



**National Toxicology Program**  
Toxicity Report Series  
Number 61

**NTP Technical Report  
on the Toxicity Studies of**

**Benzophenone**

(CAS No. 119-61-9)

**Administered in Feed  
to F344/N Rats and B6C3F<sub>1</sub> Mice**

**April 2000**

**U.S. Department of Health and Human Services  
Public Health Service  
National Institutes of Health**

## FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Toxicity Study Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Toxicity Study Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's toxic potential.

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**April 2000**

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**U.S. Department of Health and Human Services  
Public Health Service  
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## **PEER REVIEW**

The draft report on the toxicity studies of benzophenone was evaluated by the reviewers listed below. These reviewers serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determine if the design and conditions of these NTP studies are appropriate and ensure that the Toxicity Study Report presents the experimental results and conclusions fully and clearly.

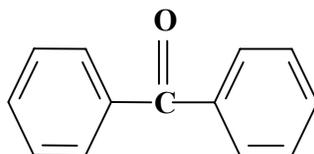
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## ABSTRACT



### BENZOPHENONE

CAS No. 119-61-9

Chemical Formula:  $C_{13}H_{10}O$       Molecular Weight: 182.22

**Synonyms:** Benzene, benzophenone (8CI); benzoyl; benzoylbenzene; benzoylbenzenophenyl; diphenyl ketone; diphenylmethanone; methanone, diphenyl-(9CI);  $\alpha$ -oxodiphenylmethane;  $\alpha$ -oxoditane; phenyl ketone

Benzophenone is used as a photoinitiator, a fragrance enhancer, an ultraviolet curing agent, and, occasionally, as a flavor ingredient; it is also used in the manufacture of insecticides, agricultural chemicals, and pharmaceuticals and is an additive for plastics, coatings, and adhesives. In 14-week studies conducted to determine the toxicity of benzophenone, groups of 10 male and 10 female F344/N rats and B6C3F<sub>1</sub> mice were given 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm benzophenone in feed. These exposure concentrations resulted in the following average daily doses: 75, 150, 300, 700, or 850 mg benzophenone per kilogram body weight for male rats; 80, 160, 300, 700, or 1,000 mg/kg for female rats; 200, 400, 800, 1,600, or 3,300 mg/kg for male mice; and 270, 540, 1,000, 1,900, or 4,200 mg/kg for female mice. Animals were evaluated for clinical pathology, reproductive system effects, liver cytochrome P<sub>450</sub> effects, and histopathology. Genetic toxicity studies were conducted in *Salmonella typhimurium* and mouse bone marrow polychromatic erythrocytes.

Benzophenone was unpalatable at 20,000 ppm. All 20,000 ppm rats had significant body weight loss and were terminated for humane reasons before the end of studies. All male mice and four female mice in the 20,000 ppm group died. There was no exposure-related mortality in the remaining groups. Significantly decreased body weights relative to the controls were observed in all exposed groups of female rats and all exposed groups of male rats except the 1,250 ppm group. Lower body weights were apparent in 10,000 ppm male mice and in 5,000 ppm or greater female mice.

In rats, the liver and kidney were identified as target organs of benzophenone toxicity. Treatment-related increases in liver weights were attributed to hypertrophy and/or cytoplasmic vacuolization of hepatocytes. Increased kidney weights were associated with a spectrum of renal changes in exposed males and females. Unique lesions observed in animals that died early as well as in survivors were well demarcated, wedge-shaped areas of prominent tubule dilatation. The lesion occurred in 2,500 ppm or greater males and in 10,000 and 20,000 ppm females. Foci of tubule regeneration were increased relative to the controls in exposed males and females.

In exposed mice, significant microscopic findings were limited to centrilobular hypertrophy in the liver that corresponded to increased liver weights. The severity of hepatocyte hypertrophy was exposure-concentration dependent, with marked severity in all 20,000 ppm animals.

Clinical chemistry analyses confirmed liver toxicity. In rats, increases in serum bile salt concentrations indicated cholestatic liver disease. On day 22, a 15-fold increase was evident in the 20,000 ppm groups, and at week 14, a twofold increase was seen in the 10,000 ppm groups. Increases in alanine aminotransferase and sorbitol dehydrogenase activities were mild in mice; however, more convincing of liver damage were increased alkaline phosphatase activities and serum bile salt concentrations, especially in 20,000 ppm females.

Biochemical data indicated that benzophenone was a relatively potent inducer of the phenobarbital-type (2B) cytochrome P<sub>450</sub> enzymes. Overall, induction was greater in rats than in mice. The gross (increased organ weights) and microscopic (hepatocellular hypertrophy) liver changes associated with benzophenone administration in rats and mice accompanied benzophenone-induced increases in pentoxyresorufin dealkylase activity.

Benzophenone was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 activation, and it did not induce micronuclei in bone marrow erythrocytes of male mice administered benzophenone by intraperitoneal injection.

In conclusion, the liver is the primary target organ of benzophenone toxicity in rats and mice based on increases in liver weights, hepatocellular hypertrophy, clinical chemistry changes, and induction of liver microsomal cytochrome P<sub>450</sub> 2B isomer. The kidney was also identified as a target organ of benzophenone toxicity in rats only, based on exposure concentration-related increases in kidney weights and microscopic changes. The no-observed-adverse-effect level for benzophenone was not achieved in these studies.