

**NATIONAL TOXICOLOGY PROGRAM**

**EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION**

**BENZOPHENONE**

CAS Number 119-61-9

October 4, 1991

Submitted to:

**NATIONAL TOXICOLOGY PROGRAM**

Submitted by:

Arthur D. Little, Inc.

Board of Scientific Counselors Draft Report

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## OVERVIEW<sup>1</sup>

Nomination History: *Benzophenone was nominated by the National Institute of Environmental Health Sciences (NIEHS) in 1987 for toxicity and carcinogenicity testing based on the potential for occupational and consumer exposure, and the lack of chronic toxicity data. NIOSH originally nominated this chemical for Salmonella testing.*

Chemical and Physical Properties: *Benzophenone is a white solid with the appearance of orthorhombic bisphenoidal prisms. This compound has a melting range of 48.0-51 °C (118-124 °F) and a boiling point of ~ 305 °C (~581 °F). Benzophenone is insoluble in water, but is soluble in alcohol, acetone, acetic acid, ether, chloroform, and benzene. This compound is photochemically reactive, incompatible with strong oxidizing and reducing agents, and may attack some unspecified plastics. The decomposition of benzophenone may produce carbon monoxide and carbon dioxide.*

Production/Uses/Exposure: *The production of benzophenone was reported in the public file of the EPA Toxic Substances Control Act (TSCA) Inventory in 1983 by four manufacturers to range from 300,000-3,001,000 pounds. No production data were available from the United States International Trade Commission's (USITC) publication, Synthetic Organic Chemicals, or from SRI's Chemical Economics Handbook. Four companies listed as importers in the EPA TSCA Inventory reported a total import volume ranging from 3,000-31,000 pounds. The USITC reported an import volume range of 2,646-1,709 pounds for the years 1979-1982, respectively.*

*Benzophenone is a component of many consumer products. It is primarily used as a photoinitiator and as a fragrance enhancer. It is also used as an ultraviolet curing agent, flavor ingredient, as a polymerization inhibitor, and in the manufacture of insecticides, agricultural chemicals, hypnotics, and other pharmaceuticals.*

*Data from the National Occupational Exposure Survey (NOES) conducted during 1981-1983, estimated that 41,520 workers, including 18,162 females, were potentially exposed to benzophenone.*

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<sup>1</sup> The information contained in this Executive Summary of Safety and Toxicity Information (ESSTI) is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

*Benzophenone has been detected in the environment in soil, water, and air. It readily adsorbs to soil at a rate proportional to the amount of organic matter in the soil. It has been found in surface and ground water, primarily from the discharge of untreated domestic and industrial sewage and waste water into rivers, streams, and other waterways. Benzophenone has been detected in the atmosphere as either a product of combustion or a secondary product of atmospheric degradation.*

*The FDA has approved the use of benzophenone as a flavoring substance and adjuvant. The EPA regulates process units that produce benzophenone. OSHA has not established a permissible exposure limit (PEL); ACGIH has not recommended an exposure limit (TLV); and NIOSH has not recommended an exposure limit (REL) for this compound.*

#### Toxicological Effects:

Human: *Benzophenone inhalation induced purulent bronchitis, allergic asthma, and erythema in one case report. This compound was positive in patch test results in 1-2% of patients tested by the North American Contact Dermatitis Research Group. In one case study, benzophenone did not induce photosensitization. In another study, benzophenone was negative in patch tests on five subjects with allergic contact dermatitis.*

*No data were found in the literature on chemical disposition, or the carcinogenic, reproductive, or teratogenic effects of benzophenone in humans.*

Animal: *In rats orally administered benzophenone, p-hydroxybenzophenone (1% of administered dose) was detected in enzyme-treated urine samples, but not in unhydrolyzed urine. No p-hydroxybenzophenone was detected in the feces. The primary pathway of benzophenone metabolism following oral administration to rabbits was reported to be reduction of the keto group to benzhydrol which was excreted, at concentrations 41-61% of the administered benzophenone dose, as a labile glucuronide in the urine. The amount of percutaneous absorption in monkeys was found to be 43 and 68% of the applied benzophenone dose for unoccluded and occluded sites, respectively.*

*Acute oral (dosed feed) exposure in rats, caused a dose-dependent increase in the absolute and the relative weights of the liver, and the relative weight of the kidney, and an increase in serum glutamic pyruvic transaminase (SGPT) . In addition, mild degenerative effects were observed in the liver and bone marrow of animals in the high dose group, indicating that the liver may be the primary target organ, and that the bone marrow may also represent a site of toxic action. The oral LD<sub>50</sub> for benzophenone has been reported to range from 1,900 - >10,000 mg/kg in rats and 1,600-2,895 mg/kg in mice. The dermal LD<sub>50</sub> was found to be 3,535 mg/kg and > 1 g/kg in rabbits and guinea pigs, respectively.*

*Benzophenone has produced slight to moderate skin irritation in guinea pigs. Benzophenone was not found to cause sensitization among guinea pigs by a variety of tests, including the maximization test. In one study, this compound was determined to have a medium dermal, and a slight ocular, irritancy potential, and in another it was reported that this compound failed to induce skin or eye irritation in rabbits.*

*Benzophenone did not induce a significant increase in skin tumors in mice that received topical applications of benzophenone for 120 weeks, or until death compared to animals treated with acetone or 7, 12-dimethylbenzanthracene, and non-treated controls. However, decreased survival rate was observed in benzophenone-treated animals compared to untreated controls. Topical application to rabbits for 160 weeks did not result in a treatment-related decrease in survival rates or local changes. No tumors were observed in rabbits exposed to benzophenone.*

*Benzophenone did not have an effect on limb regeneration in Japanese newts. No other data were found on the teratogenic effects, and no data were found on reproductive toxicology.*

Genetic Toxicology: *Benzophenone has been found to be negative in all strains of Salmonella tested. Benzophenone was also negative in the E. coli Pol A assay.*

Structure Activity Relationships: *Benzophenone is structurally related to acetophenone. Acetophenone did not affect growth or hematological parameters, or produce macroscopic or microscopic changes in rats fed this compound in the diet for 17 weeks. Acetophenone has been found to be negative in the Salmonella and in the E. coli pol A assays, but was genotoxic in cultured hamster lung cells. No data were found on the carcinogenicity of acetophenone.*

## **I. NOMINATION HISTORY AND REVIEW**

### **A. Nomination History**

1. Source: National Institute of Environmental Health Sciences (NIEHS) [NIEHS, 1987]
2. Date: December, 1987
3. Recommendations:
  - Toxicity
  - Carcinogenicity
4. Priority: --
5. Rationale/Remarks:
  - Originally nominated by NIOSH for *Salmonella* testing
  - Potential for occupational exposure
  - Used in a variety of consumer products
  - Lack of chronic toxicity data

### **B. Chemical Evaluation Committee Review**

1. Date of Review: August 8, 1991
2. Recommendation:
  - Toxicity
  - Carcinogenicity
  - Teratogenicity
3. Priority:
  - Moderate for toxicity and carcinogenicity
  - High for teratogenicity
4. NTP Chemical Selection Principle(s): 3, 6, 8
5. Rationale/Remarks:
  - High production
  - Potential for occupational and consumer exposure
  - Air and water pollutant
  - Lack of toxicity data
  - Structural interest as an aromatic ketone

### **C. Board of Scientific Counselors Review**

1. Date of Review:
2. Recommendations:
3. Priority:
4. Rationale/Remarks:

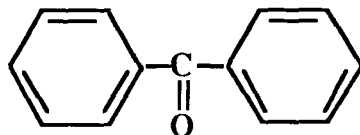
**D. Executive Committee Review**

1. Date of Review:
2. Decision:



## II. CHEMICAL AND PHYSICAL DATA

### A. Chemical Identifiers



### BENZOPHENONE

*CAS No. 119-61-9*

*RTECS No. DI9950000*

Molecular formula:  $C_{13}H_{10}O$

Molecular weight: 182.21

### B. Synonyms and Trade Names

**Synonyms:** benzophenone (8CI); methanone, diphenyl- (9CI); alpha-oxodiphenylmethane; alpha-oxoditane; benzoylbenzenepheryl; benzene, benzoyl; benzoylbenzene; diphenyl ketone; diphenylmethanone; phenyl ketone

**Trade Names:** No information was found.

### C. Chemical and Physical Properties

**Description:** Off-white chips [Lenga, 1988]; orthorhombic bisphenoidal prisms [Budavari, 1989; Weast, 1988] or white crystalline powder [J.T.Baker, 1990] with a geranium [Budavari, 1989] floral [J.T. Baker, 1990] or rose-like odor [Sax and Lewis, 1989; Furia and Bellanca, 1975].

**Melting Point:** 49.0-51.0°C (120.2-123.8°F) [Aldrich, 1990]  
48.0°C (118°F) [J.T. Baker, 1990]  
48.5°C (119.3°F) [Budavari, 1989; Furia and Bellanca, 1975]  
48.1°C (118.5°F) [Dean, 1985; Weast, 1988]  
48.0-49.5°C (118.4-121.1°F) [Lenga, 1988].

**Boiling Point:** 305.0°C (581.0°F) [J.T. Baker, 1990; Dean, 1985; Lenga, 1988; Aldrich, 1990]  
305.4°C (581.7°F) [Budavari, 1988]  
305.9°C (582.6°F) [Weast, 1989]  
276.8°C (530.2°F) @ 400 mm Hg [Budavari, 1989]  
249.8°C (481.6°F) @ 200 mm Hg [Budavari, 1989]  
224.4°C (435.9°F) @ 100 mm Hg [Budavari, 1989]

208.2°C (406.7°F) @ 60 mm Hg [Budavari, 1989]  
195.7°C (384.2°F) @ 40 mm Hg [Budavari, 1989]  
175.8°C (348.4°F) @ 20 mm Hg [Budavari, 1989]  
170.0°C (338.0°F) @ 15 mm Hg [Furia and Bellanca, 1975]  
157.6°C (315.6°F) @ 10 mm Hg [Budavari, 1989]  
141.7°C (287.0°F) @ 5 mm Hg [Budavari, 1989]  
108.2°C (226.7°F) @ 1.0 mm Hg [Budavari, 1989].

**Specific Gravity:** 1.1108 @ 18°/4°C [Budavari, 1989]  
1.0869 @ 50°/4°C [Budavari, 1989]  
1.1108 @ 15°/4°C [Dean, 1985]  
1.146 @ 20°/4°C [Weast, 1988]  
1.11 [J.T. Baker, 1990]  
1.0496 @ 95°C [Furia and Bellanca, 1975].

**Refractive Index:** 1.5975 @ 45.2°C [Budavari, 1989]  
1.6077 @ 19°C [Weast, 1988]  
1.5893 @ 45.2°C [Furia and Bellanca, 1975].

**Solubility in Water:** Insoluble in water (< 0.1% [J.T. Baker, 1990]) [Budavari, 1989; Furia and Bellanca, 1975].

**Solubility in other Solvents:** Soluble in alcohol (1 g in 7.5 mL [Budavari, 1989]; 13.3 parts in 100 parts by wt. [Dean, 1985]; 1:10 in 80% [Furia and Bellanca, 1975]) [Weast, 1988]; acetone [Weast, 1988]; ether (1 g in 6 mL [Budavari, 1989]; 17 parts in 100 parts by wt. [Dean, 1985]) [Weast, 1988; Furia and Bellanca, 1975], acetic acid [Furia and Bellanca, 1975], chloroform [Budavari, 1989], and benzene [Weast, 1988].

**Log Octanol/Water Partition Co-efficient:** 1514 (determined experimentally) [Bronaugh *et al.*, 1990].

**Reactive Chemical Hazards:** Incompatible with strong oxidizing agents [Lenga, 1988; Sax and Lewis, 1989; OHMTADS, 1991] and strong reducing agents [Lenga, 1988]; may attack some unspecified plastics [US Coast Guard, 1985]. Benzophenone is photochemically reactive [Kirk-Othmer, 1981]. Decomposition of this compound produces toxic fumes of carbon monoxide and carbon dioxide [Lenga, 1988].

**Flammability Hazards:**

- Combustible [U.S. Coast Guard, 1985; J.T.Baker, 1990]
- Flash point: >110°C (230°F) [Lenga, 1988; Aldrich, 1990]
- Vapor pressure: 1 mm Hg @ 108.2°C [Sax and Lewis, 1989]
- Vapor density: 6.3 (air = 1) [J.T.Baker, 1990]
- Autoignition temperature: No data were found.
- Flammable limits in air: No data were found.

### III. PRODUCTION/USE

#### A. Production

##### 1. Manufacturing Process

Benzophenone is prepared in 66% yield by a Friedel-Crafts acylation using benzoyl chloride with an excess of benzene in the presence of anhydrous aluminum chloride [Kirk-Othmer, 1978; Budavari, 1989; Furia and Bellanca, 1975]. An 85% yield of benzophenone has been achieved by reacting anhydrous aluminum chloride and carbon tetrachloride with dry benzene to yield dichlorodiphenylmethane which is subsequently hydrolyzed to benzophenone [Furniss *et al.*, 1987].

Benzophenone can also be manufactured by the decarboxylation of *o*-benzoylbenzoic acid in the presence of copper catalyst [Budavari, 1989], derived from copper carbonate. When decarboxylation is complete, benzophenone is isolated from the reaction mixture by distillation [Fieser, 1964].

In addition, benzophenone can be obtained from the distillation of calcium benzoate [Poucher, 1974] and by photochemical degradation from 1, 1, 4, 4-tetraphenylbutadiene [Caprino *et al.*, 1976].

##### 2. Producers and Importers

<u>U.S. Producers</u>	<u>Reference</u>
Aceto Chemical Company Arsynco Incorporated Subsidiary Carlstadt, New Jersey	OHMTADS, 1991
Alzo, Incorporated Matawan, New Jersey	USEPA, 1991
Berje Incorporated Bloomfield, New Jersey	Chemical Week Buyers' Guide, 1991
Charkit Chemical Corporation Darien, Connecticut	Chemical Week Buyers' Guide, 1991
Chemical Division-UOP Incorporated East Rutherford, New Jersey	USEPA, 1991
C I Specialty Chemicals Incorporated A Subsidiary of C Itoh & Company America New York, New York	Chemical Week Buyers' Guide, 1991
D & O Chemicals, Incorporated Englewood, New Jersey	Chemical Week Buyers' Guide, 1991

U.S. Producers (cont.)

EM Industries, Incorporated  
Hawthorne, New York

Ferro Corp Bedford Chemical Division  
Bedford, Ohio

GAF Corporation  
Rensselaer, New York

GCA Chemical Corporation  
Houston, Texas

Givaudan Corporation  
Chemical Division  
Clifton, New Jersey

Haarmann & Reimer Corporation  
Springfield, New Jersey

Hoechst Celanese Corporation  
Fine Chemicals Division  
Specialty Chemical Group  
Charlotte, North Carolina

International Bio-Synthetics Incorporated  
Charlotte, North Carolina

JMP Imports, Incorporated  
Astoria, New York

Monomer-Polymer and Dajac  
Laboratories, Incorporated  
Trevose, Pennsylvania

Norda Incorporated  
Boonton, New Jersey

Orbis Products Corporation  
Newark, New Jersey

Penta Manufacturing Company  
Fairfield, New Jersey

Quest International Fragrances  
USA Incorporated  
Mount Olive, New Jersey

Reference (cont.)

Chemical Week Buyers'  
Guide, 1991  
USEPA, 1991

Chemical Week Buyers'  
Guide, 1991

USEPA, 1991  
OHMTADS, 1991

Chemical Week Buyers'  
Guide, 1991

OHMTADS, 1991

USEPA, 1991  
Chemical Week Buyers'  
Guide, 1991

Chemical Week Buyers'  
Guide, 1991

Chemical Week Buyers'  
Guide, 1991

USEPA, 1991

Chemical Week Buyers'  
Guide, 1991

USEPA, 1991  
OHMTADS, 1991

USEPA, 1991

Chemical Week Buyers'  
Guide, 1991

Chemical Week Buyers'  
Guide, 1991

U.S. Producers (cont.)

R.W. Greeff & Company, Incorporated  
Old Greenwich, Connecticut

Schweizerhall Incorporated  
South Plainfield, New Jersey

The Upjohn Company<sup>2</sup>  
North Haven, Connecticut

Twin Lake Chemical Company  
Lockport, New York

Ungerer and Company  
Totowa, New Jersey

Warner-Lambert Company  
Parke-Davis, Division  
Holland, Michigan

Velsicol Chemical Corporation  
Rosemont, Illinois

European Producers

Bush Boake Allen Ltd.  
Widnes, United Kingdom

Haarmann & Reimer GmbH  
Holzminden, Germany

Johnson Matthey Chemicals Ltd.  
Royston, United Kingdom

Norsochem Ltd.  
Widnes, United Kingdom

Société Française d'Organo-Synthèse  
Persan, France

Reference (cont.)

Chemical Week Buyers'  
Guide, 1991

Chemical Week Buyers'  
Guide, 1991

USEPA, 1991  
SRI, 1990a  
USITC, 1989

USEPA, 1991

USEPA, 1991

USEPA, 1991  
SRI, 1990a  
USITC, 1989  
OHMTADS, 1991

American Paint and  
Coatings Journal, 1990

Reference

SRI, 1990b

SRI, 1990b

SRI, 1990b

SRI, 1990b

SRI, 1990b

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<sup>2</sup> In May 1990, the Upjohn Company agreed in principle to sell its benzophenone business to Velsicol Chemical Corporation of Rosemont, Illinois [American Paint and Coatings Journal, 1990].

<u>Importers</u>	<u>Reference</u>
EM Laboratories, Incorporated Elmsford, New York	USEPA, 1991
Haarmann & Reimer Corporation Springfield, New Jersey	USEPA, 1991
Int Flavors & Fragrances, Incorporated Union Beach, New Jersey	USEPA, 1991
JPM Imports, Incorporated Astoria, New York	USEPA, 1991
Synarome Corporation New York, New York	USEPA, 1991
Ungerer and Company Totowa, New Jersey	USEPA, 1991

### 3. Volume

#### Production Volume

Benzophenone is listed in the United States International Trade Commission's (USITC) publication Synthetic Organic Chemicals. However, no production data were available on benzophenone from this source for the years 1985-1988 [USITC, 1986-1989]<sup>3</sup>.

The volume of benzophenone manufactured in the United States is reported in the public file of the EPA Toxic Substances Control Act (TSCA) Inventory. In 1983, 4 companies listed as manufactures reported a total volume ranging from 300,000-3,001,000 pounds. Seven additional manufactures are listed but did not report volume information. Three of these seven are classified as small manufacturers (produced less than 100,000 pounds of benzophenone) [USEPA, 1991].

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<sup>3</sup> Production statistics for an individual chemical are given only when there are three or more producers, no one or two of which may be predominate. Moreover, even when there are three or more producers, statistics are not given if there is any possibility that their publications would violate the statutory provisions relating to unlawful disclosure of information accepted in confidence by the Commission. Data are reported by producers for only those items where the volume of production or sales or value of sales exceeds certain minimums. Those minimums for all sections are 5,000 pounds of production or sales of \$5,000 of value of sales with the following exceptions: plastics and resins materials--50,000 pounds or \$50,000; pigments, medicinal chemicals, flavor and perfume materials, and rubber processing chemicals--1,000 pounds or \$1,000.

No production data specific to benzophenone (CAS No. 119-61-9) were included in SRI's Chemical Economics Handbook. However, this source reports that in the mid-1980s, the general class of benzophenone ultraviolet absorbers (including 2-hydroxy-4-methoxy-benzophenone, 2-hydroxy-4-octoxy-benzophenone, and 2,4-dihydroxybenzophenone) "faced serious competition" from hindered amine light stabilizers and benzophenones subsequently lost a sizable portion of the market. SRI states that the consumption of benzophenones has recently stabilized and is now growing in parallel with the polyolefin plastics market. In 1987, the production volume of ultraviolet absorbers included 1.2-1.4 million pounds of benzophenones [SRI, 1991].

The use of benzophenone in fragrances (since the 1920s) has been reported to be 100,000 pounds per year [Opdyke, 1973].

#### Import Volume

Four companies listed as importers of benzophenone in the EPA TSCA Inventory reported a total volume of 3,000-31,000 pounds. Two additional importers were listed, but no import data were reported [USEPA, 1991].

The USITC reported that in 1979, imports totaled 2,646 pounds, but decreased to 1,323 pounds in 1980 [USEPA, 1984]. The import volume increased to 1,709 pounds in 1982 [USITC, 1983]. No import data for benzophenone were reported by the USITC for 1983 [USITC, 1984] or 1981 [USEPA, 1984]. Import data were not published for this compound by USITC after 1984 [USITC, 1991].

#### 4. Technical Product Composition

Benzophenone is available in free from chlorine (FFC) grade and technical grade [Sax and Lewis, 1987]. This compound can be purchased at a purity of 99+% [Aldrich, 1990; U.S. Coast Guard, 1985].

#### B. Use

Benzophenone is primarily used as a photoinitiator and as a fragrance enhancer [American Paint and Coatings Journal, 1990; Chem Bus Newbase, 1991]. Other uses include:

- Ultraviolet curing agent [Chem Bus Newbase, 1991] in sunglasses [OHMTADS, 1991] and ultraviolet curable ink [Polymers, Paint, Colour Journal, 1985; Emmett *et al.*, 1977]
- Derivatives used as ultraviolet absorbers [Sax and Lewis, 1987], to block UV-B, UV-A and UV-C radiation [Roelandts *et al.*, 1983]
- Flavor ingredient [Sax and Lewis, 1987]
- Perfume fixative [Stenback, 1977; OHMTADS, 1991] in soaps [Kirk-Othmer, 1981; Budavari, 1989; Tomson *et al.*, 1981; Sax and Lewis, 1987]

- Manufacture of insecticides [Kirk-Othmer, 1981; Budavari, 1989; OHMTADS, 1991] and agricultural chemicals [Polymers, Paint, Colour Journal, 1985]
- Additive for plastics, coatings and adhesive formulations [Polymers, Paint, Colour Journal, 1985]
- Manufacture of hypnotics [Kirk-Othmer, 1981; Budavari, 1989; OHMTADS, 1991] antihistamines [Kirk-Othmer, 1981; Budavari, 1989; OHMTADS, 1991] and other pharmaceuticals [Sax and Lewis, 1987; OHMTADS, 1991; Polymers, Paint, Colour Journal, 1985]
- Polymerization inhibitor for styrene [Sax and Lewis, 1987]



#### IV. EXPOSURE/REGULATORY STATUS

##### A. Consumer Exposure

Based on the use of this compound as an additive in fragrances, toiletries, pharmaceuticals, insecticides, cosmetics, and flavor ingredients, consumer exposure may be significant.

The concentration of benzophenone in various consumer products is presented in Table 1.

**Table 1. Concentrations of Benzophenone in Consumer Products.**

<u>Product</u>	<u>Concentration</u>	<u>References</u>
Non-alcoholic beverages	0.50 ppm	Furia and Bellanca, 1975
Ice cream, ices, etc.	0.61 ppm	Furia and Bellanca, 1975
Candy	1.70 ppm	Furia and Bellanca, 1975
Baked goods	2.40 ppm	Furia and Bellanca, 1975
Soap	0.02-0.15%	Opdyke, 1973
Detergent	0.002-0.015%	Opdyke, 1973
Creams, lotions	0.004-0.015%	Opdyke, 1973
Perfume	0.09-0.3%	Opdyke, 1973

##### B. Occupational Exposure

Benzophenone was 1 of 57 compounds positively identified from 35 air samples taken during the manufacture of rubber goods. The samples were obtained from 4 different locations: the vulcanization areas of a shoe sole factory and a tire retreading operation, and the extrusion areas of the tire retreading operation and an insulated cable manufacturer. Ambient air was collected on activated charcoal by means of personal samplers. Four sample tubes were collected at each location. The air samples were analyzed using a gas chromatograph-mass spectrometer equipped with a fused silica capillary column. Benzophenone was detected at levels of 0-1  $\mu\text{g}/\text{m}^3$  in the extrusion area of the electrical cable insulation plant; it was not detected in the three other areas sampled. Although benzophenone is not believed to be present in the raw materials, the authors speculate that it is produced, by an unknown mechanism, from the vulcanizing agent dicumyl peroxide which was used exclusively at the insulated cable manufacturing plant [Cocheo *et al.*, 1983].

Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) during the years 1981 to 1983, estimated that 41,520 workers, including 18,162 females, were potentially exposed to benzophenone. These data were obtained from 1,809 companies. A breakdown of the NIOSH data is presented in Table 2. The NOES data base does not contain information on the frequency, level, or duration of exposure to workers of any chemicals listed therein [NIOSH,1991].

**Table 2. National Occupational Exposure Survey Data**

<u>Description of Industry</u>	<u>Number</u>	<u>Total Employees</u>	<u>Female Employees</u>
Paper and Allied Products	181	1,581	---
Printing and Publishing	60	633	95
Chemicals and Allied Products	62	8,791	738
Leather and Leather Products	24	2,940	2,414
Stone, Clay, and Glass Products	17	3,220	2,717
Primary Metal Industries	47	2,752	---
Fabricated Metal Products	346	4,145	1,024
Machinery, Except Electrical	117	6,530	5,230
Electrical and Electronic Equipment	118	550	320
Instruments and Related Products	43	1,495	120
Miscellaneous Manufacturing Industries	14	82	55
Trucking and Warehousing	61	607	303
Business Services	24	893	187
Auto Repair, Services, and Garages	466	932	466
Health Services	228	6,366	4,493
TOTAL	1,809	41,516	18,162

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NIOSH, 1991

### C. Environmental Occurrence

Benzophenone has been reported to occur naturally in grapes [Furia and Bellanca, 1975]; however, another source states that it does not occur naturally in the environment [Opdyke, 1973].

The relatively high estimated octanol/water partition coefficient and the water insolubility of benzophenone indicate that it will partition into soil and sediment. Benzophenone is readily adsorbed to soil organic matter [USEPA, 1984]. The adsorption of benzophenone to soil is proportional to the organic content of the soil [OHMTADS, 1991]. As described below, this compound is found in the atmosphere. The EPA reports that because of its low vapor pressure, benzophenone is not expected to be present in significant quantities in the atmosphere [USEPA, 1984]. Benzophenone may bioconcentrate [USEPA, 1984].

Benzophenone has been detected in the atmosphere of the Eggegebirge forest in Germany where, for the past decade, tree damage (particularly among spruce trees) has been observed. A total of 37 forest air samples were collected using sampling tubes containing absorbent materials which were attached to personal sampling pumps. Three of the 37 samples were collected by passive sampling. Air samples were collected over periods of 1 to 24 hours. The samples were analyzed by an automatic thermodesorption device coupled with gas chromatography-mass spectrometry. Benzophenone (concentration not specified) was 1 of 209 compounds identified. The authors stated that it was difficult to determine whether the presence of ketones, including benzophenone, was the result of directly emitted substances (*i.e.*, combustion products), or secondary products of atmospheric degradation [Helmig *et al.*, 1989].

Benzophenone was found to be a component of oil burner emissions in a 1987 study performed to characterize the oil burner emissions from a standard residential oil burner. Exhaust fumes from an oil burner, combusting No. 2 fuel oil, were collected after continuous and cyclic (5 minutes on, 10 minutes off) burning, and analyzed. Benzophenone was one of the principal compounds found in the chloroform extracts from the cyclic combustion samples. The source of this compound is not known; however, it is believed that it may result from oxidative pyrolysis of unreacted, or partially reacted, fuel in the post-flame regions of the oil burner combustion chamber [Leary *et al.*, 1987].

Benzophenone was 1 of 243 organic compounds identified in secondary effluents from samples collected at 10 municipal and industrial wastewater treatment plants that discharge water into rivers in Illinois. The samples were collected as grabs (n=6), composites (n=3), and as 1/2 grab, 1/2 composite (n=1) and analyzed for total organic carbon. Following solvent extraction and resin sorption, gas chromatographic-mass spectrometric analysis was performed. Benzophenone was found in 3 grab samples taken from 3 publicly-owned treatment works facilities which, combined, serviced more than 400 industrial and manufacturing firms [Ellis *et al.*, 1982].

Benzophenone has been found in water samples taken from the Kitakyushu area of Japan. In a 1989 study, collected tap water samples were analyzed using gas chromatography-mass spectroscopy. Benzophenone was detected in tap water at a concentration of 8.8 ng/L. The authors state that domestic sewage and industrial waste may represent the main sources of the contamination [Akiyama *et al.*, 1980].

Trace amounts of benzophenone were detected in groundwater in a study conducted to evaluate the effectiveness of rapid infiltration in removing organic compounds from waste water at a rapid infiltration site in Phoenix, Arizona. Benzophenone was found in the groundwater beneath the site at concentrations ranging from 0.009-.045 µg/L. The sources of contamination were not reported [Tomson *et al.*, 1981].

In a study done for the United States Environmental Protection Agency (USEPA), benzophenone and other chromatographable trace level organics (C-TLOs) were detected in ground-water from septic tank systems. Ten septic tank systems from around the country were sampled at their distribution boxes and monitoring wells, and analyzed. Of the 10 septic systems tested, C-TLOs were found in the groundwater at 4 locations, and benzophenone was found at 3. At an apartment complex in Speonk, New York, benzophenone was found at a concentration of 0.19 µg/L at the distribution box and at concentrations of 0.0013 µg/L, 0.0060 µg/L, and 0.015 µg/L at wells 5, 15, and 50 feet from the distribution box, respectively. Levels of the compound were reported to be 0.0460 µg/L (distribution box) and 0.0015 µg/L (municipal well) at a campground in Cisco Grove, California, and 0.0522 µg/L (sewage) and 0.0242 (municipal well) at a deteriorated residential trailer park in Sun Valley, Nevada [Municipal Environmental Research Lab, 1984].

#### D. Regulatory Status

- OSHA has not established a permissible exposure limit (PEL) for benzophenone.
- The Environmental Protection Agency (EPA) regulates process units that produce benzophenone as an intermediate or a final product {40 CFR 60.489} [Office of the Federal Register, 1990b].
- The Food and Drug Administration (FDA) has approved the use of benzophenone as a flavoring substance and adjuvant in accordance with the following conditions:
  - It is used in the minimum quantity required to produce the intended effect, and otherwise in accordance with all the principles of good manufacturing practice.
  - It is used alone or in combination with flavoring substances and adjuvants generally recognized as safe in food, prior-sanctioned for such use, or regulated by an appropriate standard {21 CFR 172.515} [Office of the Federal Register, 1990a].
- The Council of Europe has approved the use of benzophenone as an artificial flavoring substitute at 2 ppm [Opdyke, 1973].

#### E. Exposure Recommendations

- ~~ACGIH has not recommended an exposure limit (TLV) for benzophenone.~~
- NIOSH has not recommended an exposure limit (REL) for benzophenone.
- The Flavor and Extract Manufacturers' Association (FEMA) granted GRAS (Generally Recognized As Safe) status to benzophenone in 1965 [Opdyke, 1973].

## V. TOXICOLOGICAL EFFECTS

### A. Chemical Disposition

#### 1. Human Data

No data were found on the chemical disposition of benzophenone in humans.

#### 2. Animal Data

- oral, rats:

The metabolism of benzophenone was studied in rats to determine whether the elimination of *p*-hydroxybenzophenone occurs as a result of the aromatic hydroxylation of benzophenone *in vivo*. Three determinations were performed: 1) the determination of *p*-hydroxybenzophenone in unhydrolyzed urine; 2) the determination of *p*-hydroxybenzophenone in enzyme-treated urine with *B*-glucuronidase/aryl sulfatase; and 3) the determination of *p*-hydroxybenzophenone in feces. A group of 10 male Sprague-Dawley rats was given an oral dose, via stomach tube, of 0.3 mL benzophenone/warm corn oil solution (1.13 grams of benzophenone dissolved in 3 mL corn oil). A second group of 9 male rats of the same strain was given an oral dose of 0.1 grams of benzophenone dissolved in 0.5 mL of warm corn oil, by stomach tube. The urine and feces were collected for 24 hours, pooled, and analyzed immediately.

Control experiments were carried out in order to eliminate the possibility that *p*-hydroxybenzophenone might be formed from benzophenone as a result of fecal contaminated urine, or through air oxidation during urine collection. Before the administration of benzophenone, the 2 sets of rats described above were each given 0.5 mL of distilled water via stomach tube at 24 hour intervals for 2 days. Individual control urine samples were collected and pooled after 24 hours for each set of animals. Two additional sets of 24-hour control urine were collected and incubated with 150 or 500 mg of benzophenone for 24 hours. All control urine was analyzed as described below for the analysis of unhydrolyzed urine. The results obtained from the control urine indicated that *p*-hydroxybenzophenone was not present in organic extracts of urine samples obtained from metabolism cages and incubated for 2 days under aerobic conditions with benzophenone.

To detect the presence of *p*-hydroxybenzophenone in unhydrolyzed urine, urine samples collected from the rats treated with benzophenone were adjusted to pH 4.0 with concentrated hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layers were combined and reduced to dryness, and remaining residues were dissolved in diethyl ether, dried, and reconstituted to 1 mL with ethyl acetate. Five microliter (5 $\mu$ l) aliquots were analyzed using thin-layer chromatography. The ethereal solutions were taken to dryness and the tan residues which remained were analyzed by mass spectrometry. No *p*-hydroxybenzophenone was detected by either method in either test group.

For the determination of *p*-hydroxybenzophenone in enzyme-treated urine, the ethyl acetate-extracted urine samples described above were adjusted to pH 4.5 with 10% sodium hydroxide. Next, 10 ml of 1.0 N acetate buffer and 50 mg of *B*-glucuronidase/aryl sulfatase were added to the urine and samples were incubated for 24 hours. The hydrolyzed urine was extracted with ethyl acetate and dried. Samples were then analyzed by thin-layer chromatography. *p*-Hydroxybenzophenone (8.8 mg-44.0  $\mu$ mole) was isolated from 1 urine extract and 11.0 mg (55.4  $\mu$ mole) of benzophenone was isolated from the second.

To investigate the presence of *p*-hydroxybenzophenone in the feces, the feces from benzophenone treated rats were homogenized with methanol. The slurries were filtered and dried, and the organic layers were reconstituted. Fecal analysis using both thin layer chromatography and mass spectrometry failed to detect any *p*-hydroxybenzophenone in pooled fecal samples from either test group.

*p*-Hydroxybenzophenone was detected only in the 24-hour urine treated with *B*-glucuronidase/aryl sulfatase. The quantity of *p*-hydroxybenzophenone isolated represented approximately 1% conversion of benzophenone to *p*-hydroxybenzophenone. The authors stated that the isolation of *p*-hydroxybenzophenone from enzyme-treated urine indicates that the keto group of *p*-hydroxybenzophenone remains unaltered (since *p*-hydroxybenzhydrol was not detected in urine and fecal samples), and that the phenol existed as either a glucuronide or sulfate conjugate. The authors further stated that both methods of detection used were sensitive enough to detect at least 1  $\mu$ g of phenol, indicating that the phenol in the fecal matter was either present in concentrations too low to detect, or was not present at all in the metabolic extracts [Stocklinski *et al.*, 1979].

- oral, rabbits:

The metabolism of benzophenone was studied in rabbits of unspecified strain that were administered, via stomach tube, 1.0 (n=1), 2.0 (n=4), 3.0 (n=2), or 4.0 (n=2) grams of benzophenone suspended in water. Urine was collected at 24 and 48 hours after dosing. The 24-hour urine of the rabbit administered 1 gram of benzophenone was ether-extracted, evaporated to dryness, and passed through an alumina column from which benzhydrol (0.1 g) was eluted. Paper chromatography of the 24-hour urine sample revealed 1 spot which reacted with naphtharesorcinol, suggesting that only 1 glucuronide was extracted. The glucuronide was subsequently isolated and determined to be benzhydrol glucuronide. Paper chromatography of the ether extract of hydrolyzed benzophenone urine revealed only benzhydrol; no 4-hydroxybenzophenone was detected. In addition, alkaline extraction of the ether solution did not yield 4-hydroxybenzophenone.

For the rabbits administered 2 grams of benzophenone, the glucuronide filtrate from the urine was prepared from the basic lead salt, neutralized, evaporated and passed over a resin column. The acidic eluate was evaporated to a gum and methylated with ethereal diazomethane. After removal of the ether, the methyl ether was dissolved in dry methanol. Evaporation yielded diphenylmethyl glucosiduronamide (600 mg). No ethereal sulphates were detected. From the urine of rats administered 3 and 4 grams of benzophenone, methyl (diphenylmethyl-tri-O-acetyl *B*-D-glucosid) uronate (40 and 60 mg, respectively) was isolated by systemic precipitation with lead acetate.

Based on these results, the authors reported that the primary route of metabolism is reduction of the keto group to yield benzhydrol, which is excreted in conjunction with glucuronic acid. In this study, 46-61% of the administered dose was excreted as a labile glucuronide. The authors further stated that benzhydrol does not appear to be hydroxylated in the aromatic ring [Robinson, 1958; Robinson and Williams, 1957].

- dermal, monkeys:

The percutaneous absorption of benzophenone was studied in monkeys. Groups of four female rhesus monkeys were administered a single dose of radiolabelled benzophenone ( $4 \mu\text{g}/\text{cm}^2$ ) in acetone to a lightly clipped  $1 \text{ cm}^2$  area of the abdomen. (The carbonyl group on the benzophenone (99.9% purity) was radiolabelled ( $5.4 \text{ mCi}/\text{mmol}$ ) to aid in the detection of the compound in urine samples.) The sites were left unoccluded, or occluded using either Saran Wrap®, or a glass chamber which was glued to the skin, and covered with parafilm.

The animals were restrained in metabolism chairs for 24 hours after the compound was applied. The application site was then washed with liquid soap and water, rinsed with water, washed again with soap and water, then rinsed with water twice to remove the residual material. Then animals were then placed in metabolism cages for 4 days for the continued collection of urine.

The amount of absorbed compound in the urine was determined by liquid scintillation counting. (Results were corrected for the amount of radioactivity for complete excretion with a parenteral correction factor.) The amount of compound absorbed for the Saran Wrap® occluded, glass chamber occluded, and unoccluded sites was determined to be  $68.7 \pm 6.4\%$ ,  $68.6 \pm 4.6\%$  and  $43.8 \pm 7.5\%$  of the administered dose, respectively [Bronaugh *et al.*, 1990].

## B. Acute

### 1. Human Data

No acute human data were found in the literature on benzophenone.

### 3. Animal Data

The acute toxicity data described below ( $\text{LD}_{50}$  studies), as well as additional  $\text{LD}_{50}$  studies found in the literature, are presented in Table 4.

- oral, rats:

The oral toxicity of benzophenone was determined in a 10-day study conducted by Eastman Kodak Company (unpublished data, 1984). Groups of 5 male rats, of an unspecified strain, were give daily oral doses of benzophenone in the diet containing 1% corn oil at concentrations of 0.1% or 1.0% for 10 consecutive days. A control group was fed a diet containing 1% corn oil. The animals were observed for signs of toxicity.

The animals receiving doses of 1.0% benzophenone ate slightly less food than controls, and had a slight reduction in body weight gain compared to controls. A dose-

dependent increase in the absolute and the relative weights of the liver, and the relative weight of the kidney was observed. The absolute weight of the kidneys from the low-dose group, but not the high-dose group, showed a slight but statistically significant increase. The hematocrit and hemoglobin concentrations, differential and total white cell counts, erythrocyte counts, and the red cell indices were comparable to the controls. Serum glutamic oxaloacetic transaminase, lactic dehydrogenase, alkaline phosphatase, glucose, sorbitol dehydrogenase and urea nitrogen levels were not affected by benzophenone at either dose. The serum glutamic pyruvic transaminase (SGPT) activity of the high-dose animals was slightly increased compared to the controls. The SPGT level of the low-dose rats was normal. No P values were reported for any of the above data.

No compound-related gross pathology was seen in either dose group. Histologically, mild degenerative effects were found in the liver and the bone marrow in the high-dose group. Two of the five high-dose rats had diffuse bone marrow vacuolation. One of these animals had minor erythroid hyperplasia. Four of the five high-dose rats had minor granular hepatic cytoplasm characterized by condensed granular matter. One of these animals also showed a moderate increase in eosinophilic staining of the cytoplasm. The authors concluded that, based on increased liver weights, the increased SGPT, and the histopathological changes observed, the liver may be the primary target organ. The bone marrow may also represent a site of toxic action [USEPA, 1984; Eastman Kodak Company, 1991].

- oral, mice:

The acute oral toxicity of benzophenone was determined using six groups of 8 male Swiss mice. The mice were fasted for 16 hours before the administration of 5 oral doses of unspecified concentrations of benzophenone suspended in 5% gum arabic. One group of mice received 5% gum arabic only. The animals were observed for 7 days for signs of toxicity, and necropsies were performed on all animals that died before the end of the 7-day study, and on all of the surviving animals at the end of the 7-day observation period.

In the animals receiving lethal doses of this compound, sedation, progressive depression of motor activity, unstable gait, tremors, and respiratory impairment were observed. No lesions or abnormalities were noted in the visceral organs of any of the animals upon necropsy. No histological examination was performed. The LD<sub>50</sub> was determined to be 2,895 mg/kg (2,441.1-3,433.5 mg/kg) [Caprino *et al.*, 1976].

- intraperitoneal, mice:

The acute toxicity of benzophenone was determined following intraperitoneal injection in male Swiss mice. Six groups of 8 fasted animals were administered 5 doses of an unspecified amount of the compound suspended in 5% gum arabic. One group of mice received 5% gum arabic only. The animals were observed for signs of toxicity for 7 days. Animals that died prior to the end of the study, and animals that survived the 7-day observation period, were necropsied.

Animals receiving lethal doses of this compound were observed to exhibit induced sedation, progressive depression of motor activity, unstable gait, tremors, and respiratory impairment. None of the animals were observed to have any gross lesions



or abnormalities of the visceral organs. No histological examination was performed. The LD<sub>50</sub> was determined to be 727 mg/kg (634.3-833.4 mg/kg) [Caprino *et al.*, 1976].

- **dermal, guinea pigs:**

The irritancy potential of benzophenone was determined in a study conducted by Eastman Kodak Company (unpublished data, 1984). An unspecified number of guinea pigs, of an unspecified strain, were exposed to benzophenone, in the form of a moistened solid, which was applied to the animals' shaved abdomen for 24 hours under an occlusive wrap. Benzophenone produced slight skin irritation as evidenced by slight erythema and desquamation, and slight to moderate edema [USEPA, 1984; Eastman Kodak Company, 1991].

- **dermal, guinea pigs:**

An unspecified number of guinea pigs, of an unspecified strain, were tested by Eastman Kodak Company (unpublished data, 1984) to determine the irritation potential of benzophenone. An unspecified amount of compound was applied daily to the animals' shaved backs and left uncovered for 10 days. The animals exhibited slight to moderate erythema and minute vesicles. This response was not exacerbated by additional treatment. There was no evidence of percutaneous absorption reported [USEPA, 1984; Eastman Kodak Company, 1991].

- **dermal, rabbits:**

The irritancy potential of benzophenone was studied using the Draize method. A group of 6 New Zealand rabbits were administered 20% benzophenone in olive oil. Doses of 0.5 ml were applied to scratched and unscratched skin at an unspecified area. After 24 and 72 hours, the animals were examined for the presence of erythema or edema. A histopathological examination of the animals' skin was also performed 3 days after the initial exposure.

Macroscopic examination revealed slight to moderate erythema (6 animals) and edema which was slight (4 animals), sometimes moderate (1 animal), or intense (1 animal). Microscopic examination showed focal necrosis with or without dyskeratosis. All of the observed skin alterations disappeared within 5 days. Based on these results, benzophenone was determined to have a medium irritancy potential with a primary cutaneous irritation index of 2.0. No information on the control animals was given [Calas *et al.*, 1977].

- **ocular, rabbits:**

In an unpublished study conducted by Eastman Kodak Company (1984), the ocular irritancy potential of benzophenone was studied in 3 rabbits of an unspecified strain. Several crystals of the compound were placed in the rabbits' conjunctival sacs. One eye of each rabbit was irrigated, and the other eye was left unwashed. Benzophenone was observed to produce slight eye irritation. The authors noted that irrigation with water immediately after treatment helped reduce the irritation [USEPA, 1984; Eastman Kodak Company, 1991].

- dermal and ocular, rabbits:

According to the Upjohn Company (1984), benzophenone tested in accordance with Department of Transportation regulations failed to cause irritation to the skin and eyes of rabbits. No other data were available [USEPA, 1984].

- aquatic:

The toxic effects of benzophenone at concentrations of 10 and 100 mg/L were studied in various aquatic species: fathead minnows, flatworms, snails, water fleas, and sideswimmers. At 100 mg/L, this compound was 100% lethal to water fleas and sideswimmers. A concentration of 10 mg/L was 50% lethal to sideswimmers. Benzophenone was not lethal to any of the other species at the two concentrations investigated [Eastman Kodak Company, 1991].

- aquatic:

The effect of benzophenone on growth, survival, and macromolecular content (see Section V.G.3) was studied in larval fathead minnows (*Pimephales promelas*). Groups of twenty-five to thirty-five 24-hour-old hatchlings were placed in chambers with soft water from Lake Superior and exposed to benzophenone for 96 hours. The benzophenone was introduced at predetermined sublethal doses which ranged from 0.99 mg/L to 8.28 mg/L. An unspecified number of fathead minnow eggs hatched in "control" water served as the control group. The chambers were exposed to 16 hours of light each day from fluorescent lights. The effect of benzophenone on larval growth was determined by measuring larval lengths. For this procedure, the larvae were decanted from the chambers, immobilized, and photographed. The film negatives were used to measure their lengths. Larval growth was reduced at 2.62 mg/L ( $P < 0.05$ ). Although the authors report that growth was relatively unresponsive to toxicant exposure in terms of percentage reduction, survival was reduced at the highest concentration of benzophenone only [Barron and Adelman, 1984].

- aquatic:

A 96-hour  $LC_{50}$  was determined for benzophenone in fathead minnows (*Pimephales promelas*). Groups of twenty to twenty-five, 30-day-old fish were placed into a total of 12 test tanks with water from Lake Superior. The fish were exposed to 5 different unspecified concentrations (tested in duplicate) of the compound introduced into the tanks by either a proportional diluter system, or by a continuous-flow minidiluter system; control tests were run simultaneously. The fish were not fed during the study and deaths were recorded after 1, 3, 6, 12, 24, 48, 72, and 96 hours. The 96-hour  $LC_{50}$  for benzophenone was determined to be 15.3 mg/L (14.2 mg/L in a duplicate test) [Veith *et al.*, 1983].

**Table 4. Acute LD<sub>50</sub> Data for Benzophenone in Animals.**

<u>Route of Exposure</u>	<u>Species/Strain</u>	<u>No. of Animals per Dose Group</u>	<u>LD<sub>50</sub>/Range (mg/kg)</u>	<u>References</u>
Oral	Rats/NS	NS	>10,000.0	Opdyke, 1973
Oral	Rats/NS	NS	1900.0	Eastman Kodak Company, 1991
Oral	Mice/Swiss	8	2,895.0 (2,441.1-3,433.5)	Caprino <i>et al.</i> , 1976
Oral	Mice/NS	NS	~1600.0	Eastman Kodak Company, 1991
Dermal	Rabbits/NS	NS	3,535.0 (2,007.1-6,226.0)	Opdyke, 1973
Dermal	Guinea Pigs/NS	NS	>1.0 g/kg	Eastman Kodak Company, 1991
Intraperitoneal	Mice/Swiss	8	727.0 (634.3-833.4)	Caprino <i>et al.</i> , 1976

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NS - Not Specified

### C. Prechronic

#### 1. Human Data/Case reports

- **inhalation, humans:**

In the abstract of a German study, it was reported that inhalation of molten benzophenone particles caused purulent bronchitis, allergic asthma, and erythema in an individual pre-disposed to allergies. These particles were detected in the air surrounding pots of molten benzophenone (approximately 85°C) to which the case subject was exposed [Bettink, 1977].

- **dermal, humans:**

The North American Contact Dermatitis Research Group (NACDRG) had previously included benzophenone in its routine patch test series, but no longer routinely includes this compound [Mitchell *et al.*, 1982]. Results from earlier patch testing with benzophenone conducted by the NACDRG are presented in Table 5.

**Table 5. Results of Standard Patch Tests With Benzophenone**

<u>Test Period</u>	<u>Benzophenone Preparation</u>	<u>No. of Patients</u>	<u>Percent Positive</u>
1978-1979	1% in pet	644	1%
1978-1980	1% in pet	547	2%
1/21/1980-4/23/1980	4-5% in pet	147	1.7%

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pet - petrolatum

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Mitchell *et al.*, 1982

- **dermal, humans:**

A case study report concerning phototoxicity among four workers employed by a manufacturer of ultraviolet-cured ink has been described. These workers, whose jobs involved weighing, mixing, or milling of the ink, complained of sun sensitivity (burning and swelling) after exposure to the ink; none of the employees had a history of photosensitivity prior to exposure to the ink. In order to determine which components of the ink might have caused photosensitization, the ultraviolet absorption spectra of all ingredients was determined, and each of the ultraviolet cured ink ingredients that absorbed ultraviolet radiation above 290 nm was evaluated for phototoxicity in Ehrlich ascites cells (see section V.G.4). Benzophenone was found to be one of the components in the ink that was potentially inducing the photosensitivity. Three of the sun sensitive individuals, and four nonsensitized employees were patch tested with benzophenone, and with seven other photoinitiators used in the ink.

Benzophenone and the other components tested were spread evenly on the gauze portion of plastic bandages and applied, in duplicate, to the subjects' backs, and were covered, secured, and occluded under several layers of hypoallergenic tape. After 24 hrs., one set of patches was removed, the skin was rinsed with 70% ethanol and water, then exposed to sunlight. Four subjects were exposed to 25 minutes of sun at noon, and 3 subjects were exposed for 35 minutes at 3:50 pm the same day (the test was conducted during July in Cincinnati). Reactions were observed during sun exposure. Forty-eight hours after application, the second set of patches, which served as the dark control, was removed, rinsed with 70% alcohol, and scored for reactions one hour later. Benzophenone did not cause any reactions on either the exposed or the occluded sites [Emmett *et al.*, 1977].

- **dermal, humans:**

A case report concerning allergic contact dermatitis among 15 employees from a newspaper printing shop where the Letterflex® process is used for the production of printing has been described. The Letterflex ® resin used at the shop was implicated as the cause of symptoms which included general symptoms (conjunctivitis, respiratory disturbances with sneezing and rhinorrhea, or nasal congestion, coughing, dyspnea,

and in one case, an asthma attack) and skin lesions. Benzophenone and an antioxidant comprise approximately 2% of the Letterflex® resin used.

All 15 of the employees were patch tested with the Letterflex® liquid resin, residue resin, exposed dry and wet plates, and new unused plates. Seven of the 15 test subjects had positive patch tests. Four tested positive to the resin, residue, and the finished plate; one was positive to the residue and hardened resin on the finished plate; one subject reacted to the finished plate only; and another subject only reacted positively to the residue and resin. Several months later, five of the seven individuals that had positive reactions were retested with the components of the resin, including benzophenone. No reactions to benzophenone were observed [Calas *et al*, 1977].

## 2. Animal Data

- dermal, guinea pigs:

Five guinea pigs of unspecified strain were tested by Eastman Kodak Company (unpublished data, 1984) to determine allergic skin reaction to benzophenone. None of the guinea pigs exhibited a positive response [USEPA, 1984; Eastman Kodak Company, 1991].

- dermal, guinea pigs:

Groups of 6-8 outbred Himalayan white-spotted guinea pigs of both sexes were used to examine potential skin irritation and contact hypersensitivity induced by benzophenone using 4 different sensitization studies: an open epicutaneous test (OET), the Draize test (DT), the maximization test (MT), and a test with Freund's complete adjuvant (FCAT). Benzophenone did not induce allergenicity in guinea pigs using any of the test procedures (OET, DT, MT, or FCAT). Descriptions of the sensitization protocols are presented below.

*Open epicutaneous test:* For induction, on day zero, 0.1 ml of undiluted and diluted (0.03, 0.1, 0.3, 1.0, 3.0, 10.0, and 30.0%) benzophenone in either acetone, ethanol, diethyl phthalate or another unspecified solvent was applied to an 8-cm<sup>2</sup> area of clipped flank skin of 6-8 guinea pigs per dose group. The application site was left uncovered and reactions were read 24 hours after application. This procedure was repeated daily at the same site for 21 days. No information on controls was provided. The maximum nonirritant and the minimal irritating concentrations were determined using "all or none criteria."<sup>4</sup> The minimum irritating concentration was determined to be 30% following 1 application and 3% after 21 applications. On days 21 and 35, the treated animals and 6-8 untreated animals were challenged, by application to the contralateral flank, with a dose of benzophenone at the minimal irritating concentration and a lower unspecified nonirritant concentration. Each concentration (0.025 ml) was delivered by pipette to an area of the skin measuring 2 cm<sup>2</sup>. The reactions were scored after 24, 48, and/or 72 hours.

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<sup>4</sup> Reactions were read using an "all or none" criterion (*i.e.*, the dose-response curve was established by end-point determination). The minimal irritating concentration was defined as the lowest concentration causing mild erythema in at least 25% of the animals in the particular dose group, and the maximal nonirritant concentration was defined as the highest concentration causing no macroscopically discernable reactions in any of the animals in the group.

*Draize test:* The animals were injected intradermally on day zero with 0.05 mg of 0.1% benzophenone in isotonic saline. The animals were administered nine, 0.1-ml injections of the compound on 9 alternate days (a total dose of 0.95 mg). On days 35 and 49, treated and untreated animals were intradermally challenged with 0.05 ml of 0.1% benzophenone. The evaluation criterion was based on the mean diameter of the papular reactions.

*Maximization test:* On day 0, the test animals were given two intradermal injections of 0.1 ml of a 5% solution of benzophenone, 0.1 ml of a 5% emulsion of benzophenone in Freund's Complete adjuvant (FCA), and 0.1 ml of FCA alone. On the eighth day of the study, an additional 250 mg of benzophenone (final concentration 25%) in petrolatum was applied to a sheared area of the neck and left under an occlusive bandage for 2 days. On day 21, a challenge dose (unspecified subirritant concentration) in petrolatum was applied to the animals' flanks for 24 hours in an occlusive patch test. The reactions were scored 24 and 48 hours post-patch removal.

*Freund's complete adjuvant test:* The test animals were injected intradermally in the neck on days 0, 2, 4, 7, and 9, with 0.5 ml of undiluted compound mixed with the same volume of FCA for a total dose of 250 mg of benzophenone. A group of control animals was treated similarly, receiving five, 0.5-ml injections of FCA, only. All of the animals were challenged on days 21 and 35 with an occlusive patch test as described in the above maximization test.

Although this compound was not found to be a sensitizer by the authors, they report that benzophenone has been reported to be allergenic by another source from which confirmatory data was not provided [Klecak *et al.*, 1977].

- **dermal, guinea pigs:**

The sensitization potential of benzophenone following both intradermal and topical application was determined in a modified Draize test using inbred Hartley strain albino guinea pigs. For the induction, groups of 10 animals (4 males/6 females or 6 males/4 females) were given four, 0.1 ml intradermal injections at 2.5 times the predetermined injection challenge concentration (ICC)<sup>5</sup> (0.25%). Each of the induction injections was given at four different locations overlying the two auxiliary and two inguinal lymph nodes.

After 14 days of nontreatment, the animals were challenged intradermally in one unshaved flank, and topically to the other, with 0.1 ml aliquots of 0.25% (ICC) and 20% (application challenge concentration (ACC)<sup>6</sup>) of the compound, respectively. Twenty-four hours after the challenge, the exposure sites were evaluated for sensitization reactions. Because no sensitization reactions to benzophenone were observed, the induction and challenge procedures were repeated, including

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<sup>5</sup> The ICC used in this study was the concentration of benzophenone that in preliminary experiments, gave slight but perceptible irritation, with no edema 24 hours after administration.

<sup>6</sup> The ACC used was the highest dose at which no irritation was observed, 24 hours after exposure, in preliminary experiments.

confirmatory challenge with controls. Along with the control challenge, 4 previously untreated animals of the same sex as the test animals were given a 0.1-ml intradermal injection of 0.25% benzophenone to one flank, and 0.1 ml of 20% benzophenone was applied topically to the other flank.

No sensitization reactions were observed following the initial challenge and rechallenge in the test animals or the control animals. The authors stated that this compound is not a sensitizer in guinea pigs under these test conditions [Sharp, 1978].

- **dermal, guinea pigs:**

Benzophenone has been tested for its sensitizing capacity in the guinea pig maximization test. Four female Hartley strain guinea pigs were induced with two, 0.05-ml intradermal injections of 1% benzophenone in olive oil, two injections of complete Freund's adjuvant (50% in distilled water), and with two injections of 1% benzophenone suspended in Freund's adjuvant. A control group was also employed, the details of which were not provided. After one week, the animals' fur was shaved, in an unspecified area, and their skin was massaged with sodium lauryl sulfate. Ten percent benzophenone in petrolatum was then applied to the shaved site for 48 hours. After a 2-week nontreatment period, the animals were challenged with 1% (2 animals) and 5% (2 animals) benzophenone in petrolatum. The results were read at 24 and 48 hours. Forty-eight hours after the challenge, biopsies of the animals' skin were performed.

None of the animals was sensitized to benzophenone at either challenge dose. Biopsies of the exposed areas of the animals treated with benzophenone revealed a slight epidermal acanthosis which was not seen in the control animals. The authors state that this finding is due to the action of petrolatum, and not a result of benzophenone treatment. No histopathological abnormalities were observed in the benzophenone treated animals [Calas *et al.*, 1977].

- **aquatic:**

In conjunction with the 96-hour acute toxicity study described in section V.B.3., the effect of benzophenone on the growth of fathead minnows (*Pimephales promelas*) was studied in a 32-day embryo-larval test, beginning with the egg stage. The larval fish were exposed to sublethal doses of benzophenone ranging from 0.99 mg/L to 8.28 mg/L for 32 days. An unspecified number of fathead minnow eggs hatched in control water served as the control group. At the conclusion of the study, the larvae were decanted from test chambers, immobilized, and photographed. Fish lengths were measured from the negatives as a determinant of growth. The weights of the larvae were determined from a subsample of the larvae from each treatment group by preserving the larvae in formalin, drying, and weighing on an electrobalance. In the embryo-larval test, it was determined that the growth in length was reduced at a benzophenone concentration of 1.78 mg/L ( $P < 0.05$ ), and growth in weight was reduced ( $P < 0.05$ ) at the lowest concentration (0.99 mg/L) [Barron and Adelman, 1984].

- **aquatic:**

The effect of benzophenone on embryonic development, survival, and growth of juvenile fathead minnows (*Pimephales promelas*) was studied by Call *et al.* to predict subchronic toxicity. In this 32-day study, groups of 50 fertilized fathead minnow eggs, less than 24 hours old, were placed in each of two egg cups per tank. The tanks were filled with water from Lake Superior and maintained at temperatures ranging from 24.4 - 25.7°C. Benzophenone was introduced into the aquarium via a diluter system each with five concentrations of benzophenone and a control, in duplicate. Benzophenone concentrations were determined by gas-liquid chromatography to be 0.991, 1.76, 3.31, 6.38, and 8.66 mg/L. The egg cups were moved up and down a distance of approximately 5 cm until completion of the hatch (4-5 days). The surviving fry were counted, and 30 were released into the aquarium for the remainder of the study. Fish were fed from the day after hatching to the end of the study (day 32).

At the conclusion of the study, the surviving fish were evaluated for length and weight. Other endpoints included percent hatch, percent abnormal plus dead fry immediately after hatch, and percentage survival of transferred fry. The highest concentration of benzophenone that produced no observable effect (reduced weight) was determined by extrapolation to be 0.54 mg/L, and the lowest concentration that produced an observable effect (reduced weight) was determined to be 0.99 mg/L. Wet weight, which was significantly reduced ( $P \leq 0.01$ ) by all concentrations of benzophenone tested, was determined to be the most sensitive parameter for benzophenone-induced toxicity. A maximum acceptable toxicant concentration estimate of 0.73 mg/L for benzophenone was derived by extrapolation of the wet weight and exposure concentration relationship.

The fish survival rate was found to be a less sensitive endpoint than the wet weight. A significant reduction ( $P \leq 0.05$  or  $P \leq 0.01$  [not specified] ) in survival was observed only at the two highest concentrations of benzophenone tested. The percentage of newly hatched fish that died, or were malformed, was affected at the two highest dose levels of benzophenone ( $P$  values not reported). Embryo hatchability did not differ from controls [Call *et al.*, 1985].

#### D. Chronic/Carcinogenicity

1. Human Data

No data were found in the literature on carcinogenicity or the chronic effects of benzophenone in humans.

2. Animal Data

- **dermal, mice:**

The carcinogenic effect of benzophenone following topical application was studied in female Swiss mice. (Swiss mice were chosen because they are sensitive to skin tumors.) Fifty mice per dose group were administered 0.02 ml doses of 5, 25, or 50% benzophenone in acetone twice weekly for 120 weeks, or until they died spontaneously, or were killed when moribund. The compound was administered on a



1-inch square area on the dorsal skin between the flanks. In addition to the test animals, 135 untreated controls, and 50 acetone-treated and 50 animals dosed with 0.5% 7, 12-dimethylbenzanthracene (DMBA) (positive control) according to the dosing scheme described above for benzophenone were used.

The animals were checked weekly, and all tumors and lesions were recorded. By week 110 of the study, all animals had died. The survival rate of the benzophenone-treated animals was lower than that of the untreated controls and comparable to that of the vehicle controls. Complete autopsies were performed on all animals that died spontaneously or were sacrificed when moribund and the skin, grossly observed tumors, and any lesions observed in the lungs, kidneys, and other organs were studied histologically.

Benzophenone did not produce a significant increase in the incidence of skin tumors compared to both the treated and untreated controls. Three benzophenone treated animals were observed to have skin tumors; 1 had a tumor on the lip (25% benzophenone) and 2 had dorsal skin tumors (5% benzophenone). Histological examination of these tumors indicated that the lip tumor was a squamous cell carcinoma and the dorsal skin tumors were both squamous cell papillomas.

The authors concluded that benzophenone was not carcinogenic in this test system [Stenbäck and Shubik, 1974].

- **dermal, rabbits:**

The local and systemic effects from chronic exposure to benzophenone following topical application were studied using New Zealand rabbits. Three groups of five rabbits (both sexes) which were 8 weeks old at the start of the experiment were given doses of benzophenone, dissolved in either acetone or methanol (not specified), twice weekly for 160 weeks, at concentrations of 5.0, 25.0, or 50.0% in a volume of 0.02 mL. The solution was applied to the inside of the animals' left ear. In addition, 14 untreated controls and 15 positive controls (9, 10-dimethyl-benz(a)anthracene-treated (DMBA)) were used. Solvent controls were not included. The animals were examined weekly for local effects and survival rates, both of these parameters were recorded.

During the 160-week study, no treatment-related decrease in survival rates or local changes attributable to exposure to benzophenone were observed. At the conclusion of the study, animals were autopsied. The skin, lungs, livers, kidneys, and other unspecified organs were examined histologically for gross tumors and other lesions. No tumors or lesions were observed in the benzophenone treated animals. Animals in the positive control group had ear tumors. The authors stated that the results presented in this study indicate a lack of toxicity and carcinogenicity from topically applied benzophenone. The authors reported that although the rabbits used were sensitive to dermal treatment, several considerations must be taken into account when interpreting results: anatomical structure of skin, epidermal thickness, cyclical hair growth pattern, absence of sweat glands, or penetration of the compound. The authors also noted that the total dose of the compound may have been too small. The authors further stated that more studies are necessary to evaluate the toxicity and carcinogenicity of compounds, such as benzophenone, that are used topically [Stenbäck, 1977].

## E. Reproductive Effects and Teratogenicity

### 1. Human Data

No information was found in the literature on the reproductive or teratogenic effects of benzophenone in humans.

### 2. Animal Data

- dermal, newts:

The effects of two potential carcinogens, 20-methylcholanthrene (MC) and benzo(a)pyrene (BP), on limb regeneration were studied in adult newts. The effects of benzophenone and other noncarcinogenic benzocompounds were also studied and compared to those of MC and BP. The forelimbs of an unspecified number of adult Japanese newts (*Cynops {Triturus} pyrrhogaster*) were amputated at a position proximal to the elbow. Seven days later, about 5 µg of the compounds, including benzophenone, were directly inserted in the anterior part of the regeneration blastema. MP and BP microcrystals were inserted into the dorsodistal portion of the elbow underneath the epidermis of the normal intact limb for the control tests. The animals were kept in aquariums until their limbs had completely regenerated (about 5 months).

On completion of regeneration, the limbs were examined histologically. Of the 10 limbs examined after administration of benzophenone exposure, 9 were found to have regenerated normally and 1 had abnormalities in carpals, metacarpals, or phalanges. No other effects such as those observed following exposure to MC and BP (e.g., absence of ulna or radius, multiple abnormalities, accessory limbs) were observed. There was no retardation of regeneration, and growth continued normally in the group treated with benzophenone. In the control groups, 1 out of 20 newts that received MC or BP were observed to have thickening of the epidermis and proliferation [Tsonis and Eguchi, 1982].

- aquatic:

In a subchronic toxicity study (see section VC.2.), conducted using fathead minnow (*Pimephales promelas*) embryos, larvae, and juveniles, benzophenone (6.38 and 8.66 mg/L) was found to affect (P value not specified) the percentage of newly hatched fish that died or were malformed. However, embryo hatchability in the treated group did not differ from controls. No other data were provided [Call *et al.*, 1985].

## F. Genetic Toxicology

### 1. Human Data

No information was found in the literature on the mutagenic effects of benzophenone in humans.

## 2. Prokaryotic Data

- *Salmonella typhimurium*:

The mutagenic effects of benzophenone were determined in the standard Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, and TA100 with or without metabolic activation. Benzophenone at concentrations of 0.0, 3.0, 10.0, 33.0, 100.0, 166.0, 333.0 and 1000.0 µg/plate in dimethyl sulfoxide were tested. The authors concluded that benzophenone was nonmutagenic in all strains of *Salmonella* with and without activation [Mortelmans *et al.*, 1986].

- *Salmonella typhimurium*:

In the Ames test, the mutagenic effects of benzophenone were tested in *Salmonella typhimurium* strains TA1537, TA1535, TA100, and TA98 without activation and in the presence of Arochlor 1254-induced S-9 rat and hamster liver metabolic activation. Benzophenone was tested at doses of 10.0-2,000.0 µg/plate. This compound was found to be nonmutagenic in all strains of *Salmonella* tested with and without activation [CCRIS, 1991].

- *Salmonella typhimurium*:

In a study conducted by the Upjohn Company (unpublished, 1984), the mutagenicity of unspecified concentrations of benzophenone was tested using *Salmonella typhimurium* strains TA100, TA98, and TA1537 with and without activation. Benzophenone was found to be nonmutagenic in all strains of *Salmonella* under all test conditions [USEPA, 1984].

- *Escherichia coli*:

Benzophenone (500 µg/well) was negative in the *Escherichiacoli* (strain P3478) pol A assay in the presence and absence of activation. However, the authors reported that this assay is not adequate for prescreening compounds for carcinogenic activity as many confirmed carcinogens that were also tested were also negative [Fluck *et al.*, 1976].

- *Escherichia coli*:

In a 1988 study conducted as part of the EPA Genetox program, benzophenone was found to be negative in the *E.coli* pol A assay without activation [RTECS, 1990].

## 2. Eukaryotic Data

- *mouse lymphoma cells*:

The genotoxicity of benzophenone was tested with metabolic activation in mouse lymphoma cells, strain L5178Y (TK+/TK-), at concentrations of 35.0-145.0 µg/mL. Benzophenone was not found to be genotoxic under the test conditions. In addition, benzophenone was tested at concentrations of 33.0-90.0 µg/mL in the absence of activation, and found to be nongenotoxic [CCRIS, 1991].

## G. Other Toxicological Effects

### 1. Immunotoxicity

No data were found in the literature on the immunotoxic effects of benzophenone.

### 2. Neurotoxicity

No data were found in the literature on the neurotoxic effects of benzophenone.

### 3. Biochemical Toxicology

- *aquatic toxicity:*

The effects of sublethal doses of benzophenone on macromolecular content in fathead minnows (*Pimephales promelas*) were determined as part of an acute 96-hour toxicity study described in section VB.3. Twenty-four-hour-old hatchlings were divided into groups of 25-35 and placed in chambers for 96 hours with soft water from Lake Superior with sublethal doses of benzophenone ranging from 0.99 mg/L to 8.28 mg/L. An unspecified number of fathead minnow eggs hatched in control water were used as a control group. Fluorescent lights provided 16 hours of light each day. At the conclusion of the study, 8-15 larvae per treatment dose were placed in an aluminum packet and then immediately frozen in liquid nitrogen. Tissue samples were stored at -80°C until analysis. The frozen larvae were analyzed for average quantity of RNA, DNA and protein per whole larva, ratios of macromolecular content, and tissue concentration.

The RNA and protein content were reduced ( $P < 0.05$ ) at 5.15 mg/L, while DNA content was reduced at 8.28 mg/L ( $P < 0.05$ ). The RNA/DNA and protein/DNA were reduced at 5.15 mg/L ( $P < 0.05$ ) and RNA/protein was reduced at 8.28 mg/L ( $P < 0.05$ ). The authors report that the decreased DNA content indicated that benzophenone-exposed fish had fewer cells and thus had experienced reduced growth rates, probably resulting from mitotic suppression. The lack of an increased protein/DNA ratio reportedly was indicative of an absence of toxicant-induced hypertrophy. The reduced RNA content per larva, with concomitant protein and DNA reductions, indicated that benzophenone-exposed larva had a reduced net rate of protein synthesis, most likely mediated through declines in RNA [Barron and Adelman, 1984].

### 4. In Vitro Studies

- *Escherichia coli:*

The ability of benzophenone to induce thymine dimers and single chain breaks in photosensitized DNA has been studied by Charlier *et al.* The production of chain breaks in benzophenone sensitized DNA upon irradiation at wavelengths of approximately 295 nm was confirmed based on the observation of the variation in the sedimentation coefficient of calf thymus DNA with the duration of irradiation in the presence of  $15 \times 10^{-4}$  M benzophenone. In addition, chain break production, based on sedimentation patterns obtained from alkaline sucrose gradients of *E. coli* DNA

irradiated in the presence of  $2 \times 10^{-4}$  benzophenone at wavelengths greater than 300 nm, was also observed. Chain breakage was also confirmed in the single-stranded polyribonucleotide, poly rA by observation of the variation in the sedimentation coefficient with the duration of irradiation. The number of chain breaks was estimated using the relationship described in footnote 7.

The relative production of single and double chain breaks was determined from measurements of sedimentation coefficients in neutral and alkaline conditions. The yield of single-chain breaks was found to be approximately six times higher than that of double stranded chain breaks. The yield of chain breaks produced in DNA by benzophenone photosensitization was found to depend on the oxygen content of the solution, with the rate of break production being increased when oxygen is removed from the solution.

The relative amount of dimers and single-strand breaks was determined as a function of the irradiation time for *E. coli* DNA in the presence of  $2 \times 10^{-4}$  M benzophenone. The number of dimers per chain was calculated on the basis of a number-average molecular weight of  $6 \times 10^6$  daltons. The number of breaks and dimers formed during irradiation increased linearly with dose at low doses. The authors reported that approximately one dimer was produced per single stranded break.

Damage to deoxyribose residues was detected by reaction of the degradation product (malonic aldehyde) with 2-thiobarbituric (TBA). To investigate the oxygen effect of photosensitized reactions, solutions were aerated by bubbling argon for 1 hour before and during irradiation. The addition of TBA to the irradiated mixture of benzophenone and DNA lead to the appearance of an absorption peak at 532 nm. The unirradiated mixture of benzophenone and DNA, or benzophenone irradiated alone, did not give any absorption peak at 532 nm in the presence of TBA. Therefore, the authors reported that it is likely that the benzophenone photosensitized production of malonic aldehyde results from damage to the deoxyribose residues of DNA. The reaction with TBA is observed when the benzophenone-DNA mixture is irradiated in the absence, as well as the presence, of oxygen.

The authors report that based on these and previous reports that excitation of benzophenone in aqueous solution produces ketyl and hydroxyl radicals, the hydroxyl radical probably induced the chain breaks observed. Since hydroxyl radicals are not quenched by oxygen, the oxygen effect can be attributed to further reactions with oxygen of primary radicals formed in DNA after attack by hydroxyl radicals [Charlier *et al.*, 1972].

- **Escherichia coli:**

The effect of benzophenone on the formation of chain breaks and thymine dimers in DNA upon photosensitization was studied using radiolabelled (tritium or carbon-14) DNA isolated from *Escherichia coli* strain B(3)T<sup>-</sup>. Samples with DNA and benzophenone were irradiated at 313 nm for an unspecified time. The concentration of benzophenone used ( $0.10 \text{ A}$ ) was based on its absorbance at 313 nm. Nitrogen was bubbled through the solution for 15 minutes prior to irradiation to remove oxygen when desired. A flow rate of 30 mL/min resulted in maximal deoxygenation in 15 minutes based on the maximum rate of thymine dimerization achieved. The number of chain breaks in the irradiated DNA, which was sedimented in a sucrose gradient,

was determined from the number-average molecular weight ( $M_n$ ).<sup>7</sup> Photodimer yields were determined following acid hydrolysis and paper chromatography of the irradiated DNA, and the number of thymine dimers per  $10^6$  daltons was calculated assuming that 1/4 of the bases were thymine.

It was determined that the number of chain breaks varied in a linear fashion with the concentration of thymine dimers for triplet sensitization in either the presence or absence of oxygen. The thymine dimer yield (expressed as the % thymine as thymine dimer) upon photosensitization with benzophenone was found to be approximately 0.5 in the presence of oxygen and 2-3 in the absence of oxygen. The number of chain breaks per dimer for the triplet sensitization of DNA in the presence of benzophenone was 0.33 and 0.12 with and without oxygen, respectively [Rahn *et al.*, 1974].

- **Ehrlich ascites cells:**

The phototoxicity of benzophenone was tested *in vitro* using Ehrlich ascites cells. The cells were harvested from a mouse 8-10 days after implantation and stained with trypan blue to ensure that the cells used were viable. Four sets (A, B, C, and D), each comprising two cell suspensions, were incubated in the dark for 2 hours. Two sets (A and B) contained  $5 \times 10^{-5}$  M benzophenone in Ringer's solution; the control sets (C and D) had Ringer's solution only. One cell suspension from sets A and C was irradiated for 10 minutes, and the second set of cell suspensions from A and C was irradiated for 1 hour. The percentage of dead cells in each sample was determined 24-hours later by staining with nonvital trypan blue.

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The mean and variance were calculated for the 4% counts obtained from each set of results. In this way, it could be determined whether an interaction between the irradiation and benzophenone had occurred. The phototoxicity assay was recorded as positive when a statistically significant ( $P < 0.05$ ) interaction between irradiation and the benzophenone was observed. Benzophenone was not found to be phototoxic following irradiation [Emmett *et al.*, 1977].

- **rabbit liver fractions:**

The reduction of ketones, including benzophenone, was studied *in vitro* using preparations of rabbit (male New Zealand White) liver fractions. An 8 mM dose of benzophenone in 0.1 ml of dimethylformamide was incubated with a 9000-gram supernatant fraction of rabbit liver in the presence of an NADP-generating system. Twenty percent of the benzophenone was reduced to benzhydrol in one hour. The authors state that the remaining activity likely depends upon residual pyridine nucleotide in the preparation. The authors conclude that ketones, including benzophenone, may be reduced in other tissues besides the liver, but that the largest reduction occurs in the cytosol [Leibman, 1971].

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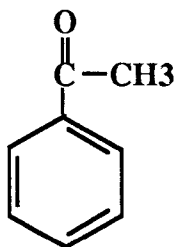
<sup>7</sup> The number-average molecular weight is determined using the following equation:

$$\text{number of chain breaks per initial strand} = \frac{M_n(\text{initial})}{M_n(\text{final})} - 1$$

## VI. STRUCTURE ACTIVITY RELATIONSHIPS

Benzophenone is structurally related to acetophenone (see Figure 1). No effects on growth, hematological parameters, or macroscopic tissue changes were observed in groups of 10 male and 10 female Osborne-Mendel rats exposed to 0, 1000, 2500, and 10,000 ppm acetophenone in the diet for 17 weeks. Microscopic examination of the 10,000 ppm group revealed no effects [IRIS, 1991]. Acetophenone was found to be negative in the *Escherichia coli* polA assay with and without activation in a 1988 study conducted as part of the EPA genotox program [RTECS, 1991]. This compound was also negative when tested in *Salmonella typhimurium* strains TA97 and TA102 with and without activation [CCRIS, 1991]. Acetophenone was reportedly found to be genotoxic to cultured hamster lung cells [RTECS, 1991]. No data were found on the carcinogenicity of acetophenone [RTECS, 1991; Cancerlit, 1991; CCRIS, 1991]. The Integrated Risk Information System file also reports that no carcinogenicity studies could be located in the available literature [IRIS, 1991].

Figure 1. Acetophenone



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## APPENDIX I. ON-LINE DATABASES SEARCHED

	<u>DATE OF SEARCH</u>	<u>TIME PERIOD</u>
<b>BRS:</b>		
HZDB	February, 1991	
<b>CIS:</b>		
TSCAPP (TSCA Plant and Production Search System)	February, 1991	
<b>DIALOG:</b>		
Analytical Abstracts Online	February, 1991	1980-1991
CA Search	February, 1991	
Chem Bus Newsbase	February, 1991	1984-1991
Chem Regs and Guidelines	February, 1991	1982-1990
Chem Saf Newsbase	February, 1991	1984-1990
Chemsearch	February, 1991	
Claims/US Patents Abs	February, 1991	
Embase	February, 1991	1982-1991
Fine Chemicals Database	February, 1991	
Heilbron	February, 1991	1989-1991
Int'l Pharm Abstracts	February, 1991	1970-1991
Kirk-Othmer Enc Chem Tech	February, 1991	
Medline	February, 1991	1966-1991
Merck Index Online	February, 1991	
Occupational Safety and Health	February, 1991	1973-1991
Toxline	February, 1991	1965-1991
TSCA Chem Sub Inv	February, 1991	
<b>MEAD:</b>		
Lexis Gen Fed; CFR	February, 1991	
<b>NLM:</b>		
Chemid	February, 1991	
Chemline	February, 1991	
CCRIS	February, 1991	
Eticback	February, 1991	1950-1989
Emicback	February, 1991	1950-1991
RTECS	February, 1991	
Toxline 65	February, 1991	1965-1980
Toxline	February, 1991	1981-1990
Toxlit	February, 1991	1981-1991
Toxlit 65	February, 1991	1965-1980
<b>STN:</b>		
Beilstein	February, 1991	1979-1991
CA	February, 1991	1967-1990
CAPreviews	February, 1991	
Chemlist	February, 1991	1979-1991

	<u>DATE OF SEARCH (Cont)</u>	<u>TIME PERIOD (Cont)</u>
CSchem	February, 1991	
Registry	February, 1991	

## APPENDIX II. SAFETY INFORMATION

- **HANDLING AND STORAGE**

Benzophenone is stable under normal laboratory conditions. It may be an irritant to the skin, eyes, mucuous membranes, and upper respiratory tract [Lenga, 1988; Aldrich, 1990]. This compound should be stored in a tightly closed container in a cold, dry, well-ventilated area away from heat, sparks, and flame [J.T. Baker, 1990]. Benzophenone is photochemically reactive and its decomposition may produce toxic fumes of carbon monoxide and carbon dioxide. Benzophenone may attack some plastics [U.S. Coast Guard, 1985].

- **EMERGENCY FIRST AID PROCEDURES**

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently was affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.



- **PROTECTIVE EQUIPMENT**

Eye: Safety goggles

Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or the NTP Health and Safety Minimum Requirements.

Respiratory Protection: A NIOSH-approved chemical cartridge respirator with an organic vapor and high-efficiency particulate filter cartridge.

- **EXTINGUISHANT**

Dry chemical, carbon dioxide or halon extinguisher.

- **MONITORING PROCEDURES**

There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for benzophenone.

- **SPILLS AND LEAKAGE**

Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

If benzophenone is spilled the following steps shall be taken:

1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.
2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.
3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.
4. Dispose of all absorbed material as hazardous waste.

- **DECONTAMINATION OF LABORATORY EQUIPMENT**

TDMS Terminal: Whenever feasible, a protective covering (e.g., plastic wrap) shall be placed over the keyboard when in use.

General Equipment: Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

- **WASTE MANAGEMENT AND DISPOSAL PROCEDURES**

Waste Management: If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemicals in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.

Waste Disposal: Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.

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