Acetophenone

Document History
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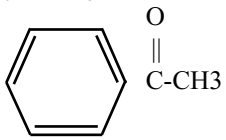
I. IDENTIFICATION

Chemical Name: Acetophenone
Synonyms: Methyl phenyl ketone, acetyl benzene, benzoyl methide, hypnone, 1-phenylethanone
CAS Number: 98-86-2
Molecular Formula: $C_6H_5COCH_3$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–8]

Note: Range is given where literature cites various values

Physical State and Appearance: Colorless liquid
Odor Description: Sweet floral (variously described as "orange blossom," "almond," etc.)
Odor Threshold: 0.2-0.6 ppm
Molecular Weight: 120.15
Conversion Factors: 1.0 ppm = 4.91 mg/m^3
1.0 mg/m^3 = 0.20 ppm
Melting Point: 19.7-20.5°C (67.5-68.9°F)
Boiling Point: 198-204°C (388-399°F) at 760 mm Hg
Vapor Pressure: 0.3-0.4 mm Hg at 25°C (77°F)
Saturated Vapor Concentration: 400-500 ppm at 25°C (77°F)
Flammability Limits: LEL: 1.4% in air; UEL: 5.2% in air
Flash Point (closed cup): 77-82°C (171-180°F)
Autoignition Temperature: 571°C (1060°F)
Specific Gravity: 1.02 at 25°C (77°F)
Solubility in Water: 0.55% by weight
Stability: Stable
Reactivity and Incompatibilities: Strong oxidizers
Partition Coefficient (log$K_{o/w}$): 1.58

III. USES:

Primary use is as a flavoring agent or fragrance in a wide variety of commercial products. Also used as a solvent and as an intermediate for production of pharmaceuticals and other compounds.[4]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

LD_{50}: rat: 815-3200 mg/kg[1,7,9–11]

LD_{50}: Mouse: 740 mg/kg[7]

2. *Eye Irritation*

Rabbit: Severe necrosis was caused by 0.005 mL of 15% solution in propylene glycol. A 5% solution resulted in somewhat lesser effect. Eyes were unwashed, and lids were retracted for one minute post instillation.[12]

Rabbit: Eyes were instilled with pure acetophenone, and then irrigated with water after two minutes. This was observed to cause no more than transient irregularity of the corneal epithelium. The eyes appeared normal within 24 hours.[13]

Rabbit: Application of two drops of saturated aqueous solution caused discomfort despite prior application of anesthetic drops. However, the eyes appeared normal within one-half hour, even though not rinsed or medicated.[13]

3. *Skin Absorption*

LD_{50}: Rabbit: 15,900 mg/kg[7]

LD_{50}: Rabbit: >20,000 mg/kg[9]

Mouse: All mice died when exposed by immersion of the tail in pure acetophenone for 4 continuous hours. The authors conclude that acetophenone is readily absorbed percutaneously.[14]

4. *Skin Irritation*

Rabbit: 515 mg applied without occlusion resulted in mild irritation.[1]

Rabbit: When held in contact with the skin for

24 hours, produced an effect described as a "mild burn."[14]

5. Skin Sensitization

Guinea pig: In a test to evaluate potential to induce dermal sensitization, utilizing a modified Draize procedure, acetophenone did not induce sensitization.[15]

6. Inhalation Toxicity

Rat: No deaths in animals exposed to saturated atmosphere for 8 hours; (concentration presumed to be 400–500 ppm, based upon vapor pressure)[9]

Mouse (Swiss OF_1): RD_{50}: 110 ppm (+/-11.6 ppm)[16]

Mouse (Swiss OF_1): RD_{50}: 100 ppm(17)

7. Other Toxicity

Mouse: LD_{50}; Intraperitoneal injection: 1,070 mg/kg[18]

Mouse: 700 mg/kg injected intravenously was not lethal, but produced clear hypnotic effects[18]

B. Subacute Toxicity:

In a toxicity evaluation performed in advance of a reproductive effect study (described below), rats (10/sex/group) were dosed by gavage for a minimum of 28 consecutive days at 0, 75, 225, or 750 mg/kg-day. There was no mortality. Decreased forelimb grip strength was observed in the high-dose males. Pre-dose and post-dose salivation was observed in both sexes in the mid-dose and high-dose groups. Decreased weight gain, decreased food consumption, and increased blood cholesterol levels were also observed in both sexes in the highest dose group. The no-observed-adverse-effect level (NOAEL) for all outcomes was reported as 75 mg/kg-day, while that for decreased forelimb grip strength was 225 mg/kg-day.[19] The toxicological significance of the only effect reported at 225 mg/kg (pre-dose and post-dose salivation) is not clear.

C. Subchronic Toxicity:

In a 30-day feeding study, rats (5/sex/group) were given nominal doses in their diet ranging from 1 to 102 mg/kg-day. The report does not indicate what intermediate doses were included in the study. No effects were seen in any dose group. This included observations for weight gain, food consumption, histopathology, and mortality.[10]

In another feeding study, rats were provided with a diet containing 0, 1000, 2500, or 10,000 ppm by weight of acetophenone over a 17-week period. No effects, including microscopic effects were seen, even in the high dose group. It was observed through weekly analysis that about 31% of the acetophenone in the feed was lost, apparently due to evaporation, over the week in which each batch of feed was used.[20] The high dose group (10,000 ppm) probably represents a NOAEL of approximately 400 mg/kg-day, based on the reported loss rate of acetophenone from the food and typical food consumption and body weights for rats.

D. Chronic Toxicity/Carcinogenicity:

No data found.

E. Reproductive/Developmental Toxicity

In a reproductive study, rats were dosed via gavage at 0, 75, 225, or 750 mg/kg-day. Males were dosed for at least 28 days prior to mating. Females continued to be dosed through day 3 of lactation. In the high dose group, there was a decrease in the live birth index, pup survival rate through lactation, and in mean pup body weights. The study reported a NOAEL for reproductive effects in rats at 225 mg/kg-day.[19]

F. Genotoxicity/Mutagenicity

Acetophenone was not mutagenic in Ames assays using *S. typhimurium* TA97, TA98, TA100, TA102, TA1535, TA1537 or TA1538, with or without S-9 activation.[21–23]

G. Metabolism/Pharmacokinetics

Acetophenone is apparently metabolized primarily in the liver by several alternative pathways. The metabolic products are primarily excreted in the urine.[24–26]

V. HUMAN USE AND EXPERIENCE

Acetophenone was reported not to induce sensitization in humans when tested using a 2% solution in petrolatum.[14]

Acetophenone has been detected in human breast milk.[27]

Acetophenone was observed as a component in 47 of 50 subjects in a study designed to evaluate the prevalence of volatile organic compounds in alveolar breath in humans. The subjects were not occupationally exposed to acetophenone. The authors conclude that the gradient observed between inspired air and alveolar breath indicates that the acetophenone may be metabolic in origin. The concentrations observed were not reported, however.[28]

VI. RATIONALE

Acetophenone has a low degree of acute toxicity. The RD_{50} was reported to be 100 ppm. Subacute and subchronic feeding studies indicate moderate toxicity, with NOAELs reported in the range of 75–400 mg/kg-day. The lowest reported observed effect in repeated dose studies, at 225 mg/kg-day, is of questionable toxicological significance.

The one reproductive study available indicates a low potential for reproductive effects with a NOAEL of 225 mg/kg-day.

Limited available data indicates that acetophenone is unlikely to cause sensitization.

Acetophenone has been shown to be an eye and skin irritant. Although there are no published reports of respiratory irritation in humans, it is to be presumed from the known irritancy by contact, and from the RD50 study results in mice, that it would be a respiratory irritant at some level for humans.

If it is assumed that all inhaled acetophenone vapor is absorbed, the lowest reported NOAEL would be equivalent to exposure to an airborne concentration of approximately 100 ppm over 8 hours. An OEL is recommended that provides a margin of safety below the lowest reported effect and is expected to be sufficiently low to prevent eye and respiratory irritation.

VII. RECOMMENDED OEL

8-hour TWA, 10 ppm (50 mg/m^3)

VIII. REFERENCES

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