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SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Benzoin

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16. Abstract (Limit: 200 words) Information on potential occupational hazards from exposure to benzoin (119539) was reviewed. Topics discussed included chemical and physical properties, production, uses, manufacturers and distributors, manufacturing processes, occupational exposure, and biological effects. The annual production of benzoin is approximately 90,000 pounds per year with an historical growth rate of about 6 percent per year. The compound is used in the production of polyester resin wetting and emulsifying agents; stilbestrol products; medicines; ether derivatives; personal use products such as perfumes, creams, and cosmetics; and as a synthetic flavoring agent. Studies have shown that acute oral exposure causes labored respiration, depression, dyspnea, urine stains, ataxia and unkempt fur in rats. In addition, mice also demonstrated enlarged lymph nodes in both males and females and enlarged spleens in males. Toxic effects in mice and rats fed diets containing benzoin for 13 weeks included interstitial nephritis, discoloration of the liver, green tinged kidney cortices, scattered vacuolated hepatocytes, and depression in weight gain. In carcinogenesis studies, the incidence of lymphomas and leukemia in dosed male rats increased with dose level, but not significantly. Mice demonstrated a significant increase in the incidence of lymphomas and leukemias at low dose levels. Bioassays have indicated that benzoin is not carcinogenic to male or female F344-rats or B6C3F1-mice. No evidence of mutagenicity, teratogenicity, or reproductive effects was found in animal studies. Allergic contact dermatitis has been reported in humans.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms
NIOSH-Publication, NIOSH-Contract, Contract-210-79-0030, Pharmaceutical-industry, Food-additives, Chemical-manufacturing-industry, Resins, Carbonyls, Occupational-exposure, Toxic-effects

c. COSATI Field/Group

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	20. Security Class (This Page)	22. Price

TABLE OF CONTENTS

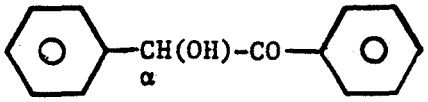
SUMMARY

Current annual production of benzoin is on the order of 90 thousand pounds per year. It is principally used as a photopolymerization catalyst in polyester resin manufacture. Other uses include application as a raw material for the production of wetting and emulsifying agents, stilbestrol products, medicines, and ether derivatives and as an ingredient in perfumes, creams, and cosmetics. Benzoin is manufactured by the self-condensation of benzaldehyde in the presence of potassium cyanide.

The toxicity of benzoin, a chemical approved for use as a flavor ingredient in food, has not been extensively examined. Based on the limited data available, benzoin appears to be a compound of relatively low toxicity (oral LD50 of 5620 mg/kg in male mice). Oral administration of benzoin to rats causes inflammation of the kidneys, but at low doses (125 to 500 ppm in the diet) the kidney damage is not severe. Under the conditions of a National Cancer Institute bioassay (oral administration) benzoin was not carcinogenic to laboratory mice or rats. In humans, no significant health effects, other than occasional allergic contact dermatitis, have been observed as a result of the use of benzoin as a topical dressing.

1. Chemical Name: Benzoin

2. Chemical Structure:



3. Synonyms: Ethanone, 2-hydroxy-1,2-diphenyl
2-Hydroxy-1,2-diphenylethanone
Benzoylphenyl carbinol
α-Hydroxy-α-phenylacetophenone
Bitter-almond-oil-camphor
2-Hydroxy-2-phenylacetophenone

4. Chemical Abstracts Service (CAS) Number: 119-53-9

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: DI1590000

6. Chemical and Physical Properties

Description:	white or yellowish crystals with a slight odor
Molecular Wt:	212.22
Boiling Point:	344°C (at 768 mm Hg)
Melting Point:	133° to 137°C
Vapor Pressure:	1 mm Hg (135.6°C)
Solubility:	soluble in 3335 parts water (≃ 0.03 g/100 g water) soluble in 5 parts pyridine (DL-form), hot alcohol (DL-form), hot methanol (L-form), chloroform (DL-form), pyridine (D-form). very soluble in hot acetic acid (DL-form), hot alcohol (D and L forms), acetone (D and L forms), hot methanol (D-form) slightly soluble in ether (DL-form)
Specific Gravity:	1.31^{20}_{4}
Stability:	combustible

7. Production

Current annual production of benzoin is on the order of 90 thousand pounds per year (Williams, 1978); this is up from the 1958 production of 27 thousand pounds (Deinet and DiBella, 1964). Therefore, the historical growth rate has been about 6% per year.

8. Uses

Benzoin is principally used as a photopolymerization catalyst in polyester resin manufacture. It is also employed as a raw material for the production of wetting and emulsifying agents, stilbestrol products, medicines, and ether derivatives (Williams, 1978; Deinet and DiBella, 1964; Clark and Neidig, 1948). Benzoin may also be present in a variety of personal-use products, including perfumes, creams, and cosmetics (Hoffman and Adams, 1978). Benzoin is approved by the U.S. Food and Drug Administration for use as a synthetic flavor (CFR, 1978).

9. Manufacturers and Distributors

The following companies are listed as manufacturers of benzoin (SRI International, 1980; USITC, 1979):

Napp Chemicals, Inc.	Lodi, NJ
Stauffer Chemical Co.	Edison, NJ
Greenwood Chemical Co.	Greenwood, VA

In addition to the manufacturers, the following companies are distributors (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Anachemia Chem.
Atomergic Chemetals
J.T. Baker Chem.
BASF Wyandotte
Berje Chem. Prod.
Biochemical Labs
Bio-Clinical Labs
Chemical Dynamics
Chemical Procurement Labs
Chem Services
Eastern Chem.
Electron Microscopy Sci.
EM Labs
Fisher Sci.
Gallard-Schlesinger Chem.
Generichem Corp.
Givaudon Corp.
Henley and Co.
ICN/K and K
LaChat Chem.
LaPine Sci.
Madis, Dr Labs Inc.
J. Manhaimar Inc.
MCB Reagents
Mide Chem.
Monomer-Polymer and Dajac
Pacific Gateway
Pfaltz and Bauer
Polysciences
Rhone-Poulenc Chem.
Ruhrkohle Trading Corp.
Sigma Chem.
Spex Ind.
TransWorld Chem.
Tridom Chem.

Data available from the U.S. EPA (1980) regarding producers of benzoin and production volumes are presented in Table 1.

10. Manufacturing Process

Benzoin is manufactured by the self-condensation of benzaldehyde in the presence of potassium cyanide (Williams, 1978; Deinet and DiBella, 1964). The following represents the chemical reaction:

The following patent information describes a general method for making benzoin (Cass and Bordner, 1945): benzaldehyde is added to a mixture of methyl alcohol and water containing about 5% sodium cyanide as a condensing agent. The temperature is kept at 75°; benzoin separates out as a slurry and is removed from the solvent. The latter is returned to the reaction vessel and used in a continuous process.

The flow diagram in Figure 1 is adapted from the above information.

11. Impurities or Additives

Commercially available benzoin has the following specifications (Stauffer, n.d.):

Assay (2,4-DNPH):	98.5% min.
Melting Point:	130°C min.
Residue on Ignition (non-sulfated):	0.2% lmax.
Loss on Drying:	0.5% max.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 15,430 workers are potentially exposed to benzoin.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to benzoin were not found in the literature searched.

Table 1. Producers of Benzoin and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Stauffer Chemical Co. Edison, NJ	Manufacturer	1 to 10 thousand lb
Naarden-UOP Fragrances Long Island City, NY	Manufacturer	0 to 1000 lb
Nickstadt-Moeller, Inc. Ridgefield, NJ	Small Manufacturer	confidential
NAPP Chemical Inc. Lodi, NJ	Manufacturer	10 to 100 thousand lb
Proctor Chemical Co. Salisbury, NC	Manufacturer	zero
Carroll Products, Inc. Wood River Junction, RI	Produced Site Limited	zero
Rhone-Poulene Inc. Freeport, TX	Importer	10 to 100 thousand lb

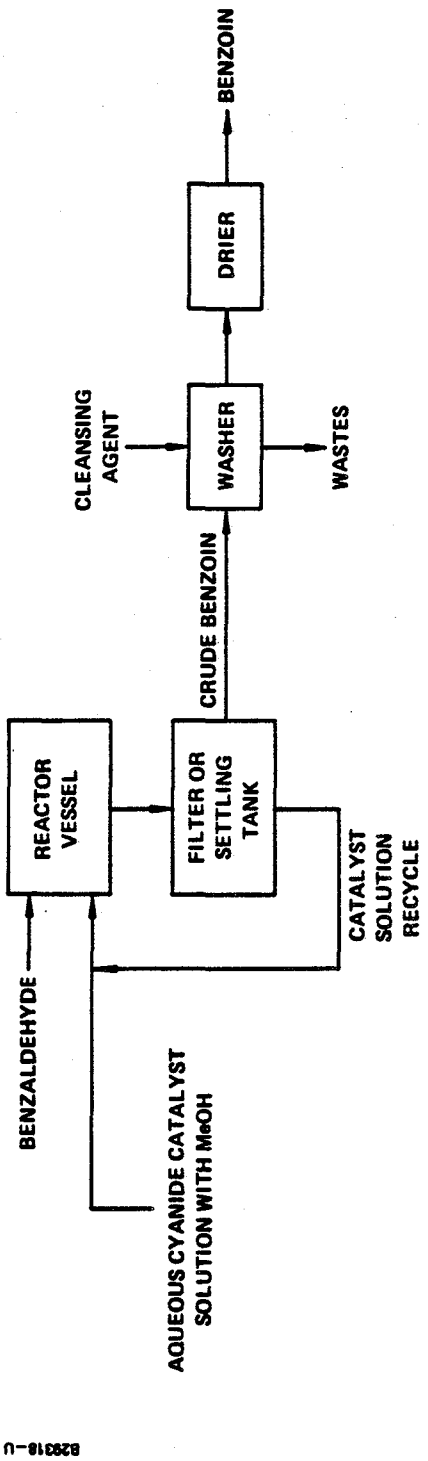


Figure 1. Manufacture of Benzoin (adapted from Cass and Bardner, 1945)

14. Biological Effects

A. Animal Studies

With the exception of results from studies performed for the Carcinogenesis Testing Program of the National Cancer Institute (NCI, 1980), no toxicological data for benzoin were found in the literature searched.

1. Acute Exposures

Acute toxicity data generated for the NCI (1980) were the result of preliminary experiments designed to determine the concentrations of benzoin to be used in a long-term bioassay of benzoin for possible carcinogenicity. These preliminary experiments involved the use of a limited number of test animals. In the range-finding study, groups of 2 male and 2 female F344 rats and B6C3F1 mice were administered, by gavage, single doses of benzoin at levels ranging from 31.6 to 10,000 mg/kg. In a second experiment, groups of 5 males and 5 females of each species were administered benzoin by gavage at 5 dose levels, ranging from 100 to 10,000 mg/kg/day for the rats and from 215 to 4,640 mg/kg/day for the mice for a period of 14 days. The acute toxic effects observed in these two studies are presented in Table 2.

2. Subchronic Exposures

In a 90-day subchronic study conducted for the NCI (1980), groups of 10 male and 10 female rats were fed diets containing 0, 500, 1500, 5000, 15,000, or 50,000 ppm benzoin. Dose levels for similar groups of mice were 0, 620, 1250, 2500, 5000, or 10,000 ppm benzoin. The toxic effects of benzoin observed in this study are summarized in Table 3. A dose-related increase in the incidence and severity of interstitial nephritis was observed in all treated rats, but no evidence of any compound-related effect was detected during the 90-day study for mice.

Table 2. Acute Effects of Oral Exposure to Benzoin (NCI, 1980)

Species	Dosage	Response
Rats	31.6 - 10,000 mg/kg	No deaths.
Rats	≤ 3,160 mg/kg	No chemical-related effects.
Rats	10,000 mg/kg	Benzoin-related effects consisted of depression, dyspnea, urine stains, ataxia, and unkempt fur.
Rats	100-10,000 mg/kg/day x 14 days	No deaths (males); dose-associated decrease in weight gain by males.
Rats	8,268 mg/kg/day x 14 days	14-day repeated dose; LD50 for females.
Rats	10,000 mg/kg/day x 14 days	Loss of weight by females. Hunched appearance and labored respiration in all rats.
Rats	10,000 and 3,160 mg/kg/day x 14 days	Solid silvery-white material present in stomach at necropsy.
Mice	5,620 mg/kg	LD50 for males.
Mice	10,000 mg/kg	LD50 for females. Depressed and labored respiration in all mice. Dark red areas on the livers of mice that died.
Mice	<10,000 mg/kg	No clinical signs observed.
Mice	215-4,640 mg/kg/day x 14 days	No deaths.
Mice	4,640 mg/kg/day x 14 days	Enlarged lymph nodes in both males and females. Enlarged spleens in males.

Table 3. Toxic Effects Observed in Mice and Rats Fed Diets Containing Benzoin for 13 Weeks (NCI, 1980)

Species	Concentration (ppm)	Effect
Rats (10 male and 10 female)	500 - 50,000	No deaths. Dose-related increase in the incidence and severity of interstitial nephritis in all treated rats. Discoloration of the liver in 1 to 4 females at all dose levels.
Rats	50,000	Green-tinged kidney cortices in 4 males and 2 females. (Also observed in 3 other rats at lower dose levels.)
Rats	50,000 and 15,000	Scattered vacuolated hepatocytes present in the livers of all females.
Rats	50,000; 15,000; and 5,000	Depression in the mean body weight gain of more than 10%.
Rats	500 and 250	Increased incidence of interstitial nephritis characterized by focal areas of regenerative tubule epithelium and lymphocytes was observed in the kidneys of male rats.
Mice	620 - 10,000	No deaths. No compound-related effects were detected.

A second subchronic study, using 5 dose levels of benzoin ranging from 30 to 500 ppm, was conducted to determine the dose level at which there would be no benzoin-related interstitial nephritis in the kidneys of rats (NCI, 1980). Survival was 100% for all groups. An increased incidence of interstitial nephritis was observed in the kidneys of male rats receiving 250 or 500 ppm benzoin (Table 3). The incidence of nephritis in all other dosed groups was comparable to that observed in the controls.

3. Chronic Exposures

No information was found in the literature searched.

4. Carcinogenicity

Benzoin was selected for carcinogenicity testing by the National Cancer Institute because it is used as a flavor ingredient in food and as a chemical intermediate (NCI, 1980). For the bioassay, 50 male rats (F344) were fed diets containing 125 or 250 ppm benzoin for 104 weeks. Similar groups of female rats were fed diets containing 250 or 500 ppm benzoin. Diets containing 2500 or 5000 ppm benzoin were fed to groups of 50 mice (B6C3F1) of each sex for 104 weeks. Matched controls consisted of groups of 50 untreated rats and mice of each sex.

Results of the bioassay showed that the incidence of lymphomas and leukemia in dosed male rats increased with dose level, but that the trend was not statistically significant (NCI, 1980). In mice, there was a significant increase in the incidence of lymphomas and leukemias in the low dose females, but not in the high dose females. Therefore, the increased incidences of lymphomas and leukemias in the female mice were not clearly related to administration of benzoin. Under the conditions of the bioassay, it was concluded that benzoin was not carcinogenic to male or female F344 rats or B6C3F1 mice.

In the NCI (1980) study, no significant difference in survival was observed for the dosed and control groups of either rats or mice as computed by the Tarone test. Results of the Cox test, however, indicated a shortened survival of male rats in the low dose group. Mean body weights of dosed animals were similar to animals of the control groups for both rats and mice. Significant pathologic changes observed in dosed animals consisted only of increased incidence of chronic inflammation in the kidneys of male and female rats and hyperplasia of the adrenal medulla in male rats. No significant benzoin-related pathologic changes were reported for mice.

5. Mutagenicity

No information was found in the literature searched.

6. Teratogenicity

No information was found in the literature searched.

7. Reproductive Effects

No information was found in the literature searched.

8. Other Relevant Information

In washed rabbit liver microsomal preparations, Watabe and Akamatsu (1975) demonstrated the *in vitro* conversion of benzoin to benzoic acid in the presence of an NADPH-generating system.

B. Human Studies

1. Pharmacokinetics

No information was found in the literature searched.

2. Health Effects

Tincture of benzoin (10% benzoin, 2% aloe, 8% storax, and 4% tolic balsam in alcohol) is widely used as a topical dressing prior to application of adhesive tapes, plaster casts, and other dressings. Allergic contact dermatitis resulting from use of this compound has been reported (Cullen *et al.*, 1974;

Cooper and Fair, 1978; Coskey, 1978). The major dermatological manifestation of allergic contact dermatitis is eczema, but an incident has been reported in which benzoin, applied as tincture of benzoin under a plaster cast, caused both eczema and a generalized noneczematous exanthem (Spott and Shelley, 1970). The latter reaction is typical of a drug reaction, but, in this case, it resulted from absorption of the local contact allergen. Benzoin is also present in a variety of perfume and cosmetic products. Cases of contact dermatitis due to benzoin in greasepaint makeup were reported by Hoffman and Adams (1978).

Rosenhall and Zettershom (1973) reported that ingestion of small doses of benzoin (dose not specified) caused 21 of 53 patients with asthma or rhinitis of a vasomotor type to react with asthma symptoms (coughing, itching, hives, etc.). The symptom-provoking doses were at levels that might easily be found as food additives in the daily diet.

3. Target Organ Toxicity

No information was found in the literature searched.

4. Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No references to current toxicological or environmental studies of benzoin were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for benzoin were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were found.

18. Other Pertinent Data

No other information that may aid in the occupational hazard assessment of benzoin was found in the literature searched.

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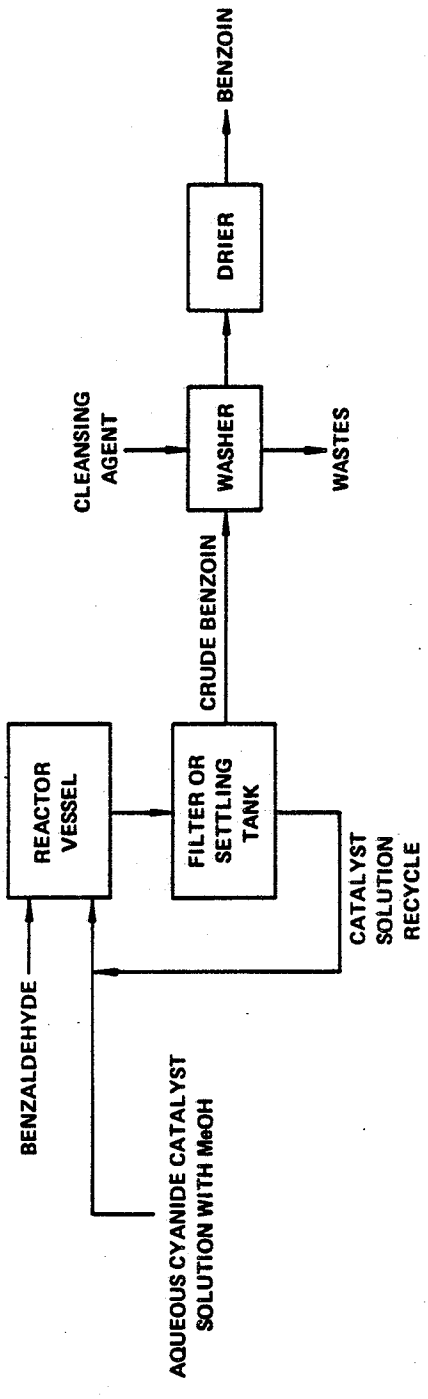
BENZOIN
DRIER
CLEANSING AGENT
WASHER
WASTES
CRUDE BENZOIN
REACTOR VESSEL
FILTER OR SETTLING TANK
CATALYST SOLUTION RECYCLE
BENZALDEHYDE
AQUEOUS CYANIDE CATALYST SOLUTION WITH MeOH
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