data regarding the amounts of benzoic acid and sodium benzoate produced for addition to food, FASEB (1973) estimated daily per capita dietary intakes of benzoic acid of 0.9 mg and of sodium benzoate of 34 mg.

3.4. SUMMARY

Benzoic acid was reported to be present in the exhaust from gasoline and diesel-powered vehicles (Hampton et al., 1982; Kawamura et al., 1985). A mean concentration of 0.010 ppb was detected in the Los Angeles atmosphere (Kawamura et al., 1985). Human exposure to benzoic acid in the United States from inhalation of air cannot be estimated until more monitoring data are available. Benzoic acid was detected in industrial and municipal

TABLE 3-1

Estimated Possible Human Daily Dietary Intakes of Benzoic Acid and Sodium Benzoate[a]

Age Group	Total mg				mg/kg body weight[b]			
	Benzoic Acid		Sodium Benzoate		Benzoic Acid		Sodium Benzoate	
	Average	Maximum	Average	Maximum	Average	Maximum	Average	Maximum
0-5 months	0.6	1	10	21	0.1	0.2	2	4
6-11 months	6	21	111	313	0.8	2.6	14	39
12-23 months	116	46	188	404	1.4	4.2	17	37
2-65+ years	34	87	328	669	0.6	1.4	5.5	11

[a]Source: FASEB, 1973

[b]Body weights used as the basis of these estimations: 0-5 months, 5 kg; 6-11 months, 8 kg; 12-23 months, 11 kg; 2-65+ years, 60 kg

effluents, leachates from waste disposal sites, raw surface water and drinking water (Ellis et al., 1982; Lindstrom and Osterberg, 1986; Francis et al., 1980; Reinhard et al., 1984; Stuermer et al., 1982; Goerlitz et al., 1985; Stepan et al., 1981; Fielding et al., 1981). Benzoic acid at a concentration of 15 ppb was reported in the drinking water from Ottumwa, IA (U.S. EPA, 1975). Human exposure to this compound from ingestion of drinking water in the United States cannot be estimated until more drinking water monitoring data are available. Benzoic acid is present naturally in some foods. Benzoic acid and sodium benzoate are also added to food as preservatives. Based on production data, estimated per capita daily intakes are 0.9 mg for benzoic acid and 34 mg for sodium benzoate (FASEB, 1973).

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

Data concerning acute toxicity of benzoic acid to aquatic organisms are presented in Table 4-1. Interpretation of these data are complicated by the fact that the form of the acid (free acid, neutralized acid or salt) used in the studies was not always stated explicitly. According to Doudoroff and Katz (1950), the toxicity of benzoic acid is due primarily to the undissociated acid in solution and not to pH depression.

All of the available data apply to freshwater species. The lowest reported toxic concentration for freshwater fishes was 180 mg/ℓ, a 96-hour LC_{50} for mosquitofish, Gambusia affinis (Wallen et al., 1957). Among invertebrates, the lowest reported toxic concentration was 31 mg/ℓ, a threshold for inhibition of cell multiplication in the protozoan, Uronema parduczi (Bringmann and Kuehn, 1981). Additional data were provided by Ewell et al. (1986) who indicated that 96-hour LC_{50} values for the following species were all >100 mg/ℓ: pillbug, Asellus intermedus; water flea, Daphnia magna; flatworm, Dugesia tigrina; sideswimmer, Gammarus fasciatus; snail, Helisoma trivolvis; segmented worm, Lumbriculus variegatus; and fathead minnow, Pimephales promelas.

4.2. CHRONIC EFFECTS

Pertinent data regarding chronic toxicity of benzoic acid to aquatic organisms could not be located in the available literature as cited in Appendix A.

4.3. PLANT EFFECTS

The available data concerning toxicity of benzoic acid to aquatic plants are presented in Table 4-1. The most sensitive of three algal species tested was the blue-green alga, Microcystis aeruginosa, with a threshold of 55 mg/ℓ for inhibition of cell multiplication (Bringmann and Kuehn, 1978).

TABLE 4-1

Acute Toxicity of Benzoic Acid to Aquatic Organisms

Species	Concentration (mg/ℓ)	Effect	Reference
FISH			
Fathead minnow (*Pimephales promelas*)	484	96-hour LC_{50}[a]	Geiger et al., 1985
Mosquitofish (*Gambusia affinis*)	180	96-hour LC_{50}[b]	Wallen et al., 1957
	56	96-hour NOEC	
Golden orfe (*Leuciscus idus*)	460	48-hour LC_{50}	Juhnke and Luedemann, 1978
	400	48-hour LC_0	
Goldfish (*Carassius auratus*)	200	lethal (96 hours)	Ellis, 1937
Orangespotted sunfish (*Lepomis humilis*)	550	lethal	Shelford, 1917
INVERTEBRATES			
Flagellate protozoan (*Entosiphon sulcatum*)	218	toxicity threshold[c]	Bringmann and Kuehn, 1980
(*Chilomonas paramecium*)	356	toxicity threshold[c]	Bringmann and Kuehn, 1981
Ciliate protozoan (*Uronema parduczi*)	31	toxicity threshold[c]	Bringmann and Kuehn, 1981

TABLE 4-1 (cont.)

Species	Concentration (mg/ℓ)	Effect	Reference
INVERTEBRATES (cont.)			
Water flea (Daphnia magna)	500	24-hour EC_{50}[d]	Bringmann and Kuehn, 1982
	260	24-hour EC_0 [d]	
	102	24-hour EC_{50}[e]	
	77	24-hour EC_0 [e]	
	1540	24-hour LC_{50}[f]	Bringmann and Kuehn, 1977
	540	24-hour LC_0 [f]	
PLANTS			
Blue-green alga (Microcystis aeruginosa)	55	toxicity threshold[c]	Bringmann and Kuehn, 1978
Green alga (Scenedesmus quadricauda)	1630	toxicity threshold[c]	Bringmann and Kuehn, 1980
BACTERIA			
Pseudomonas putida	480	toxicity threshold[c]	Bringmann and Kuehn, 1980

[a]Sodium salt
[b]Turbid water
[c]Inhibition of cell multiplication
[d]Immobilization, neutralized
[e]Immobilization, not nuetralized
[f]Acid neutralized

4.4. SUMMARY

The data concerning aquatic toxicity of benzoic acid were limited. The lowest reported toxic concentration was 31 mg/ℓ, a threshold for inhibition of cell multiplication in the protozoan, Uronema parduczi (Bringmann and Kuehn, 1981).

5. PHARMACOKINETICS

Benzoic acid is used as a food preservative (FEMA, 1984) and has limited use as a pharmaceutical [e.g., in the treatment of hyperammonemia in infants (Green et al., 1983)]. Consequently, the pharmacokinetics of this compound has been investigated both in humans and animals. Table 5-1 summarizes several pharmacokinetic studies of benzoic acid in several species.

5.1. ABSORPTION

Informatics, Inc. (1972) concluded that the gastrointestinal absorption of benzoic acid in humans is rapid and complete. Urinary excretion by humans of 95-99% of oral doses confirms this conclusion (see Table 5-1) (Bridges et al., 1970; Riihmaki, 1979). Urinary excretion in subhuman primates ranged from 33-75.5% of an oral dose (Bridges et al., 1970; Hall and James, 1980). Virtually complete gastrointestinal absorption has also been shown for rats (Hall and James, 1980; Jones, 1982; Bridges et al., 1970), hamsters and dogs (Bridges et al., 1970). For species in which urinary recovery amounted to ~30-60% of the dose, it is not clear if the excretion data reflect saturation of absorption, urinary excretion or biotransformation mechanisms; excretion by an alternate route; or tissue retention resulting in less material available for excretion.

Most of the data in Table 5-1 reflect excretion within 24 hours. The recovery of the equivalent of virtually the entire dose of benzoic acid from the urine within 24 hours indicates that the material was rapidly absorbed from the gastrointestinal tract. Riihmaki (1979) noted that urinary excretion of hippuric acid, the major metabolite of benzoic acid in humans, was rapid, with a rate constant of 1.0 $hour^{-1}$ within 4-5 hours of treatment. In rats, excretion was virtually complete within 6 hours of treatment (Hall and James, 1980).

TABLE 5-1

Urinary Excretion Products of Benzoic Acid in Several Species

Species/ Strain/Sex	Dose (mg/kg)[a]/ Route	Material Given/ Vehicle	Time After Dosing (hours)	Percent of Dose Excreted in Urine as:				Reference
				Benzoic Acid	Hippuric Acid	Benzoyl Glucuronide	Total	
Human/NA/M	1/oral	ring ^{14}C-Na benzoate/NR	24	0	>99	0	>99	Bridges et al., 1970
Human/NA/M	71.5/oral	benzoic acid/NR	24	NR	95	NR	95	Rithmaki, 1979
Human/NA/M	22.2/oral	Na benzoate/water	≥8	NR	95	1.8	96.8[b]	Amsel and Levy, 1969
Rhesus monkey/ NA/F	20/oral	ring ^{14}C-Na benzoate/food	24	0	47	0	47	Bridges et al., 1970
Squirrel monkey/NA/F	50/oral	ring ^{14}C-Na benzoate/food	24	7.6	39.2	~1.4	47.5	Bridges et al., 1970
Marmoset/ NA/NR[c]	1/oral	carboxyl ^{14}C-Na benzoate/cytocon syrup	6	2.0	66.2	4.7	75.5	Hall and James, 1980
Marmoset/ NA/NR[c]	40/oral	carboxyl ^{14}C-Na benzoate/cytocon syrup	24	26.8	23.0	18.4	69	Hall and James, 1980
Marmoset/ NA/NR[c]	100/oral	carboxyl ^{14}C-Na benzoate/cytocon syrup	24	10.8	24.4	21.9	57.7	Hall and James, 1980
Marmoset/ NA/NR[d]	1/oral	carboxyl ^{14}C-Na benzoate/cytocon syrup	6	0.2	72.4	4.4	77.7	Hall and James, 1980
Marmoset/ NA/NR[d]	40/oral	carboxyl ^{14}C-Na benzoate/cytocon syrup	6	0.3	28.2	14.0	43	Hall and James, 1980
Marmoset/ NA/NR[d]	100/oral	carboxyl ^{14}C-Na benzoate/cytocon syrup	6	0	13.9	18.1	32	Hall and James, 1980
Rat/Wistar/F	50/oral	ring ^{14}C-Na benzoate/aqueous	24	1.0	99	trace	100	Bridges et al., 1970

TABLE 5-1 (cont.)

Species/ Strain/Sex	Dose (mg/kg)[a]/ Route	Material Given/ Vehicle	Time After Dosing (hours)	Percent of Dose Excreted in Urine as:				Reference
				Benzoic Acid	Hippuric Acid	Benzoyl Glucuronide	Total	
Rat/Wistar/F[c]	1/oral	carboxyl ^{14}C-Na benzoate/Cytacon syrup	6	0.2	80.8	1.5	83	Hall and James, 1980
Rat/Wistar/F[c]	50/oral	carboxyl ^{14}C-Na benzoate/Cytacon syrup	24	trace	99	1.0	100	Hall and James, 1980
Rat/Wistar/F[c]	100/oral	carboxyl ^{14}C-Na benzoate/Cytacon syrup	24	3.0	90.2	2.1	96	Hall and James, 1980
Rat/Wistar/F[e]	1/oral	carboxyl ^{14}C-Na benzoate/Cytacon syrup	6	0.5	86.8	5.7	94	Hall and James, 1980
Rat/Wistar/F[e]	40/oral	carboxyl ^{14}C-Na benzoate/Cytacon syrup	6	1.4	57.2	18.2	78	Hall and James, 1980
Rat/Wistar/F[e]	100/oral	carboxyl ^{14}C-Na benzoate/Cytacon syrup	6	0.7	52.1	16.5	72	Hall and James, 1980
Rat/Sprague-Dawley/M	0.01-1000 mg/kg/oral	carboxyl ^{14}C-Na benzoic acid/ aqueous	24	NR	80-100	NR	80-100[f]	Jones, 1982
Rat/Wistar/M	10/i.p.	carboxyl ^{14}C-Na benzoate/NR	24	7.3	74.4	1.1	88.0	Huckle et al., 1981
Rat/Wistar/M[g]	200/i.p.	carboxyl ^{14}C-Na benzoate/NR	24	0	81.2	trace	82	Thabrew et al., 1980
Rat/Wistar/M[h]	200/i.p.	carboxyl ^{14}C-Na benzoate/NR	24	0	59.9	20.3	81	Thabrew et al., 1980
Mouse/I.C.I./F	56/oral	ring ^{14}C-Na benzoate/aqueous	24	trace	52.3	2.8	55	Bridges et al., 1970
Hamster/ golden/F	52/oral	ring ^{14}C-Na benzoate/aqueous	24	1.0	96	1.0	99	Bridges et al., 1970

TABLE 5-1 (cont.)

Species/ Strain/Sex	Dose (mg/kg)[a]/ Route	Material Given/ Vehicle	Time After Dosing (hours)	Percent of Dose Excreted in Urine as:				Reference
				Benzoic Acid	Hippuric Acid	Benzoyl Glucuronide	Total	
Hamster/ Syrian/F	10/i.p.	carboxy ^{14}C-Na benzoate/NR	24	2.1	49.6	0.6	52.6	Huckle et al., 1981
Guinea pig/ English/F	49/oral	ring ^{14}C-Na benzoate/aqueous	24	trace	77.4	2.4	79	Bridges et al., 1970
Guinea pig/ Durkin-Hartley/F	10/i.p.	carboxy ^{14}C-Na benzoate/NR	24	1.8	64.7	1.5	70.8	Huckle et al., 1981
Rabbit/New Zealand white/F	49/oral	ring ^{14}C-Na benzoate/food	24	0	60	0	60	Bridges et al., 1970
Rabbit/New Zealand white/F	200/oral	ring ^{14}C-Na benzoate/food	24	trace	84.3	1.7	86	Bridges et al., 1970
Rabbit/New Zealand white/F	10/i.p.	carboxy ^{14}C-Na benzoate/NR	24	4.9	73.6	NR	78.6	Huckle et al., 1981
Pig/NA/F	50/oral	ring ^{14}C-Na benzoate/food	24	5.4	44.0	trace	49.5	Bridges et al., 1970
Cat/mongrel/F	51/oral	ring ^{14}C-Na benzoate/milk	24	trace	29, 86[l]	0	29, 86[l]	Bridges et al., 1970
Cat/mongrel/M	10/i.p.	carboxy ^{14}C-Na benzoate/NR	24	5.5	72.4	NR	80.7	Huckle et al., 1981
Dog/mongrel/M,F	51/oral	ring ^{14}C-Na benzoate/food	24	0	77	17	94	Bridges et al., 1970
Ferret/ mongrel/F	50/oral	ring ^{14}C-Na benzoate/food	24	6.2	48.3	15.2	69	Bridges et al., 1970

[a]Doses are expressed as mg benzoic acid
[b]Calculated as the sum of hippuric acid and benzoyl glucuronide
[c]These experiments were performed with adult animals.
[d]These experiments were performed with 4- to 7-day-old animals.
[e]These experiments were performed with 9- to 10-day-old rats.
[f]In addition to urinary excretion, at 0.01 mg/kg ~3% of the dose of radioactivity was recovered as $^{14}CO_2$ in expired air
[g]These experiments were performed with well-fed rats.
[h]These rats were reduced to a marasmic-kwashiorkor condition by ad libitum feeding on a 3.45% protein diet for 5 weeks before treatment.
[i]Results from two cats

NR = Not reported

Since benzoic acid is a weak organic acid with a pK_a of 4.2 (Serjeant and Dempsey, 1979), its gastrointestinal absorption would be expected to decrease as pH increased above 4.2 and to increase as pH dropped below 4.2. Using an in situ preparation of rat jejenum, Hoegerle and Winne (1983) demonstrated that absorption decreased as the pH of the perfusion solution was raised from 4-10.5. The absorption curve, however, was considerably flatter than that predicted by the unmodified pH-partition theory, and more nearly reflected pH as measured in the "unstirred" layer of perfusion solution in contact with the jejunal villi rather than pH as measured in the lumen. In an earlier experiment, Ochsenfahrt and Winne (1974) showed that altering the tonicity of the perfusing solution in a preparation of rat jejunum influenced the rate of absorption. A positive net flux of water from the intestinal lumen to the circulation (hypotonic perfusing solution) increased the appearance of ^{14}C-benzoic acid-associated radioactivity in the blood by up to 47%. A negative net flux of water (movement from circulation to gut lumen) created by perfusion with a hypertonic solution retarded uptake of ^{14}C-benzoic acid-associated radioactivity by up to 28%.

Data were not located regarding the pulmonary absorption of benzoic acid. Huang et al. (1985), however, demonstrated that both the ionized and un-ionized forms of benzoic acid are absorbed from solution by the nasal epithelium of rats. Using rats surgically altered to permit perfusion of the nasal cavity, these investigators circulated 20 mℓ of 0.0015 M solutions of sodium benzoate at pH 2.4-7.2 at a rate of 2 mℓ/minute for 60 minutes. Absorption of benzoic acid was determined to be 44% at pH 2.5 and only 13% at pH 7.19. These data suggest that absorption of benzoic acid through the respiratory epithelium may be expected and that the rate of

absorption may depend upon the physical form of the material in contact with the epithelium and upon conditions that influence pH at the epithelial surface.

The dermal absorption of benzoic acid has been studied using guinea pigs and *in vitro* skin preparations from humans and rats. In the guinea pig study, an estimated 31.4% of a 4 $\mu g/cm^2$ dose in acetone was absorbed in a 24-hour period (Andersen et al., 1980). ^{14}C-Labeled benzoic acid was used and radioactivity was determined in urine collected for 5 days. The guinea pig system was "calibrated" by measuring urinary recovery of radioactivity following intraperitoneal injection of the labeled compound. In the *in vitro* experiment (Bronaugh and Stewart, 1985), 24-hour absorption of benzoic acid applied at 5 mg/cm^2 in a commonly-used cosmetic lotion was 27.5% in human skin and 19.9% in rat skin. Abrading ~6.4% of the skin surface by scratching through the epidermis with a hypodermic needle increased percutaneous absorption ~2-fold.

5.2. DISTRIBUTION

Quantitative data regarding the tissue distribution of benzoic acid and its metabolites could not be located in the available literature as cited in Appendix A. The rate and extent of benzoic acid elimination, however, suggest that tissue retention is not highly significant in the pharmacokinetics and toxicity of the compound (FASEB, 1973).

5.3. METABOLISM

The results of the pharmacokinetic studies summarized in Table 5-1 indicate that hippuric acid is the predominant metabolite in mammals and that benzoyl glucuronide is secondary. In human experiments (Bridges et al., 1970; Riihmaki, 1979; Amsel and Levy, 1969) and in many rat (Bridges et al., 1970; Hall and James, 1980; Jones, 1982) and hamster (Bridges et al.,

1970) experiments, ≥90% of the dose was recovered as hippuric acid within 24 hours. Hippuric acid is formed by conjugation of benzoic acid with the amino acid glycine; benzoyl glucuronide results from conjugation with glucuronic acid. In the experiments summarized in Table 5-1, benzoyl glucuronide accounted for 0-22% of the dose.

Several experiments in humans and animals show that the conversion of benzoic acid to hippuric acid is a rate saturable process dependent upon the availability of glycine. Amsel and Levy (1969) estimated a maximum rate of formation of hippuric acid in humans of 1730 mg/hour with an estimated rate constant of 1.2 $hour^{-1}$. Increasing the dose to 5.0 g (~55.6 mg/kg) increased the excretion of benzoyl glucuronide from 1.8 to 3.2-3.4% of the dose, but the maximum rate of hippuric acid formation only increased to 2090-2100 mg/hour. When glycine (5 g, 1 hour before the sodium benzoate and 2 g each hour thereafter) was given with the larger dose of sodium benzoate, the maximum rate of hippuric acid formation increased to 4050 mg/hour and the rate constant to 1.4 $hour^{-1}$; the excretion of benzoyl glucuronide dropped to the equivalent of 0.6% of the dose.

Riihmaki (1979) (see Table 5-1) estimated a maximum rate of hippuric acid synthesis of 180-198 μmol/minute (~1320-1450 mg/hour) at 2 hours in a human. This rate remained constant for an additional 3 hours, and a rate constant of 1.0 $hours^{-1}$ was estimated. The excretion rate then fell rapidly until ~8 hours after treatment. Riihmaki (1979) suggested that the 3-hour plateau in the excretion rate indicated that the pathway for metabolism of benzoic acid to hippuric acid had become saturated.

In an early experiment, Quick (1931) administered oral doses of 1, 2, 3 or 5 g benzoic acid with or without the simultaneous administration of glycine to a 52 kg man and measured urinary hippuric acid over a 3- to

6-hour post-treatment period. At every dosage level the simultaneous oral administration of glycine resulted in more rapid excretion of hippuric acid, attributed to more rapid conversion of benzoic to hippuric acid rather than to an alteration of the rate of renal clearance.

Data from studies of orally-treated adult and 4- to 7-day-old marmosets (Hall and James, 1980) suggest that a dose-dependent saturation of the conversion of benzoic acid to hippuric acid occurred, resulting in a proportionate decrease in hippuric acid excretion and increase in benzoyl glucuronide and unchanged benzoic acid excretion. No evidence of saturation in the formation/excretion of hippuric acid, however, was observed in adult rats treated with oral doses of benzoic acid ranging from 0.01-1000 mg/kg (Hall and James, 1980; Jones, 1982). In an in vitro study using isolated hepatocytes from Sprague-Dawley rats, however, Wendler and Tremblay (1982) noted that conversion of benzoate to hippurate was limited by the availability of glycine. Adding exogenous glycine during a 1-hour incubation accelerated hippurate formation by 420%.

In weanling rats that had a marasmic-kwashiorkor condition, which was due to consumption of a 3.45% protein diet for 5 weeks, Thabrew et al. (1980) noted a marked decrease in their ability to metabolize benzoic acid to hippuric acid. These rats excreted 59.9% of the dose as hippuric acid and 20.3% as benzoyl glucuronide. Normally-fed rats excreted 81.2% of a 200 mg/kg intraperitoneal dose as hippuric acid and excreted only a trace as benzoyl glucuronide. The investigators suggested that the increased importance of glucuronic acid conjugation in the marasmic-kwashiorkor rats reflected decreased glycine available for conjugation and increased UDP-glucuronyl transferase activity in protein deficient rats. When marasmic-kwashiorkor rats were returned to the control diet, normal conversion of benzoic acid to hippuric acid returned in 2 weeks.

As sodium benzoate is occasionally used therapeutically in newborn infants to treat apnea associated with prematurity and hyperammonemia resulting from congenital defects in the urea cycle, Green et al. (1983) gave therapeutic doses of 3.5 mmol/kg/day (~427 mg/kg/day) sodium benzoate intravenously to four hyperammonemic infants. Generally "more than half" of the excreted material was hippurate. The remainder was excreted as unchanged parent compound. In this study the term "excreted" included material eliminated in the urine and collected by peritoneal dialysis. Although no supportive data were presented, Edwards and Voegeli (1984) suggested that neonates have reduced ability compared with adults to conjugate benzoic acid with glycine.

Baines et al. (1978) and Hall and James (1980) noted that the metabolism of benzoic acid was age-dependent in rats. Baines et al. (1978) administered ^{14}C-sodium benzoate (dose and route not specified) to adult rats and recovered hippuric acid in the urine nearly equivalent in amount to the administered dose. In neonatal rats, however, ~20% of urinary radiolabel was identified as benzoyl glucuronide. The investigators attributed these results to higher levels of UDP-glucuronyl transferase and lower levels of glycine-N-acyltransferase in the livers of neonatal rats compared with adult rats. A similar trend was observed in the metabolism of ^{14}C-benzoic acid by young vs. adult rats in the experiment by Hall and James (1980) (see Table 5-1). Young rats (9- to 10-day-old) appeared to be less capable than adults in transforming 40-100 mg/kg oral doses of benzoic acid to hippuric acid. Reduced ability of the young to transform benzoic acid to hippuric acid was not apparent in young vs. adult marmosets (Hall and James, 1980) (see Table 5-1). Conjugation with glucuronic acid is more important in marmosets than in humans or rats.

Although the predominant metabolite of benzoic acid produced by the animals listed in Table 5-1 appears to be hippuric acid, benzoyl glucuronide is produced in small quantities by most of these animals and in significant quantities by carnivores such as dogs and ferrets (Bridges et al., 1970). Quick (1932) administered oral doses of benzoic acid to bilaterally nephrectomized dogs. Upon sacrifice on the next day, hippuric acid was not found in the blood, and the investigator concluded that the kidney was the sole site of conversion of benzoic acid to hippuric acid in the dog.

Kao et al. (1978) demonstrated species differences in the metabolism of benzoic acid using in vitro preparations from hepatocytes and renal tubules of male Wistar rats, Syrian hamsters, a beagle dog and albino ferrets. Ring-labeled ^{14}C-benzoic acid was used and metabolites were separated, identified and quantified. Liver preparations from the rats and hamsters rapidly converted the dose of benzoic acid to nearly equivalent amounts of hippuric acid. In addition, small amounts of benzoyl glucuronide (equivalent to <5% of the initial dose of benzoic acid) were produced. Liver preparations from the dog and ferret, however, produced no hippuric acid but only benzoyl glucuronide, equivalent to ~8 and 11% of the initial dose in these two species, respectively. The kidney preparations from the rat, dog and ferret converted nearly the entire dose of benzoic acid to hippuric acid. Only the kidney preparation from the rat produced a trace amount of benzoyl glucuronide. The kidney preparation of the hamster was not nearly as efficient as that of the other species, as only ~13% of the dose was transformed to hippuric acid, the only metabolite produced.

The data reviewed in Table 5-1 indicate that benzoic acid is extensively metabolized in most species, although adult marmosets may excrete substantial amounts of unchanged compound. The fate of the unrecovered portion of

the dose was not explained. Jones (1982) recovered ~3% of an oral 0.01 mg/kg dose of [carboxy-^{14}C]-benzoic acid in rats as expired $^{14}CO_2$ within 24 hours. Decarboxylation may contribute substantially to the elimination of benzoic acid in certain species or when conditions result in saturation of other metabolic pathways. In addition, other minor metabolites of benzoic acid have been identified in in vitro studies. Sato et al. (1956) incubated benzoic acid with rat liver slices in an incubation medium containing ^{35}S-sulfate and identified the sulfate conjugate of 4-hydroxybenzoic acid. Liver microsomal preparations from guinea pigs and rabbits converted benzoic acid to "trace levels" of 3-hydroxybenzoic acid (Daly et al., 1968). These results suggest that oxidation, probably followed by conjugation, plays a significant role in the metabolism of benzoic acid, at least under certain conditions.

Other explanations for the incomplete recovery include incomplete gastrointestinal absorption or the excretion of benzoic acid and its metabolites through the bile or by direct secretion into the intestinal tract, although investigations in rats and mice (Section 5.4.) indicate that these are minor routes of excretion for these species.

5.4. EXCRETION

Data regarding the urinary excretion of benzoic acid and its metabolites are presented in Table 5-1. For humans, rats, hamsters and dogs, excretion appears to occur rapidly and nearly completely through the urine. Urinary excretion removes the metabolites hippuric acid and benzoyl glucuronide. In contrast, little unchanged benzoic acid is excreted by the kidney [with the possible exception of adult marmosets (Hall and James, 1980)]. In monkeys, pigs, rabbits, mice, guinea pigs, cats and ferrets, urinary excretion

appears to account for a substantially smaller proportion of an oral dose, although considerable interlaboratory variation is noted. Route of administration appears to have no impact on urinary excretion.

Jones (1982) determined that ~3% of an oral dose of 0.01 mg/kg carboxyl ^{14}C-benzoic acid was expired as $^{14}CO_2$ in treated rats in 24 hours. The respiratory tract may be a more important route of excretion in other species or with larger doses or in the presence of other conditions that saturate conjugation with glycine to form hippuric acid.

Following intraperitoneal administration of a 10 mg/kg dose of [carboxy-^{14}C]-benzoic acid as the sodium salt to rats, hamsters, guinea pigs, rabbits, sheep, cats and ferrets, Huckle et al. (1981) recovered <5% of the dose of radioactivity in the feces by 72 hours and concluded that fecal excretion was not important in the elimination of benzoic acid and its metabolites. In ddN mice given a 100 mg/kg intraperitoneal dose of radiolabeled benzoic acid (position of label not specified), followed by collection of urine, bile and feces for up to three 24-hour periods, urinary excretion of radiolabel accounted for 100.9±1.5% of the dose (Kato, 1972). In female Wistar rats given a 410 μmol/kg (50 mg/kg) dose by intraperitoneal injection (Hirom et al., 1976) or in Donryu rats given an oral 50 mg/kg dose (Kato, 1972) of radiolabeled benzoic acid, biliary excretion accounted for 1 and 2.5% of the dose, respectively. Biliary and intestinal excretion may be more important in species in which urinary recovery accounted for smaller portions of an oral or parenteral dose.

5.5. SUMMARY

Gastrointestinal absorption of benzoic acid appears to be virtually complete and fairly rapid in humans (Bridges et al., 1970; Riihmaki, 1979; Amsel and Levy, 1969), rats (Bridges et al., 1970; Hall and James, 1980;

Jones, 1982), hamsters and dogs (Bridges et al., 1970); urinary excretion products account for ≥90% of the dose within 24 hours of treatment. In situ studies in rats indicate that increasing intestinal pH above 4.2 decreases the rate of absorption (Hoegerle and Winne, 1983) and increasing or decreasing the net flux of water from the intestine by altering the tonicity of the perfusion solution (Ochsenfahrt and Winne, 1974) increases or decreases, respectively, the uptake rate of benzoic acid. Data were not located regarding inhalation absorption; however, in an in situ nasal cavity perfusion study in rats, absorption of benzoic acid occurred and the rate depended on the pH of the perfusing solution (Huang et al., 1985).

The dermal absorption of 31.4% of a 4 $\mu g/cm^2$ dose has been demonstrated in guinea pigs (Andersen et al., 1980). With in vitro preparations of human and rat skin, Bronaugh and Stewart (1985) showed that scarification increased percutaneous absorption ~2-fold.

Data were not located regarding the distribution or retention of benzoic acid or its metabolites, but the rapidity and extent of benzoic acid elimination suggest that retention is probably not important in the pharmacokinetics and toxicity of the compound (FASEB, 1973).

In humans and common laboratory species (Bridges et al., 1970; Riihmaki, 1979; Amsel and Levy, 1969; Hall and James, 1980; Jones, 1982; Huckle et al., 1981; Thabrew et al., 1980) hippuric acid, formed by conjugation with the amino acid glycine, is the predominant metabolite (up to 100% of the dose) and benzoyl glucuronide, formed by conjugation with glucuronic acid, is a lesser metabolite (0-22% of the dose). The rate and extent of conversion of benzoic acid to hippuric acid is dependent upon the availability of glycine, and can be increased by the administration of exogenous glycine (Quick, 1931; Riihmaki, 1979; Amsel and Levy, 1969). The proportion

excreted as hippuric acid by humans and rats is reduced in the very young (Green et al., 1983; Edwards and Voegeli, 1984; Baines et al., 1978; Hall and James, 1980). The liver and kidney appear to be the major sites of conversion to hippuric acid and benzoyl glucuronide, but there are marked species differences in the rate, extent and products of metabolism at each site (Kao et al., 1978). CO_2 resulting from decarboxylation is a minor metabolite in rats (Jones, 1982), but its importance has not been investigated in other species. In vitro studies suggest that hydroxylation of the benzene ring, probably followed by conjugation, may also occur (Sato et al., 1956; Daly et al., 1968).

For humans, rats and dogs excretion appears to occur rapidly and nearly completely through the urine (Bridges et al., 1970; Riihmaki, 1979, Amsel and Levy, 1969; Hall and James, 1980). Renal excretion of the metabolites hippuric acid and benzoyl glucuronide is rapid. In rats, ~3% of an oral dose was expired as CO_2 (Jones, 1982). This mode of elimination may be more significant in other species or if preferential routes of elimination become saturated. Biliary and intestinal excretion has not been adequately studied in those species in which urinary excretion accounted for a smaller portion of the dose. In many species, fecal excretion of radioactivity following an intraperitoneal dose of [carboxy-^{14}C]-benzoic acid is <5% (Huckle et al., 1981).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures.

6.1.1.1. SUBCHRONIC -- IRDC (1981) reported a 4-week inhalation study with technical grade benzoic acid in young Sprague-Dawley rats. Groups of 10 rats/sex were exposed to target concentrations of 0, 0.02, 0.2 or 2.0 mg/ℓ, 6 hours/day, 5 days/week. Dry flaked material was used to generate a dust aerosol with an equivalent aerodynamic diameter of 4.7 μ. Actual concentrations were measured to be 0, 0.025, 0.25 and 1.2 mg/ℓ (0, 25, 250 and 1200 mg/m³). Parameters of toxicity evaluated included clinical signs and mortality, body weight gain, hematology, blood chemistry focused on liver function and damage, gross necropsy and organ weights, extensive histology of controls and high-dose rats, and histologic examination of the lungs of low- and middle-dose rats.

A reddish nasal discharge was consistently observed in middle- and high-dose rats, indicating upper respiratory irritation. One male and one female in the high-dose group died during exposure. A statistically ($p<0.01$) and biologically significant decrease in rate of body weight gain occurred in both sexes in the high-dose groups. The only treatment-related hematologic effect was a reduction in platelet count in both sexes ($p<0.01$) in the high-dose group. Sporadic changes in blood chemistry were not attributed to treatment, and there were no gross pathologic effects attributed to treatment. A decrease in both absolute organ weights and organ-to-brain weight ratios was observed in the livers of high-dose males and the kidneys, trachea and lungs of high-dose females. Reduced absolute kidney weight also occurred in middle-dose females. Histopathologic alterations were restricted to the lungs and consisted of interstitial fibrosis and

interstitial inflammatory cell infiltration. A dose-related increased incidence and intensity of these inflammation effects were noted in all treated groups, which was attributed to the persistent irritating effect of the test material.

6.1.1.2. CHRONIC -- Pertinent data regarding the chronic inhalation toxicity of benzoic acid could not be located in the available literature as cited in Appendix A.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- Subchronic investigations with both benzoic acid and sodium benzoate have been conducted in several laboratory species and humans. Shtenberg and Ignat'ev (1970) administered daily gavage doses of benzoic acid (reagent grade, vehicle not reported) at 80 mg/kg to a group of 50 male and 50 female white mice for 3 months. Controls were maintained but their numbers and treatment were not described. The mice were observed for general condition and behavior, survival, food and water intake, body weight gain and, at the end of the 3-month exposure period, response to stresses such as hunger and poisoning with carbon tetrachloride. In spite of nearly equivalent food intake, male mice gained only 63% and females 71% as much as their respective controls. Treated mice had greater mortality than controls when stressed with carbon tetrachloride poisoning.

Kreis et al. (1967) fed diets containing 3% benzoic acid to groups of 5-15 male Royal Wistar rats for $\leq$5 days. Effects noted by day 5 included weight loss, a number of CNS signs and mortality of ~1/2 of the rats. The most significant lesions were located in the brain and included necrosis of the ganglionic cells of several different regions. Some of the rats that survived the 5-day dietary exposure were maintained on control diets for an additional 19-30 days, at which time they were sacrificed. The lesions that

were observed in the rats that died were also observed in surviving rats after this recovery period. In addition, groups of 5-10 rats were maintained on a diet containing 1.1% benzoic acid for 7, 14 or 35 days. Reduced growth rate and impaired food efficiency were evident, but there were no gross or microscopic lesions in the heart, liver, kidneys or brain.

Behavioral signs of CNS impairment, often accompanied by death were also observed in cats given 1-4 doses of 300-890 mg/kg/day benzoic acid in meat (Bedford and Clarke, 1972). Clinical observation and examination of clinicopathologic parameters of liver and kidney function revealed no effects among four cats treated with 130-160 mg/kg/day for 23 days.

In humans, a single oral 10 g dose of benzoic acid had no effect on body temperature, pulse, respiration or other clinical parameters (Gerlach, 1909). Similarly, no externally visible effects were observed following 44 consecutive days at 0.5 or 1.0 g/day or after 82 doses in 86 days or 88 doses in 92 days af 1 g/day. After 6 days of treatment, there were no effects on serum albumin or the ultilization of nitrates or lipids in food. In another study using humans, a treatment protocol was designed in which 12 volunteers ingested benzoic acid in capsules at 1 g/day for 5 days, 1.5 g/day for the next 5 days, 2 g/day for the next 5 days and 2.5 g/day for the last 5 days, resulting in a total dose of 35 g over a 20-day period (Wiley and Bigelow, 1908). Because marked symptoms of discomfort, irritation, weakness and malaise occurred in 9/12 volunteers the course of treatment was not completed.

Several short-term studies in laboratory animals were also performed with sodium benzoate. In a range-finding study, Smyth and Carpenter (1948) gave groups of five male and five female Sherman rats sodium benzoate in the diet for 30 days at dosages ranging from 16-1009 mg/kg bw/day. The

parameters evaluated included survival, appetite, growth rate and a limited histological examination. No adverse effects were reported at 1009 mg/kg/day, the highest dosage tested.

Griffith (1929) fed diets containing sodium benzoate at 0, 1.5, 2.0, 2.5 or 3% to young male white rats for 40 days to study its effects on growth rate. Food consumption was equivalent at all dietary levels. There were no effects on growth at $\leq$2.5%. At 3%, growth was "distinctly less" than control rats and one-third of the rats in this group died. The incorporation of glycine or gelatin in the 3% sodium benzoate diet resulted in normal growth rate, but the effect on survival was not reported. In another study of the effects of sodium benzoate in the diet on the growth of rats, White (1941) observed marked stunting at 5% within 3-6 weeks. With the exception of a few rats that did not tolerate the sodium benzoate, no gross signs of toxicity were observed.

Harshbarger (1942) pair-fed diets containing 3% sodium benzoate to 4-week-old white rats for 4-5 weeks. Marked reduction in growth rate and food conversion efficiency were observed. In the treated groups, 2/8 rats died. Sodium benzoate at 1% in the diet had no effect on growth or survival. In another study, sodium benzoate was incorporated into the diets of groups of six male and six female 23-day-old Sherman rats at 0, 2 or 5% for 28 days (Fanelli and Halliday, 1963). All high-dose rats died between the first and second weeks, following severe CNS signs. A slight but significant depression in the rate of body weight gain in males was observed at 2%. From data provided by the investigators, estimated equivalent doses of sodium benzoate were 2002 and 2171 mg/kg/day for males and females, respectively, at 2% in the diet.

In a toxicity test with sodium benzoate, groups of five male and five female young Sherman rats were fed diets containing sodium benzoate at 0, 1.0, 2.0, 4.0 or 8.0% for 90 days (Deuel et al., 1954). Parameters evaluated included food consumption, weight gain, relative liver and kidney weight, gross pathology and microscopic pathology, apparently limited to the liver and kidney. Experimental results from both sexes were combined. The investigators estimated intakes of 0, 640, 1320, 2620 and 6290 mg/kg/day for controls and low to high treated groups, respectively. One control rat and one low-dose group rat and two each from the two higher dose groups died from infections. In addition, four treatment-related deaths occurred at 8% sodium benzoate. Decreased rate of body weight gain and increased relative liver and kidney weights were also observed at 8%. "Frequent pathological lesions" not otherwise specified were noted in rats on the 8% diet. One rat with slight cloudy swelling of the liver was observed in each of the lower dose groups but not in controls; however, the investigators noted that this is a common lesion in rats and was not treatment-related.

6.1.2.2. CHRONIC -- In a 17-month study, groups of 25 male and 25 female young cross-bred white mice (10-15 g) were given benzoic acid at 40 mg/kg/day in a paste before the main feeding (Shtenberg and Ignat'ev, 1970). A control group (not otherwise specified) was maintained. Parameters of toxicity evaluated were food consumption, weight gain, general appearance and behavior, survival, response to stress and organ weights; however, only stress response results were reported over the 17-month feeding period. When subjected to a 5-day fast during which benzoic acid treatment was continued by gavage administration, mortality was 50.0% compared with 12.5% in controls, and weight loss was 26.0% of body weight in treated mice compared with 17.8% in controls. Following the fast, controls regained weight in only 1.6 days, compared with 2.7 days for treated mice.

In an 18-month study with benzoic acid, mice were treated at 0, 40 and 80 mg/kg/day by an unspecified route for 3, 8 or 18 months (Ignat'ev, 1965). As reported by Informatics, Inc. (1972), evaluated parameters of toxicity included general appearance, survival, reproduction, food and water utilization, weight gain, blood tests, urine tests, histopathology, carcinogenicity and response to various stressors. Depressed weight gain was reported at 80 mg/kg/day in both sexes. In addition, viability was decreased, organ weights were affected and the ability of the liver to detoxify carbon tetrachloride was reduced. Data were not presented, however, and these effects cannot be evaluated. Informatics, Inc. (1972) noted that "this study was reported in several other papers, none of which provided data sufficient to justify the conclusions reached."

In an 18-month study using young (100-120 g) Wistar rats (Shtenberg and Ignat'ev, 1970), groups of 10 males and 10 females received 40 mg/kg/day in a paste before the main feeding. A control group received basal diet alone. Food and water consumption, body weight gain, blood tests and response to stress were examined, but data reported were minimal. It appears that treated males may have had reduced food and water intake, compared with controls. Informatics, Inc. (1972) presented minimal data from another report from the same laboratory, in which there were no effects on body weight, survival or gross or microscopic morphology of "parenchymatous organs" from rats fed benzoic acid at 80 mg/kg/day for 18 months (Ignat'ev, 1965).

In a long-term growth experiment using Wistar rats, groups of 20 females and 30 males (5-week-old, 50-60 g) were fed diets containing 1.5% benzoic acid (Marquardt, 1960). A control group consisted of 12 females and 13 males. Decreased food intake and suppressed growth were noted up through 18

months of exposure. The experiment was in progress at the time of the report. Similar results were reported in another experiment in which groups of 20 male Wistar rats and 20 male Osborne-Mendel rats were fed diets containing benzoic acid at 1.5%. The control groups consisted of 10 male rats per strain.

A chronic toxicity-reproduction study was performed with benzoic acid at 0, 0.5 or 1.0% in the diets of groups of 20 male and 20 female Bayer-Elberfeld rats (Kieckebusch and Lang, 1960). The rats were pair-fed for the first 8 weeks after which additional feeding was allowed. Mating was permitted when rats were 11-12 weeks old. Benzoic acid feeding was continued for 4 generations. Evaluated parameters of toxicity included estimation of efficiency of protein utilization, litter size (number and weight) and histological examination (not otherwise detailed) of the 4 generations. There were no signs of toxicity over the entire lifespan of the F_0 generation or in the 4 generations of offspring. A significant increase in lifespan was noted; at 0.5%, some rats lived >1000 days and one rat on the 1% diet level lived for 1346 days.

6.1.3. Other Relevant Information. For benzoic acid, oral LD_{50} values of 2000 mg/kg have been reported for dogs, cats and guinea pigs (NIOSH, 1986; Sax, 1984), rabbits (Sax, 1984) and mice (FEMA, 1984). For rats, LD_{50} values range from 1050 mg/kg (Sax, 1984) to 2000-2530 mg/kg (NIOSH, 1986; FEMA, 1984). Sodium benzoate appears to be somewhat less toxic; oral LD_{50}s for rats are ~4100 mg/kg (Sax, 1984; Windholz, 1983). Benzoic acid is considered a mild skin irritant and a severe eye irritant in rabbits (Sax, 1984).

Benzoic acid and sodium benzoate have been associated with hypersensitivity reactions and urticaria in exposed persons. Clemmensen and Hjorth

(1982) described an outbreak of urticaria in 18/20 children following intake and "accidental perioral application" of mayonnaise containing benzoic acid. Healthy adults reacted positively to the closed 20-minute patch test with sorbic acid and benzoic acid, both of which were contained in the mayonnaise. Because the reaction in experimental subjects was only partially blocked with locally applied antihistamine, the authors concluded that the reaction was due to nonimmunologic mechanisms and recommended no restrictions in the use of benzoic acid as a preservative in food.

Ros et al. (1976) and Michaelsson and Juhlin (1973) studied the induction of urticaria in humans by benzene ring-containing azo-food dyes, preservatives and drugs. Patients suffering from urticaria were given small repeated oral doses of individual compounds to elicit an urticaria response (provocation test). Doses of 50, 250 or 500 mg/administration were given until a response was observed. In the initial test with 37 patients, 22 showed a positive response to sodium benzoate (Michaelsson and Juhlin, 1973). Rigid dietary control resulted in marked improvement in 61/72 urticaria patients in a larger more recent study (Ros et al., 1976).

Nethercott et al. (1984) observed contact urticaria in three workers handling sodium benzoate in a pharmaceutical manufacturing plant. These workers noted that physical exertion during exposure exacerbated their reaction. The authors hypothesized that perspiration lowered the skin pH sufficiently to convert the sodium benzoate to benzoic acid. Patch tests with sodium benzoate and benzoic acid in the three affected workers and in three "control" workers revealed that benzoic acid was the more active chemical.

Humans with a congenital ornithine carbamoyl transferase deficiency may suffer from seizures associated with hyperammonemia resulting from an

inability to convert ammonia to urea. Takeda et al. (1983) described the successful therapeutic use of oral sodium benzoate to reduce the severity and frequency of seizures in an 8-year-old girl. Treatment was with 200 mg/kg/day of sodium benzoate in three divided doses. Clinical and laboratory examination revealed no signs of toxicity. Administration of benzoate was associated with increased excretion of hippuric acid, an alternative mechanism of reducing body burden of ammonia.

Amsel and Levy (1970) orally administered sodium benzoate equivalent to 2-5 g benzoic acid to healthy young male volunteers after a standardized light breakfast. Ethanol at 50 mℓ in orange juice was given orally 15 minutes before or 90 minutes after the sodium benzoate. Control experiments were carried out without ethanol. Within 1 hour of administration, ethanol decreased urinary output of hippurate. The investigators determined that the renal excretion of hippurate was not affected by the ethanol, but that the rate of conversion of benzoate to hippurate was reduced. They suggested that ethanol interfered with mobilization of glycine to an available pool and that the decrease in hippurate formation occurred when readily utilizable glycine was exhausted.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of benzoic acid or sodium benzoate could not be located in the available literature as cited in Appendix A.

6.2.2. Oral. In a carcinogenicity study, groups of 50 male and 50 female albino Swiss mice were provided drinking water containing sodium benzoate at 2% from 39 days of age until natural death or sacrifice in a moribund condition (Toth, 1984). Selection of the 2% water concentration was based on the mortality and weight loss at 4% in a 35-day test that evaluated survival,

body weight, chemical intake and histopathology. Results of the 35-day study at 0.5, 1, 2 and 8% were not reported. Controls in the chronic test consisted of 100 males and 100 females. Average daily water consumption was 6.2 mℓ for treated males and 5.9 mℓ for treated females, from which the investigator calculated daily dosages of 124.0 mg/day for males and 119.2 mg/day for females. Assuming an average body weight of 0.030 kg, these dosages are equivalent to 4133 and 3973 mg/kg/day for males and females, respectively. Complete necropsies were performed on all mice, and histopathologic examinations of all mice included 11 major organs and all gross lesions. Treatment with sodium benzoate had no effect on survival or the incidences of any tumor types.

In another report, white cross-bred mice were given daily oral doses of 40 mg/kg benzoic acid combined with 80 mg/kg sodium bisulfite in a paste before the main feeding for 17 months (Shtenberg and Ignat'ev, 1970). Malignant tumors (not otherwise specified) occurred in 8/100 mice in the treated group and in 1/8 in the third generations of the treated groups. No tumors were observed in controls.

The NTP (1987) has not scheduled benzoic acid or sodium benzoate for carcinogenicity testing.

6.2.3. Other Relevant Information. Dinerman and Ignat'ev (1966) indicated that exposure to 0.2% benzoic acid in the diet increased the susceptibility of mice to intraperitoneal inoculation with Ehrlich ascites carcinoma cells. Inoculation of the tumor cells took place after exposure to benzoic acid for 3 months. Mice were weighed and abdominal measurements were made before injections and every 4 days thereafter until death or sacrifice at 53 days for treated mice or 66 days for controls. Ascites tumors developed in 62/90 (68.8%) of benzoic acid-treated mice, but only in

16/49 (32.6%) of basal diet-fed controls. The investigators also reported that carcinoma development was more intensive and survival time was shorter in mice treated with benzoic acid.

6.3. MUTAGENICITY

Benzoic acid and sodium benzoate have been tested for mutagenicity or genotoxicity in prokaryotes (McCann et al., 1975), eukaryotes (Litton Bionetics, Inc., 1974) and several mammalian test systems (Litton Bionetics, Inc., 1974, 1975; Oikawa et al., 1980). Results have been consistently and unequivocally negative (Table 6-1).

6.4. TERATOGENICITY

FDRL (1972) performed an oral developmental toxicity study with sodium benzoate using CD-1 mice, Wistar rats, golden hamsters and Dutch-belted rabbits. The compound was dissolved in water and administered by gavage to groups of 25-30 mated mice and 24 mated rats at 0, 1.75, 8.0, 38.0 or 175 mg/kg/day on gestation days 6-15. Mice were sacrificed for examination on gestation day 17 and rats on gestation day 20. Hamsters (22/group) were treated on gestation days 6-10 with dosages of 0, 3.0, 14.0, 65.0 or 300.0 mg/kg/day and sacrificed for examination on gestation day 14. In mice, rats and hamsters, the day in which sperm appeared in a vaginal smear was designated gestation day 0. Rabbits (14-32/group) were treated at 0, 2.5, 12.0, 54.0 or 250.0 mg/kg/day on gestation days 6-18 and were killed on gestation day 29. The day of insemination was designated gestation day 0. For mice, rats and hamsters, one-third of the fetuses from each litter were examined for visceral malformations and two-thirds were examined for skeletal malformations. Rabbit fetuses delivered live were placed in an incubator for 24 hours to evaluate neonatal survival, after which all fetuses were evaluated for both visceral and skeletal malformations.

TABLE 6-1

Mutagenicity Testing of Benzoic Acid and Sodium Benzoate

Assay	Indicator Organism	Compound/Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA1535, TA1537	benzoic acid/NR	plate test	10 µg/plate	S-9	-	NC	McCann et al., 1975
Reverse mutation	S. typhimurium TA1530, G-46	sodium benzoate/NR	host mediated: oral in ICR male mice	50, 500 or 5000 mg/kg single dose or 5 consecutive days	NA	-	Also negative in standard plate incorporation test without metabolic activation	Litton Bionetics, Inc., 1974
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538	benzoic acid/ analytical grade	plate test or suspension test	0.5%	±S-9	-	S-9 from lung, liver or testes of mice, rats or monkeys	Litton Bionetics, Inc., 1974
Mitotic recombination	S. cerevisiae D4	benzoic acid/ analytical grade	plate test or suspension test	NR	±S-9	-	S-9 from lung, liver or testes of mice, rats or monkeys	Litton Bionetics, Inc., 1974
Mitotic recombination	S. cerevisiae D3	sodium benzoate/NR	host mediated: oral in ICR male mice	50, 500 or 5000 mg/kg single dose or 5 consecutive days	NA	-	Also negative in standard plate test without metabolic activation	Litton Bionetics, Inc., 1974
Chromosomal aberration	human embryonic lung (WI-38) cells	sodium benzoate/NR	cell culture	2.0, 20.0, 200.0 µg/ml	NA	-	NC	Litton Bionetics, Inc., 1974
Chromosomal aberration	bone marrow cells	sodium benzoate/NR	oral in male Sprague-Dawley rats	50, 500 or 5000 mg/kg single dose or 5 consecutive days	NA	-	NC	Litton Bionetics, Inc., 1974
Sister chromatid exchange	CHO-KI cells	benzoic acid/ analytical grade	cell culture	10^{-3} to 10^{-2} M	NA	-	NC	Oikawa et al., 1980
Dominant lethal	male Sprague-Dawley rats	sodium benzoate/NR	oral	50, 500 or 5000 mg/kg single dose or 5 consecutive days	NA	-	NC	Litton Bionetics, Inc., 1974

NA = Not applicable; NR = not reported; NC = no comment

Treatment with four dosage levels of sodium benzoate was not associated with maternal or fetal toxicity in any of the test species. The incidence of visceral or skeletal anomalies was not significantly elevated in any treated groups, nor was there any apparent difference in neonatal mortality in rabbits.

Minor and Becker (1971) administered sodium benzoate by intraperitoneal injection to groups of mated Sprague-Dawley rats (evidence of copulation designated gestation day 1) on gestation days 9, 10 and 11 and to other groups on gestion days 12, 13 and 14. Dosages used in both series were 100, 315 and 1000 mg/kg. Controls consisted of groups receiving sodium chloride at 90 ("low controls") or 600 mg/kg ("high controls"). In both the 9- to 11- and 12- to 14-day series, adverse effects were observed only at 1000 mg/kg. In the 9- to 11-day series, these included gross anomalies (not otherwise specified), reduced fetal body weight and increased fetal death. In the 12- to 14-day series adverse effects included reduced fetal body weight and increased fetal death, but no gross anomalies. Apparently, fetal sectioning and skeletal clearing and staining were not performed.

6.5. OTHER REPRODUCTIVE EFFECTS

In a chronic toxicity-reproduction study (Kieckebusch and Lang, 1960) (see Section 6.1.2.2.), groups of 20 male and 20 female Bayer-Elberfeld rats were fed diets containing 0, 0.5 or 1.0% benzoic acid in a multigeneration study. There were no adverse effects on reproduction. In another study using white rats (Peretianu et al., 1956), benzoic acid in the diet at 0.1-0.5 g% (<1 g/kg bw/day) had no effects on reproduction. Benzoic acid at 10% (>1 g/kg bw/day) produced "alterations" in reproduction.

6.6. SUMMARY

Inhalation of benzoic acid was irritating to the lungs of rats and resulted in histologically detectable signs of inflammation (IRDC, 1981). Inflammatory changes were noted in all treated groups of rats exposed to 25, 250 or 1200 mg/m^3, 6 hours/day, 5 days/week for 4 weeks.

Several investigators studied the subchronic toxicity of orally administered benzoic acid and sodium benzoate in laboratory animals and humans. A subchronic study reported a reduced rate of body weight gain in mice with benzoic acid at 80 mg/kg/day (Shtenberg and Ignat'ev, 1970). Cats, on the other hand, tolerated a 130-160 mg/kg/day dosage of benzoic acid for 23 days without clinical signs or clinicopathologic evidence of liver or kidney impairment (Bedford and Clarke, 1972).

A number of subchronic dietary studies were performed with rats using benzoic acid (Kreis et al., 1967) and sodium benzoate (Smyth and Carpenter, 1948; Griffith, 1929; White, 1941; Harshbarger, 1942; Fanelli and Halliday, 1963; Deuel et al., 1954). In the study with benzoic acid, reduced growth rate and impaired efficiency of feed conversion were observed at 1.1% of the diet, the only concentration tested. With sodium benzoate, mortality occurred at dietary levels $\geq$3.0% (Griffith, 1929; Harshbarger, 1942; Fanelli and Halliday, 1963; Deuel et al., 1954). Depression of body weight gain was reported for a dietary level of sodium benzoate of 2% but no mortality (Fanelli and Halliday, 1963).

In 20- to 92-day oral studies using humans, no externally visible adverse effects were noted at 7 or 14 mg/kg/day (Gerlach, 1909), but irritation, discomfort, weakness and malaise were observed at 25 mg/kg/day (Wiley and Bigelow, 1908). In hypersensitive humans, oral (Clemmensen and Hjorth,

1982; Ros et al., 1976; Michaelsson and Juhlin, 1973) or occupational exposure (Nethercott et al., 1984) to benzoic acid or sodium benzoate may lead to urticaria.

Long-term oral studies using rats and mice were performed with benzoic acid. Shtenberg and Ignat'ev (1970) reported that mice treated with 40 mg/kg/day for 17 months had reduced ability to cope with stress, manifested as an increased incidence of mortality and greater weight loss, compared with controls, during a 5-day fast after the 17-month exposure period. In another report (Ignat'ev, 1965), 80 mg/kg/day administered to mice was associated with reduced viability and weight gain, and altered organ weights.

In rats exposed to benzoic acid for ≥18 months, decreased food intake and growth were observed at 1.5% in the diet (Marquardt, 1960), but not at ≤1.0% in the diet (Kieckebusch and Lang, 1960).

Data were not located regarding the inhalation carcinogenicity of benzoic acid or its soluble alkali salts. In a drinking water study using mice, exposure to 2% sodium benzoate for the lifetime resulted in no increased incidence of tumors (Toth, 1984). Effects of benzoic acid and sodium benzoate have been consistently negative in mutagenicity tests in prokaryotes (McCann et al., 1975), eukaryotes (Litton Bionetics, Inc., 1974) and mammalian test systems (Litton Bionetics, Inc., 1974; Oikawa et al., 1980).

Oral administration of sodium benzoate appeared to cause no maternal toxicity, fetal toxicity or teratogenicity in mice, rats, hamsters or rabbits (FDRL, 1972). The highest dosages tested were 175.0, 175.0, 300.0 and 250.0 mg/kg/day, respectively, in these species. Intraperitoneal injection of 1000 mg/kg sodium benzoate in rats, however, was associated with fetal toxicity and gross anomalies (Minor and Becker, 1971).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Benzoic acid and sodium benzoate have been granted GRAS status by the FDA when used as a chemical preservative in food at concentrations of 0.1% (FASEB, 1973; FEMA, 1984). Benzoic acid is approved for use as an antimicrobial at concentrations ranging from 0.1-0.00001% (listed in decreasing order of content) in condiments, relishes, sugar substitutes, imitation dairy products, nonalcoholic and alcoholic beverages, frozen dairy products, fats and oils, gelatin pudding and cheese (Subcommittee on Review of the GRAS List, 1972). Sodium benzoate is also approved as an antimicrobial for use in foods (listed in decreasing order of content) at levels of 0.29-0.00004% in sweet sauces, baked goods, condiments and relishes, processed vegetables, seasonings and flavors, jams and jellies, fats and oils, gelatin pudding, confectioners frosting, processed fruit, imitation dairy products, gravies, nonalcoholic and alcoholic beverages, fruit ices, milk products, soft candy, frozen dairy products, instant coffee and tea, meat products, breakfast cereals, hard candy and cheese (Subcommittee on Review of the GRAS List, 1972).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the effects of benzoic acid could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of benzoic acid or sodium benzoate could not be located in the available literature as cited in Appendix A.

8.1.2. Oral. Toth (1984) exposed albino Swiss mice to drinking water containing 2% sodium benzoate from 39 days of age throughout their lifetime. There were no effects on survival or the incidences of any tumor types. In another study, an increased incidence of malignant tumors was reported at a benzoic acid dose of 40 mg/kg/day for 17 months in mice (Shtenberg and Ignat'ev, 1970), but the study was not adequately reported for critical analysis.

8.1.3. Other Routes. Dinerman and Ignat'ev (1966) reported that mice fed a diet containing 0.2% benzoic acid for 3 months were more susceptible to Ehrlich ascites tumor cells injected intraperitoneally.

8.1.4. Weight of Evidence. The negative carcinogenicity results from the drinking water study by Toth (1984) constitute inadequate evidence to evaluate the carcinogenic potency of benzoic acid in mice. The other reports suggesting an association of carcinogenicity with benzoic acid are considered inadequate for evaluation. Data were not located regarding the carcinogenic potency of benzoic acid in humans. Therefore, benzoic acid is classified as an EPA Group D - not classifiable as to carcinogenic potential in humans.

8.1.5. Quantitative Risk Estimates. The lack of adequate positive data precludes estimation of carcinogenic potencies for benzoic acid or sodium benzoate for either inhalation or oral exposure.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Only one subchronic inhalation study was located. IRDC (1981) described a 4-week study in which groups of 10 young Sprague-Dawley rats/sex were exposed to benzoic acid dust at 0, 25, 250 or 1200 mg/m^3, 6 hours/day, 5 days/week. Histopathological evidence of irritation manifested as interstitial lesions of inflammation were observed at all exposure levels, with both the incidence and intensity increasing in a dose-related fashion. The lowest exposure may be considered a LOAEL, but the short exposure time does not allow for quantitative risk assessment based on this level in this study. Data are, therefore, considered inadequate for derivation of a subchronic RfD for inhalation exposure to benzoic acid.

8.2.1.2. CHRONIC EXPOSURES -- Data regarding chronic inhalation exposure to benzoic acid or sodium benzoate could not be located in the available literature as cited in Appendix A. Furthermore, no criteria or standards for occupational exposure were located and data are insufficient for derivation of a chronic inhalation RfD.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Several subchronic oral studies have been performed with benzoic acid and sodium benzoate in laboratory animals. Shtenberg and Ignat'ev (1970) reported reduced rates of body weight gain and reduced tolerance to carbon tetrachloride poisoning in mice receiving benzoic acid at oral doses of 80 mg/kg/day for 3 months. Cats, on the other hand, showed no clinical signs of toxicity or clinicopathological evidence of liver or kidney impairment from benzoic acid doses of 130-160 mg/kg/day for 23 days (Bedford and Clarke, 1972).

The effects of sodium benzoate on survival and growth of rats has been studied by a number of investigators (Smyth and Carpenter, 1948; Griffith, 1929; White, 1941; Harshbarger, 1942; Fanelli and Halliday, 1963; Deuel et al., 1954) in dietary experiments ranging from 28-90 days. Sodium benzoate at ≥3% of the diet (1500 mg/kg/day, assuming a food factor of 0.05, and equivalent to benzoic acid at 1271 mg/kg/day) resulted in mortality and reduced growth (Griffith, 1929; Harshbarner, 1942; Fanelli and Halliday, 1963; Deuel et al., 1954). No adverse effects in rats were reported for sodium benzoate at dietary levels ranging from 1% (Harshbarger, 1942) to 4% (Deuel et al., 1954). These dietary levels are equivalent to 500-2620 mg/kg/day sodium benzoate and 424-2220 mg/kg/day benzoic acid. The dietary levels associated with no adverse effects overlap with levels associated with mortality, which suggests an unusually steep dose-response for benzoic acid and sodium benzoate.

Gerlach (1909) reported no externally visible effects in humans ingesting benzoic acid at 0.5-1.0 g/day for 44 consecutive days or after 82 doses in 86 days or 88 doses in 92 days at 1 g/day (14 mg/kg/day). Wiley and Bigelow (1908), however, observed irritation, discomfort, weakness and malaise in humans exposed to ≤1.75 g/day over a 20-day period (25 mg/kg/day). These data illustrate the unusually steep slope of the dose-response curve for benzoic acid in humans. The data base for subchronic oral exposure to benzoic acid is judged to be inadequate for quantitative risk assessment. The chronic oral RfDs of 312 mg/day or 4 mg/kg/day for a 70 kg human for benzoic acid (Section 8.2.2.2.) is suggested as the subchronic oral RfD for these compounds.

8.2.2.2. CHRONIC EXPOSURES -- The only chronic oral data available involve administration of benzoic acid to rats and mice (Shtenberg and

Ignat'ev, 1970; Ignat'ev, 1965; Marquardt, 1960; Kieckebusch and Lang, 1960). A dose of 40 mg/kg/day for 17 months was associated with decreased resistance to stress in mice and possibly with reduced food and water intake in rats after 18 months (Shtenberg and Ignat'ev, 1970). In another report (Ignat'ev, 1965), 80 mg/kg/day in rats for 18 months was not associated with adverse effects on body weight, survival or gross or microscopic pathology. In other long-term dietary studies using rats, 1.5% in the diet (750 mg/kg/day) for 18 months was associated with decreased food intake and growth (Marquardt, 1960), but 1.0% of the diet (500 mg/kg/day) for lifetime resulted in no signs of toxicity and no adverse reproductive effects over 4 generations (Kieckebusch and Lang, 1960).

If the 40 mg/kg/day dose in the Shtenberg and Ignat'ev (1970) study, at which mice had decreased resistance to stress, is considered to be the LOAEL, application of an uncertainty factor of 1000 would result in an RfD of 0.04 mg/kg/day or 2.8 mg/day for a 70 kg person. This RfD, however, is at the low end of the range of estimated per capita daily exposure of humans to benzoic acid and sodium benzoate.

The Subcommittee on Review of the GRAS List (1972) and FASEB (1973) estimated possible intakes of benzoic acid and sodium benzoate of 0.9-34 and 34-328 mg/day, respectively, based on a comprehensive survey of the amounts of benzoic acid and sodium benzoate produced for addition to food as a preservative.

Benzoic acid is a weak organic acid with a pKa of 4.2, and sodium benzoate is highly soluble in water. In the stomach, both benzoic acid and sodium benzoate are expected to exist principally in the ionized form, as benzoate. Given that both benzoic acid and sodium benzoate are absorbed rapidly and completely from the gastrointestinal tract, it seems reasonable

to consider dietary exposure to benzoic acid and sodium benzoate as exposure to the same compound, i.e., benzoic acid. By correcting for differences in molecular weight, 328 mg of sodium benzoate (high end of range of estimated daily intake) is equivalent to 278 mg benzoic acid. Adding this value to the upper end of the range of estimated daily intake for benzoic acid of 34 mg, a total daily per capita intake for benzoic acid equivalent to 312 mg/day can be estimated. Since benzoic acid and sodium benzoate are accorded GRAS status (FASEB, 1973; FEMA, 1984), the daily estimated intake of 312 mg/day for benzoic acid may be considered a human NOEL and may serve as the basis for a chronic oral RfD. Application of an uncertainty factor of 10 to protect sensitive individuals is not necessary, since sensitive individuals are included in the intake values for general population. Therefore, the chronic oral RfD for benzoic acid is 312 mg/day or 4 mg/kg/day for a 70 kg human. This RfD is well below the oral dose of 1750 mg/day (25 mg/kg/day) of benzoic acid reported to cause irritation, discomfort, weakness and malaise in humans in the early study by Wiley and Bigelow (1908). Administration of benzoic acid to humans in this study was by capsule, which represents a bolus dose. It is possible that an equivalent dose administered in the diet would not cause the symptoms that resulted from the bolus dose. This RfD can also be used for such salts of benzoic acid as sodium or potassium benzoate by multiplying the RfD for benzoic acid by the ratio of the molecular weight of the salt to benzoic acid.

Many derivatives of benzoic acid that may decompose to form benzoate are accorded GRAS status and are incorporated as additives into food (FEMA, 1984). The chronic oral RfD for benzoic acid is not intended to protect against toxicity associated with these derivatives.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

Subchronic inhalation and oral and chronic oral studies in laboratory animals and subchronic oral studies in humans with benzoic acid and sodium benzoate are summarized in Table 9-1. In Chapter 8, a chronic RfD for benzoic acid was calculated given the assumption that at physiological pH, both benzoic acid and sodium benzoate are expected to exist principally as the benzoate anion. In Table 9-1, the dosage of benzoic acid or sodium benzoate is expressed in terms of benzoic acid in mg/kg/day, and the equivalent human dose is expressed as mg benzoic acid.

Effects attributed to chronic oral exposure to benzoic acid appear to be limited to mortality or reduced survival (RV_e=10) and depressed rate of body weight gain (RV_e=4). In addition, Shtenberg and Ignat'ev (1970) and Ignat'ev (1965) attributed effects on viability, weight gain, organ weights and tolerance to stress to low levels of benzoic acid in rats and mice. Because the data were insufficiently reported, these studies were not used in the derivation of an RQ. Human oral exposure to benzoic acid resulted in irritation, discomfort, weakness and malaise. Inhalation exposure to benzoic acid results in histopathological lesions of inflammation (RV_e=6).

CSs for these effects, calculated for benzoic acid using the data points in Table 9-1 associated with the lowest equivalent human dose of benzoic acid for each effect, are presented in Table 9-2. CSs range from 4 (RQ of 5000) to 28 (RQ of 100) indicating a wide range in the toxic potency of benzoic acid under different conditions. The toxic potency of benzoic acid appears to be much greater by inhalation than oral exposure. In calculating a CS for decreased growth, data from two studies using benzoic acid were considered. In a 35-day study by Kreis et al. (1967), reduced growth and

TABLE 9-1

Toxicity Summary for Benzoic Acid and Sodium Benzoate

Route	Species/ Strain	Sex/No.	Average Body Weight (kg)	Compound/ Purity/Vehicle	Exposure	Transformed Animal Dose (mg/kg/day)	Animal Dose Expressed as Benzoic Acid (mg/kg/day)[a]	Equivalent Human Dose Expressed as Benzoic Acid (mg/kg/day)[b]	Response	Reference
Inhalation	rat/ Sprague-Dawley	M/10	0.296[c]	benzoic acid/ technical/NA	0 mg/m³, 6 hours/day, 6 days/week for 4 weeks	0	0	0	None	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	M/10	0.300[c]	benzoic acid/ technical/NA	25 mg/m³, 6 hours/day, 6 days/week for 4 weeks	3.6[d]	3.6	0.6	Histopathology: lung inflammation	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	M/10	0.289[c]	benzoic acid/ technical/NA	250 mg/m³, 6 hours/day, 6 days/week for 4 weeks	36.4[d]	36.4	5.8	Histopathology: lung inflammation	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	M/10	0.265[c]	benzoic acid/ technical/NA	1200 mg/m³, 6 hours/day, 6 days/week for 4 weeks	179.8[d]	179.8	28.0	Mortality	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	F/10	0.212[c]	benzoic acid/ technical/NA	0 mg/m³, 6 hours/day, 6 days/week for 4 weeks	0	0	0	None	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	F/10	0.201[c]	benzoic acid/ technical/NA	25 mg/m³, 6 hours/day, 6 days/week for 4 weeks	4.1[d]	4.1	0.6	Histopathology: lung inflammation	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	F/10	0.198[c]	benzoic acid/ technical/NA	250 mg/m³, 6 hours/day, 6 days/week for 4 weeks	41.2[d]	41.2	5.8	Histopathology: lung inflammation	IRDC, 1981
Inhalation	rat/ Sprague-Dawley	F/10	0.192[c]	benzoic acid/ technical/NA	1200 mg/m³, 6 hours/day, 6 days/week for 4 weeks	200.2[d]	200.2	28.0	Mortality	IRDC, 1981

Route	Species/ Strain	Sex/No.	Average Body Weight (kg)	Compound/ Purity/Vehicle	Exposure	Transformed Animal Dose (mg/kg/day)	Animal Dose Expressed as Benzoic Acid (mg/kg/day)[a]	Equivalent Human Dose Expressed as Benzoic Acid (mg/kg/day)[b]	Response	Reference
Oral	human/NR	NR/NR	70[e]	benzoic acid/ NR/NR	0.5 or 1.0 g/day for 44 days	NA	NA	7 or 14	No externally visible effects	Gerlach, 1909
Oral	human/NR	NR/NR	70[e]	benzoic acid/ NR/NR	1.0 g/day for 82/86 days or 88/ 92 days	NA	NA	14	No externally visible effects	Gerlach, 1909
Oral	human/NR	NR/NR	70[e]	benzoic acid/ NR/NR	TWA 1.75 g/ 20 days	NA	NA	25	Irritation, discomfort, weakness, malaise	Wiley and Bigelow, 1908
Oral (gavage)	mice/white cross-bred	M/50, F/50[f]	0.030[e]	benzoic acid/ reagent/NR	80 mg/kg/day for 3 months	80	80	6.0	Reduced rate of body weight gain; reduced tolerance to CCl_4 poisoning	Shtenberg and Ignat'ev, 1970
Oral	cats/NR	NR/4	3.65[c]	benzoic acid/ NR/meat	130-160 mg/ kg/day for 23 days	130-160	130-160	48.6-59.8	No clinical signs or clinicopathologic signs of liver or kidney impairment	Bedford and Clarke, 1972
Oral (diet)	rats/Royal Wistar	M/5-10[f]	0.350[e]	benzoic acid/ NR/NA	1.1% diet for 7, 14 or 35 days	550[g]	550	94.0	Reduced growth rate and impaired efficiency of food utilization	Kreis et al., 1967
Oral (diet)	rats/ Sherman	M/5, F/5	0.350[e]	Na benzoate/ NR/NA	16-1009 mg/ kg/day dietary exposure for 30 days	16-1009	14-855	2.4-146.2	No effect on appetite, survival, growth or histopathology	Smyth and Carpenter, 1948
Oral (diet)	rats/ White	M/NR	0.350[e]	Na benzoate/ NR/NA	1.5, 2.0, 2.5% in diet for 40 days	750, 1000, 1250[g]	636, 847, 1059	109, 145, 181	No effect on growth	Griffith, 1929

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex/No.	Average Body Weight (kg)	Compound/ Purity/Vehicle	Exposure	Transformed Animal Dose (mg/kg/day)	Animal Dose Expressed as Benzoic Acid (mg/kg/day)[a]	Equivalent Human Dose Expressed as Benzoic Acid (mg/kg/day)[b]	Response	Reference
Oral (diet)	rats/ White	M/NR	0.350[e]	Na benzoate/ NR/NA	3.0% in diet for 40 days	1500[g]	1271	217	Mortality and reduced growth	Griffith, 1929
Oral (diet)	rat/NR	M/106[h]	0.350[e]	Na benzoate/ NR/NA	5% of diet for 3-6 weeks	2500[g]	2119	362	Stunted growth	White, 1941
Oral (diet)	rat/White	both sexes/ 16 total[i]	0.350[e]	Na benzoate/ NR/NA	3% of diet for 4-5 weeks	1500[g]	1271	217	Mortality; markedly reduced growth and feed conversion	Harshbarger, 1942
Oral (diet)	rat/White	both sexes/ 16 total[i]	0.350[e]	Na benzoate/ NR/NA	1% of diet for 4-5 weeks	500[g]	424	72	No effects on survival or growth	Harshbarger, 1942
Oral (diet)	rat/Sherman	M/6	0.145	Na benzoate/ NR/NA	0% of diet for 28 days	0	0	0	No adverse effects	Fanelli and Halliday, 1963
Oral (diet)	rat/Sherman	M/6	0.121	Na benzoate/ NR/NA	2% of diet for 28 days	2002[c]	1697	204	Slight reduction in rate of body weight gain	Fanelli and Halliday, 1963
Oral (diet)	rat/Sherman	M/6	0.057	Na benzoate/ NR/NA	5% of diet for ≤11 days	5686[c]	4818	449.9	All dead by day 11	Fanelli and Halliday, 1963
Oral (diet)	rat/Sherman	F/6	0.115	Na benzoate/ NR/NA	0% of diet for 28 days	0	0	0	No adverse effects	Fanelli and Halliday, 1963
Oral (diet)	rat/Sherman	F/6	0.104	Na benzoate/ NR/NA	2% of diet for 28 days	2171[c]	1839	209.8	No effects on rate of body weight gain	Fanelli and Halliday, 1963
Oral (diet)	rat/Sherman	F/6	0.053	Na benzoate/ NR/NA	5% of diet for ≤13 days	7780[c]	6593	600.9	All dead by day 13	Fanelli and Halliday, 1963
Oral (diet)	rat/Sherman	M/5, F/5	0.350[e]	Na benzoate/ NR/NA	0% of diet for 90 days	0	0	0	No adverse effects	Deuel et al., 1954
Oral (diet)	rat/Sherman	M/5, F/5	0.350[e]	Na benzoate/ NR/NA	1% of diet for 90 days	640[c]	542	92.7	No treatment associated adverse effects	Deuel et al., 1954

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex/No.	Average Body Weight (kg)	Compound/ Purity/Vehicle	Exposure	Transformed Animal Dose (mg/kg/day)	Animal Dose Expressed as Benzoic Acid (mg/kg/day)[a]	Equivalent Human Dose Expressed as Benzoic Acid (mg/kg/day)[b]	Response	Reference
Oral (diet)	rat/Sherman	M/5, F/5	0.350[e]	Na benzoate/ NR/NA	2% of diet for 90 days	1320[c]	1118	191.3	No treatment associated adverse effects	Deuel et al., 1954
Oral (diet)	rat/Sherman	M/5, F/5	0.350[e]	Na benzoate/ NR/NA	4% of diet for 90 days	2620[c]	2220	379.7	No treatment associated adverse effects	Deuel et al., 1954
Oral (diet)	rat/Sherman	M/5, F/5	0.350[e]	Na benzoate/ NR/NA	8% of diet for 90 days	6290[c]	5330	911.4	Mortality, histopathological lesions	Deuel et al., 1954
Oral	mice/White cross-bred	M/25, F/25[f]	0.030[e]	benzoic acid/ reagent/NR	40 mg/kg/day for 17 months	40	40	3.0	Decreased resistance to stress at end of exposure period	Shtenberg and Ignat'ev, 1970
Oral	mice/NR	NR/NR[f]	0.030[e]	benzoic acid/ NR/NR	40 mg/kg/day for 3, 8 or 18 months	40	40	3.0	Effects not reported	Ignat'ev, 1965
Oral	mice/NR	NR/NR[f]	0.030[e]	benzoic acid/ NR/NR	80 mg/kg/day for 3, 8 or 18 months	80	80	6.0	Effects on viability, weight gain, organ weights	Ignat'ev, 1965
Oral	rats/Wistar	M/10, F/10	0.350[e]	benzoic acid/ NR/NR	0 mg/kg/day for 18 months	0	0	0	No adverse effects	Shtenberg and Ignat'ev, 1970
Oral	rats/Wistar	M/10, F/10	0.350[e]	benzoic acid/ NR/NR	40 mg/kg/day for 18 months	40	40	6.8	Possibly reduced food and water intakes	Shtenberg and Ignat'ev, 1970
Oral	rats/NR	NR/NR	0.350[e]	benzoic acid/ NR/NR	80 mg/kg/day for 18 months	80	80	13.7	No effects on body weight, survival, macro- or microscopic pathology	Ignat'ev, 1965
Oral (diet)	rats/Wistar	M/13, F/12	0.350[e]	benzoic acid/ NR/NR	0% of diet for 18 months	0	0	0	No adverse effects	Marquardt, 1960

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex/No.	Average Body Weight (kg)	Compound/ Purity/Vehicle	Exposure	Transformed Animal Dose (mg/kg/day)	Animal Dose Expressed as Benzoic Acid (mg/kg/day)[a]	Equivalent Human Dose Expressed as Benzoic Acid (mg/kg/day)[b]	Response	Reference
Oral (diet)	rats/Wistar	M/30, F/20	0.350[e]	benzoic acid/ NR/NR	1.5% of diet for 18 months	750[g]	750	128	Decreased food intake and growth[j]	Marquardt, 1960
Oral (diet)	rats/Bayer-Elberfeld	M/20, F/20	0.350[e]	benzoic acid/ NR/NR	0% of diet for lifetime	0	0	0	No adverse effects	Kleckebusch and Lang, 1960
Oral (diet)	rats/Bayer-Elberfeld	M/20, F/20	0.350[e]	benzoic acid/ NR/NR	0.5% of diet for lifetime	250[g]	250	42.7	No signs of toxicity; significantly increased lifespan	Kleckebusch and Lang, 1960
Oral (diet)	rats/Bayer-Elberfeld	M/20, F/20	0.350[e]	benzoic acid/ NR/NR	1.0% of diet for lifetime	500[g]	500	85.5	No signs of toxicity or adverse reproductive effects over 4 generations	Kleckebusch and Lang, 1960

[a]Calculated by multiplying the transformed animal dose by 121.11/122.12, the ratio of the molecular weight of benzoate to benzoic acid, or by 121.11/144.11, the ratio of the molecular weight of benzoate to sodium benzoate, for benzoic acid and sodium benzoate, respectively.

[b]Calculated by multiplying the animal dose expressed as mg/kg/day benzoate by the cube root of the ratio of the animal body weight to the reference body weight for man of 70 kg.

[c]Estimated from data provided by investigators.

[d]Calculated by expanding to continuous exposure and assuming a daily inhalation volume for rats of 0.105 x (body weight/0.113)$^{2/3}$ (U.S. EPA, 1980).

[e]Not reported; reference value from U.S. EPA (1980) assumed.

[f]It was reported that controls were maintained but data were not provided.

[g]Assuming a food factor of 5% (U.S. EPA, 1980).

[h]A control group of 115 male rats were maintained.

[i]A control group of 8 rats were maintained.

[j]Similar results were also reported for 20 male Wistar rats and 20 male Osborne-Mendel rats fed diets containing 1.5% benzoic acid.

NA = Not applicable; NR = not reported

TABLE 9-2

Composite Scores for Benzoic Acid and Sodium Benzoate

Route	Compound	Animal Dose (mg/kg/day)	Animal Dose Expressed as Benzoic Acid (mg/kg/day)	Chronic Human MED Expressed as Benzoic Acid (mg/day)[a]	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation	benzoic acid	3.6	3.6	4.2[b]	4.6	Histopathologic inflammatory lesions in lung	6	28	100	IRDC, 1981
Oral (diet)	benzoic acid	750	750	8960[c]	1	Decreased growth	4	4	5000	Marquardt, 1960
Oral (diet)	sodium benzoate	6290	5330	6380[d]	1	Mortality	10	10	1000	Deuel et al., 1954

[a]Calculated by multiplying the animal dose expressed as mg/kg/day benzoic acid by the cube root of the ratio of the animal body weight to the reference human body weight of 70 kg.

[b]Based on data for low dose male rats with a body weight of 0.300 kg. An uncertainty factor of 10 was applied to expand to chronic exposure.

[c]Based on reference body weight of 0.350 kg.

[d]An uncertainty factor of 10 was applied to expand to chronic exposure; reference body weight for rats of 0.350 kg was assumed.

impaired food utilization were observed in rats at 550 mg/kg/day. In an 18-month study by Marquardt (1960), the dosage to rats was 750 mg/kg/day. Either dosage results in a chronic human MED >1000 mg/day and an RV_d of 1. A CS of 10 was calculated for mortality in a 90-day study (Deuel et al., 1954). The CS of 28 (RQ of 100) associated with inflammation in the lungs by inhalation exposure (IRDC, 1981) is chosen to represent the toxicity of benzoic acid (Table 9-3).

9.2. BASED ON CARCINOGENICITY

Carcinogenicity data, summarized in Section 6.2., consist of a negative study using albino Swiss mice exposed to sodium benzoate in drinking water at a concentration of 2% for their natural lifespan (Toth, 1984). Data regarding carcinogenicity in humans were lacking and benzoic acid was classified in CAG Group D - not classifiable as to human carcinogenic potential. Data, therefore, were not sufficient for derivation of an F factor and this compound is not placed in a Potency Group. Hazard ranking for benzoic acid, therefore, cannot be based on carcinogenicity.

TABLE 9-3

Benzoic Acid

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	4.2 mg/day
Effect:	Inflammatory lesions in lungs
Reference:	IRDC, 1981
RV_d:	4.6
RV_e:	6
Composite Score:	28
RQ:	100

*Equivalent human dose

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in January, 1987. In addition, hand searches were made of Chemical Abstracts (Collective Indices 5-9), and the following secondary sources should be reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984, USITC Publ. 1422, Washington, DC.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

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APPENDIX B

Summary Table for Benzoic Acid

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Carcinogenicity	ID	ID	ID	ID	ID
Oral Exposure					
Subchronic	human	per capita daily dietary intake of benzoic acid equivalent to 312 mg/day	none	312 mg/day or 4.0 mg/kg/day	FASEB, 1973
Chronic	human	per capita daily dietary intake of benzoic acid equivalent to 312 mg/day	none	312 mg/day or 4.0 mg/kg/day	FASEB, 1973
Carcinogenicity	ID	ID	ID	ID	ID
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		100			IRDC, 1981

ID = Insufficient data