

## Benzoic acid; CASRN 65-85-0

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR Benzoic acid

**File First On-Line 09/07/1988**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	yes	09/07/1988
<b>Inhalation RfC (I.B.)</b>	not evaluated	
<b>Carcinogenicity Assessment (II.)</b>	yes	08/01/1989

### I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

#### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Benzoic acid

CASRN — 65-85-0

Last Revised — 09/07/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
<b>No adverse effects observed</b>	NOAEL: 34 mg/day benzoic acid and 328 mg/day for sodium benzoate (converted to 312 mg/day benzoic acid)	1	1	4E+0 mg/kg/day
<b>Human daily per capita intakes</b>				
<b>FDA, 1973; Selected Committee on Review of the GRAS List</b>	LOAEL: none			

\*Conversion Factors -- 328 mg/day sodium benzoate x [122.12 (MW benzoic acid)/144.11 (MW sodium benzoate)] = 278 mg/day benzoic acid. 278 mg/day benzoic acid from sodium benzoate + 34 mg/day benzoic acid = 312 mg/day; assuming adult human body weight of 70 kg, the exposure dose is 312 divided by 70 = 4.4 mg/kg/day.

### I.A.2. Principal and Supporting Studies (Oral RfD)

FDA (Food and Drug Administration). 1973. Evaluation of the Health Aspects of Benzoic Acid and Sodium Benzoate as Food Ingredients. DHEW, Washington, DC. Report No. SCOGS-7. NTIS PB-223837/6.

Early studies (Gerlach, 1909) indicate that laboratory animals are inappropriate models for studying the toxicity of benzoic acid in humans (FDRL, 1972) (see Additional Comments). Based on data regarding the amounts of benzoic acid and sodium benzoate produced as a food preservative, FDA (1973) estimated a daily per capita intake of 0.9-34 mg for benzoic acid and 34-328 mg for sodium benzoate. At these levels, there are no reports of toxic effects in humans. These compounds have Generally Recognized as Safe (GRAS) status by FDA. Therefore, the upper ranges can be considered NOAELs for benzoic acid and sodium benzoate. In the stomach, both benzoic acid and sodium benzoate exist in their ionized form, benzoate, which is absorbed

rapidly and completely by the GI tract. Therefore, exposure to sodium benzoate is comparable to exposure to benzoic acid if molecular weight differences are corrected for; here, 328 mg sodium benzoate is equivalent to 278 mg benzoic acid. Adding 278 to the daily intake for benzoic acid of 34 mg yields a total of 312 mg benzoic acid (see Conversion Factors). If no uncertainty factor is used, the RfD is 312 mg/day for a 70 kg human or 4 mg/kg/day.

#### **I.A.3. Uncertainty and Modifying Factors (Oral RfD)**

UF — An uncertainty factor of 10 for the protection of sensitive subgroups was considered unnecessary; although reactions to benzoate and structurally related compounds do occur, an uncertainty factor of 10 would be of little value to the sensitive individuals.

MF — None

#### **I.A.4. Additional Studies/Comments (Oral RfD)**

Sodium benzoate appeared to have no maternal toxicity, fetal toxicity, or teratogenicity in mice, rats, hamsters, or rabbits when given orally (FDRL, 1972). The highest doses tested were 175.0 in mice and rats, 300.0 in hamsters, and 250.0 mg/kg/day in rabbits.

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). 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). However, another report from this laboratory (Ignat'ev, 1965) indicated that 80 mg/kg/day in rats for 18 months was not associated with adverse effects on body weight, survival, or gross or microscopic pathology. If 40 mg/kg/day in mice in the study by Shtenberg and Ignat'ev (1970) 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, which is near the lower end of the range of the estimated daily human exposure to benzoic acid (not including exposure to sodium benzoate). The lower RfD based on animal data is not unexpected, however, since application of uncertainty factors is intentionally conservative in the absence of human data. Since human data are available in this case, it is not appropriate to use the animal data for the RfD.

Other long-term dietary studies (Marquardt, 1960) showed decreased food intake and body weight in rats fed 1.5% benzoic acid (750 mg/kg/day); at a dose of 1.0% in the diet (50 mg/kg/day) there were no signs of toxicity or adverse reproductive effects.

Gerlach (1909) reported no externally visible effects in humans ingesting benzoic acid at 0.5-1.0 g/day for 44 consecutive days or for 82/86 or 88/92 days. Assuming a human body weight of 70

kg, this level corresponds to a dose of 14 mg/kg/day. Wiley and Bigelow (1908), however, observed irritation, discomfort, weakness, and malaise in humans given oral bolus doses of less than or equal to 1.75 g/day over a 20-day period (25 mg/kg/day). The RfD (4 mg/kg/day) is well below these doses.

#### **I.A.5. Confidence in the Oral RfD**

Study — Medium

Database — Medium

RfD — Medium

Medium confidence is placed in the FDA (1973) estimate of per capita intake. Medium confidence in the database reflects the inappropriateness of using animal data as the basis of the RfD for humans and the lack of reported effects in humans at the estimated intakes. Thus, confidence in the RfD is medium.

#### **I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document — U.S. EPA, 1987

Limited peer review and extensive Agency-wide review 1987.

Other EPA Documentation — None

Agency Work Group Review — 09/17/1987

Verification Date — 09/17/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Benzoic acid conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

#### **I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

#### **I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Benzoic acid  
CASRN — 65-85-0

Not available at this time.

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Benzoic acid  
CASRN — 65-85-0  
Last Revised — 08/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

### **II.A. Evidence for Human Carcinogenicity**

#### **II.A.1. Weight-of-Evidence Characterization**

Classification — D; not classifiable as to human carcinogenicity

Basis — No human data and inadequate data from animal bioassays.

## **II.A.2. Human Carcinogenicity Data**

None.

## **II.A.3. Animal Carcinogenicity Data**

Inadequate. In a lifetime study, Toth (1984) administered sodium benzoate (of 99% purity) to 50 male and 50 female 5 week-old albino Swiss mice at a level of 2% in the drinking water. Control groups consisted of 100 mice/sex. The dose level was selected based on results of a subchronic study in which levels of 4 and 8% were considered to be too toxic. The 2% level was equivalent to sodium benzoate doses of 4133 mg/kg/day for males and 3973 mg/kg/day for females. Based on average measured daily water consumptions of 6.2 mL for males and 5.9 mL for females and an assumed average body weight of 0.03 kg. The equivalent benzoic acid doses, adjusted for molecular weight differences between sodium benzoate and benzoic acid, are 3502 mg/kg/day and 3367 mg/kg/day for males and females, respectively. Histopathologic examinations of all mice included 11 organs and all gross lesions. The treatment had no apparent effect on survival or tumor incidence.

As part of a 5-generation reproduction study, Shtenberg and Ignat'ev (1970) administered test compounds in a paste in daily doses of 40 mg/kg benzoic acid combined with 80 mg/kg sodium bisulfite in a paste before feeding an otherwise unspecified basic diet to a group of 50 white cross-bred mice/sex for 17 months. Another group received benzoic acid only; no further details were given. An unspecified number of control animals received only basic diet. Malignant tumors (not otherwise specified) occurred in 8/100 treated mice and 1/8 mice in the third generation of the treated group. Tumor incidences were not reported for untreated mice.

## **II.A.4. Supporting Data for Carcinogenicity**

Dinerman and Ignat'ev (1966) reported that a 3-month exposure to 0.2% benzoic acid in the diet increased the susceptibility of mice to the development of carcinomas following intraperitoneal inoculation with Erlich ascites carcinoma cells. Tumors developed in 62/90 (68.8%) of benzoic acid- treated mice and in 16/49 (32.6%) of the control mice.

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). No positive results have been reported.

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## **II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure**

Not available.

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## **II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

Not available.

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## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1987

The 1987 Health and Environmental Effects Document has received OHEA review.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review — 03/01/1989

Verification Date — 03/01/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Benzoic acid conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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### **III. [reserved]**

### **IV. [reserved]**

### **V. [reserved]**

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## **VI. Bibliography**

Substance Name — Benzoic acid

CASRN — 65-85-0

### **VI.A. Oral RfD References**

FDA (Food and Drug Administration). 1973. Evaluation of the Health Aspects of Benzoic Acid and Sodium Benzoate as Food Ingredients. DHEW, Washington, DC. Report No. SCOGS-7. NTIS PB-223 837/6.

FDRL (Food and Drug Research Labs., Inc.). 1972. Teratologic Evaluation of FDA 71-37 (Sodium Benzoate). p.\75-79.

Gerlach, V. 1909. VII. Summary of the results. In: Physiological Activity of Benzoic Acid and Sodium Benzoate, V. Gerlach, Ed. Verlag von Heinrich Staadt, Wiesbaden. p.\90-92. (Cited in Informatics, Inc., 1972)

Ignat'ev, A.D. 1965. Experimental information contributing to a hygienic characterization of the combined effect produced by some food presentations. Vop. Pitan. 24(3): 61-68. (Cited in Informatics, Inc., 1972)

Informatics, Inc. 1972. GRAS (Generally Recognized as Safe) Food Ingredients: Benzoic Acid and Sodium Benzoate. p. 75-79.

Shtenberg, A.J. and A.D. Ignat'ev. 1970. Toxicological evaluation of some combinations of food preservatives. Food Cosmet. Toxicol. 8(4): 369-380.

U.S. EPA. 1987. Health and Environmental Effects Document for Benzoic Acid. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

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Wiley, H.M. and W.D. Bigelow. 1908. Influence of benzoic acid and benzoates on digestion and health. Bulletin 84, pt. IV, Bureau of Chemistry, U.S. Dept. Agriculture. (Cited in Informatics, Inc., 1972)

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## VI.B. Inhalation RfD References

None

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## VI.C. Carcinogenicity Assessment References

Dinerman, A.A and A.D. Ignat'ev. 1966. Effect of certain food preservatives on the development of tumors in mice. *Gig. Sanit.* 31(9): 38-42. (Eng. trans.)

Litton Bionetics, Inc. 1974. Mutagenic Evaluation of Compound FDA 71-37, Sodium Benzoate. Report No. LBI 2446-297, FDA, Washington, DC, PB-245-453/6.

Litton Bionetics, Inc. 1975. Mutagenic Evaluation of Compound FDA 73-70, Benzoic Acid Certified A.C.S. Report No. LBI-2468-376; FDABF-GRAS-376 PB-245- 500/4.

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. *Proc. Natl. Acad. Sci.* 72: 5135-5139.

Oikawa, A., H. Tohda, M. Kanai, M. Miwa and T. Sugimura. 1980. Inhibitors of poly(adenosine diphosphate ribose) induced sister chromatid exchanges. *Biochem. Biophys. Res. Commun.* 97(4): 1311-1316.

Shtenberg, A.J. and A.D. Ignat'ev. 1970. Toxicological evaluation of some combinations of food preservatives. *Food Cosmet. Toxicol.* 8(4): 369-380.

Toth, B. 1984. Lack of tumorigenicity of sodium benzoate in mice. *Fund. Appl. Toxicol.* 4(3): 494-496.

U.S. EPA. 1987. Health and Environmental Effects Document for Benzoic Acid. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

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## VII. Revision History

Substance Name — Benzoic acid  
CASRN — 65-85-0

Date	Section	Description
09/07/1988	I.A.	Oral RfD summary on-line
08/01/1989	II.	Carcinogen summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

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## VIII. Synonyms

Substance Name — Benzoic acid  
CASRN — 65-85-0  
Last Revised — 09/07/1988

- 65-85-0
- benzenecarboxylic acid
- Benzoic acid
- carboxybenzene
- dracylic acid
- phenyl carboxylic acid
- phenylformic acid