BENZOPHENONE

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Published: 1991
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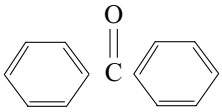
I. IDENTIFICATION

Chemical Name: Benzophenone
Synonyms: Benzoylbenzene; Diphenyl ketone; Diphenylmethanone; Phenyl ketone
CAS Number: 119–61–9
Molecular Formula: $C_{13}H_{10}O$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1-7]

Physical State: White, flaked/crystalline solid
Molecular Weight: 182.22
Conversion Factors: 1.0 ppm = 7.45 mg/m^3
1.0 mg/m^3 = 0.134 ppm
Melting Point: 48.1°C (119°F) for α crystalline form (rhombic); 26°C (79°F) for ß crystalline form (monoclinic)
Boiling Point: 305.9°C (583°F) at 760 mm Hg
Vapor Pressure: 0.006 mm Hg at 48°C (119°F)
Note: vapor pressure data below melting point not available
Saturated Vapor Concentration: 7 ppm at 48°C (119°F)
Odor Description and Threshold: Rose-like odor (odor threshold not available)
Flammability Limits: Not available
Flash Point: 579°C (1075°F)
Autoignition Temperature: Not available
Specific Gravity: 1.1 at 4°C (39°F)
Solubility in Water: negligible
Stability: Stable
Reactivity and Incompatibilities: Incompatible with oxidizers, alkalis and reducing agents

III. USES[6,8-9]

Benzophenone is used primarily as an intermediate in manufacturing other organic compounds such as ultraviolet absorbers, pesticides and pharmaceuticals. It is also used as a flavoring additive, as an odor fixative in cosmetics/perfumes, and as a polymerization inhibitor. Benzophenone also occurs naturally in some foods.

IV. TOXICOLOGY DATA

A. Acute Toxicity and Irritancy

1. Oral

Rat: LD_{50}: >10,000 mg/kg[10]
Rat (male): LD_{50}: 1,900 mg/kg[11]
Mouse: LD_{50}: 2,895 mg/kg[12]
Mouse: LD_{50}: 1,600 mg/kg[11]

2. Eye

Several crystals placed in the conjunctival sac of rabbits (3 washed; 3 unwashed) produced slight irritation[11]

3. Skin

a. Absorption

Rabbit: LD_{50}: 3,535 mg/kg[10]

Rhesus Monkey: Percutaneous absorption reported to be 44% and 69% for non-occluded and occluded sites, respectively (duration of exposure not specified)[8]

b. Irritation

Rabbit: Application of 20% solution of benzophenone in olive oil resulted in generally slight irritation, but with 1 of 6 animals demonstrating moderate irritation and another 1 of 6 demonstrating intense irritation.[13]

Guinea pig: Moistened solid held in contact to the depilated abdomen of guinea pigs under an occlusive wrap for 24 hours produced slight skin irritation.[11]

c. Sensitization

Benzophenone did not produce sensitization when tested in guinea pigs, using the

Magnusson & Kligman maximization test method.[13]

Benzophenone did not produce sensitization in guinea pigs, when tested by a modified Draize procedure.[14]

4. *Inhalation: No data available*

5. *Other*

Benzophenone did not demonstrate phototoxicity in a screening test for photosensitization using *Erlich ascites* cells *in vitro*.[15]

Mouse: Intraperitoneal; LD_{50}: 727 mg/kg[12]

B. Mutagenicity/Genotoxicity

Benzophenone was not mutagenic in an "Ames Test" using *S. typhimurium* TA1535, TA1537, TA97, TA-98 or TA-100, with and without S-9 activation.[8,16]

Benzophenone did not induce micronuclei in the mouse bone marrow erythrocyte test.[8]

C. Metabolism and Pharmacokinetics

In rabbits, benzophenone is primarily metabolized by reduction of the keto group to yield benzhydrol. About half the administered dose was excreted in the urine.[8]

D. Developmental / Reproductive Toxicity

No data available.

E. Subacute

Guinea pigs were given benzophenone via intraperitoneal injection at 5 mg/kg-day for 15 days. Upon examination at sacrifice, liver changes similar to those caused by chronic hepatitis were observed. The number of animals in the treatment and control groups was not specified.[17]

F. Subchronic Toxicity

Rats were given benzophenone mixed in their feed for periods of either 28 or 90 days. Nominal doses of 0, 20, 100 or 500 mg/kg-day were studied, with 10 to 32 animals of each sex per exposure level. All mid and high dose animals were sacrificed and examined at the end of the first 4 weeks. Half of the control and half of the low dose animals were also sacrificed and examined at 4 weeks. Besides monitoring growth, the animals were observed daily for behavior. Hematology, blood chemistry, and urinalysis tests were performed on all animals just prior to sacrifice. The test animals were also examined for gross and microscopic histopathology. Animals at 100 and 500 mg/kg-day experienced significantly lower weight gains than control animals. There was a slight but significant decrease in hemoglobin in the high dose animals at 4 weeks. There were some significant changes in blood chemistry at 4 weeks, particularly in the mid and high dose animals. In the low dose animals, the only significant difference in clinical chemistry analyses at 4 weeks was increased albumin. There were no significant clinical chemistry differences between exposed and control animals at 13 weeks. Increased organ weights for liver and kidney were observed in mid and high dose animals, but not at 20 mg/kg-day. Changes in the liver (hepatocyte hypertrophy) of the mid and high dose animals were observed upon histopathological examination. Histopathological examination of low dose animals did not indicate any significant differences from controls at either 28 or 90 days. The authors conclude that, under conditions of this study, 20 mg/kg-day was a No Observed Adverse Effect Level.[9]

Mice and rats were exposed to benzophenone via incorporation into their feed at various levels for 14 weeks. There were ten animals per exposure group, with concentrations in the feed of 0; 1,250; 2,500; 5,000; 10,000 or 20,000 ppm. The primary objective of the study was to determine the maximum tolerated dose for a carcinogenicity bioassay to be performed subsequently. The exposure levels were calculated by the authors to represent average daily doses, in mg/kg-day, as shown in Table 1.

At the highest dose level, the feed was unpalatable to rats and these animals had to be terminated prior to the end of the study for humane reasons. Mortality in the high dose mice was 100% in males and 40% in females. The NOAEL level for

TABLE 1

Benzophenone in Feed	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male Mice	0	200	400	800	1,600	3,300
Female Mice	0	270	540	1,000	1,900	4,200
Male Rats	0	75	150	300	700	850
Female Rats	0	80	160	300	700	1,000

impaired weight gain was 1250 ppm in all cases, except for female rats where no NOAEL was demonstrated (even the lowest exposure group, 75 mg/kg-day, was adversely affected). The animals were examined for hematology and blood chemistry. Gross and microscopic histopathological examinations were performed upon sacrifice. Various abnormalities were observed, and the authors concluded that the primary target organ was the liver, with a lesser impact on the kidneys. A NOAEL for liver and kidney effects was not demonstrated by the results of this study. The authors also concluded that benzophenone induces cytochrome $P_{450}2b$, which NTP cites as positively correlated with potential hepatocarcinogenicity in other compounds tested.[8]

G. Chronic Toxicity and Carcinogenicity

Rabbits and mice were exposed to benzophenone to determine the potential to induce cancer via dermal contact. There were five rabbits per exposure group. Each rabbit was exposed by applying 0.02 ml of test solution to the inside of one ear twice per week for the life of the animals. Mice were exposed by dropping 0.02ml of test solution to a shaved area between the shoulders, also twice per week for the life of the animals. Test solutions of 5%, 25% and 50% benzophenone (in acetone or methanol, which is not specified) were used. In addition to examination of the skin, all other grossly observed lesions of internal organs were studied histlogically. None of the rabbits developed tumors. Three skin tumors occurred in the treated mice, but the authors concluded that the treated mice did not develop tumors to an extent statistically different than controls.[18-19]

V. HUMAN USE AND EXPERIENCE

One study reported on efforts to determine the source of photosensitization of workers in a printing operation using ultraviolet cured inks. Patch testing of three sensitized workers and four asymptomatic workers demonstrated that none were sensitized to benzophenone, although it was one of the main components in the materials to which the workers were exposed.[15]

In another test, 25 volunteers were tested using a maximization protocol to evaluate the sensitization potential of benzophenone. The test material was applied as 6% solution in petrolatum.. There were no reactions. [10]

In a series of air samples performed in a rubber manufacturing facility, benzophenone was detectable in only 1 of 35 samples, and this was at 0.1 micrograms per cubic meter. Toxicity, if any, associated with conditions prevalent at the time of sampling, was not reported.[20]

VI. RATIONALE

Both of the subchronic feeding studies available for benzophenone indicate liver injury in experimental animals. The one which explored lower doses indicated a No Observed Adverse Effect Level (NOAEL) of 20 mg/kg-day. No inhalation or chronic oral data are available.

Acute toxicity is low. The low order of acute dermal toxicity testing indicates that dermal absorption is not an important route of exposure for the workplace.

Limited data indicate that benzophenone is not genotoxic. Tests also indicate that it is not a sensitizer.

Therefore, the best basis available for the OEL would be the NOAEL observed in the subchronic feeding studies. In deriving a safety factor for the recommended OEL, consideration is given to interspecies differences, differences in route of exposure, extrapolation from subchronic data, variability in worker susceptibility and the fact that the effect on the target organ appears to be serious and possibly irreversible.

Vapor pressure data, while limited, indicates that essentially all benzophenone in the workplace at concentrations of interest would be in particulate form.

VII. RECOMMENDED OEL

8-hour Time-Weighted Average (TWA): 0.5 mg/m^3

VIII. REFERENCES

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