Benzoyl Chloride

Document History
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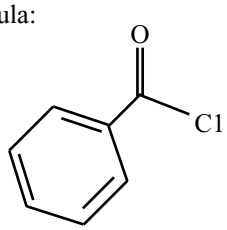
I. IDENTIFICATION

Chemical Name: Benzoyl chloride
Synonyms: Alpha-chlorobenzaldehyde; Benzene carbonyl chloride; Benzoic acid, chloride
CAS Number: 98-88-4
UN/NA Number: 1736
Molecular Formula: C_6H_5COCl
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–3]

Physical State and Appearance: Colorless liquid
Odor Description: Pungent, penetrating, and highly irritating
Molecular Weight: 140.57
Conversion Factor: 1 mg/m^3 = 0. 171 ppm (20°C and 760 mm Hg)
1 ppm = 5.75 mg/m^3
Melting Point: -1°C (30°F)
Boiling Point: 197.2°C (38.7°F) at 760 mm Hg
Vapor Pressure: 1 mm Hg at 32.1°C (90°F)
0.5 mm Hg at 20°C (68°F)
Density: 1.21 g/cm^3 at 20°C (68°F)
Saturated Vapor Concentration: 680 ppm at 25°C (77°F) (by extrapolation)
Flammability Limits: 1.2% – 4.9% in air
Flash Point: (closed cup) 72°C (162°F)
(open cup) 88°C (190°F)
Autoignition Temperature: 85°C (185°F)
Specific Gravity: 1.207 at 25°C (77°F)
Solubility in Water: In aqueous systems it is almost instantly converted to hydrogen chloride and to a lesser extent, benzoic acid in a direct 1:1 (mole to mole) ratio where.[3]
$C_7H_5OCl + H_2O \rightarrow HCl + C_7H_6O_2$
Benzoyl chloride + Water → Hydrogen chloride + Benzoic Acid
Stability: Normally stable under cool, dry conditions.
Reactivity and Incompatibilities: Reacts vigorously with oxidizing materials, alkalies, and steam; decomposes violently on contact with dimethyl sulfoxide; decomposed by alcohols, amines, and other organic compounds containing reactive hydrogen. Even at low pH, the half-life is less than 10 minutes.

III. USES[3–7]

Major industrial uses are in acetylation and benzoylation of alcohols, phenols and amines, as a chemical intermediate used in dye synthesis and in the production of benzoyl peroxide, which is a polymerization initiator. Benzoyl chloride is produced by reacting toluene and chlorine to form benzotrichloride, which is then treated with benzoic acid and zinc chloride to produce benzoyl chloride. Benzoyl chloride is on the EPA High Production Volume (HPV) list.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral*

Rats: LD_{50}, 1140–2618 mg/kg[6,8,9]

2. *Eye Irritation*

Rabbit: Severe lachrimator, severely irritating, and may cause corneal opacity.[6,9,10]

3. *Skin Absorption*

Rabbit: LD_{50}: 790 mg/kg[8]

Rabbit: LD_{50}: >2000 mg/ kg[6,9]

4. *Skin Irritation*

Rabbit: extremely irritating.[6]

5. *Skin Sensitization*

Benzoyl chloride induced a sensitization

response of about 90% in a guinea pig maximization test.[6,11]

6. Inhalation Toxicity

4-hour LC_{50} male Wistar rats: 1.45 mg/L (252 ppm)[3]

10 males/group exposed to 0.190 mg/L (33 ppm), 0.504 mg/L (88 ppm), 0.708 mg/L (123 ppm), 1.453 mg/L (253 ppm), 1.980 mg/L (344 ppm) benzoyl chloride/L air, nose-only, for 4 hours at room temperature. Post exposure observation time of 21 days. Necropsy was performed on rats that died during exposure, during the observation period, and on rats that survived.

Mortality: no rats died up to 0.708 mg/L;

1.453 mg/L (253 ppm): 5/10 rats died within 1 to 19 days post exposure

1.980 mg/L (344 ppm): 6/10 rats died within 4hours to 2 days post exposure

Signs of intoxication were: inactivity, piloerection, unkempt fur, and difficulties in breathing up to 19 days post-exposure in all rats. Rats that died during the test showed dark red colored lungs with emphysema, some rats showed lung edema. Rats that survived showed no pathologic findings up to 0.708 mg/L. At higher concentrations had lungs with emphysema and mottling, and some showed enlarged adrenals.

4-hour LC_{50} female Wistar rats: >1.98 mg/L (344 ppm)[12,13]

Both male and female Wistar rats were exposed to benzoyl chloride. At 1.45 (252 ppm) and 1.98 mg/L (344 ppm), 5/10 and 6/10 males as well as 1/10 and 3/10 females died, respectively. Clinical signs included inactivity, piloerection, unkempt fur, and difficulties in breathing up to 19 days post-exposure in all rats. Pathological examination of rats that died showed dark red colored lungs with emphysema; some rats showed lung edema. Surviving rats at the two highest exposure levels exhibited lung emphysema with mottled appearance; some showed enlarged adrenals.[12,13]

4-hour LC50 Spartan rats: > 2.0 mg/L <200 mg/L (Aerosol)[3]

Groups of 5 male and 5 female rats were placed in a sealed 59 L glass chamber and exposed for 4 hours to a dynamic atmosphere containing mist of the test substance. Rats were observed continually throughout the exposure and for a period of 14 days post-exposure. All rats were necropsied upon death or study termination.

2.0 mg/L:

1/10 rats died on the 6th day of the observation period. Clinical signs during exposure: increased followed by decreased motor activity; eye squint; salivation; lacrimation; slight and/or marked dyspnea, nasal porphyrin discharge. Clinical signs (Days 1 to 7): decreased motor activity, dyspnea, and diarrhea. From Day 8–14 surviving rats appeared normal and exhibited normal body weight gains.

200mg/L:

All rats died within 4 hours after initiation of the exposure. Clinical signs during exposure: erythema, gasping dyspnea, and those noted for 2.0 mg/L.

4-hour LC_{50}, rats: >4.2 mg/L (731 ppm)[1]

4-hour LC_{50}, rats: >2 mg/L (348 ppm)[6]

2-hour LC_{50} rats: >1.87 mg/L (325 ppm) purity not noted[3]

Mortality: 0/10 males and 2/10 females

1-hr LC_{50} rats: >2.343 mg/L (408 ppm) (purity not noted)[12,15]

10 males and 10 females exposed to 2343 mg benzoyl chloride/L air, nose-only, for 1 hour at room temperature, post exposure observation time: 21 days, necropsy was performed on rats that died during exposure and during observation period and on rats that survived. Mortality: 0/10 (m), 2/10 (f), time of death after 8–11 days. All rats showed difficulties in breathing, piloerection, inactivity for up to 19 days. Necropsy at the end of the observation time revealed lungs with emphysema and/or mottled appearance.

B. Subacute Toxicity

No information found.

C. Subchronic Toxicity

No information found.

D. Chronic Toxicity/Carcinogenicity

Mice — Two groups of ten female ICR mice received two and three times weekly applications to the skin for 43 weeks.[14] The mice displayed marked irritation of the eyes, skin and respiratory

tract, and two mice in the lower dose group (533 mg total dose/animal) each had one skin tumor (one papilloma and one squamous-cell carcinoma). Three lung adenomas occurred in the higher dose group (1065 mg total dose/animal), while no tumors occurred in a solvent-control group.

In a second experiment, applications of 2.8 mg was applied to skin of 20 female ICR mice for 50 weeks (278 mg total dose/animal) produced a 10% incidence of skin cancer within 560 days.[14] Lung adenomas developed in five treated and two control animals.

Mice (strain, number, age, and sex not specified) exposed to benzoyl chloride vaporized at 50°C (concentration was not specified) for 30 minutes/day, 2 days/week for 5 months developed lung tumors at an incidence rate of 10.7% (3/28) and skin tumors at an incidence rate of 7.1% (2/28). However, the authors reported these incidences were not significantly different from controls. For comparison (since workers are most often exposed both to benzotrichloride and benzoyl chloride), the same study was performed with benzotrichloride. The incidence of pulmonary tumors from benzotrichloride was significantly higher than control mice, suggesting that the carcinogenicity of benzotrichloride is much higher than benzoyl chloride, and that benzotrichloride is the primary cause of malignancies developing among workers engaged in manufacturing benzoyl chloride.[15]

IARC classifies benzoyl chloride in Group 2A: The agent is probably carcinogenic to humans. IARC classified benzoyl chloride in this category because there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals, along with strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans.[7]

E. Reproductive/Developmental Toxicity

No information found.

F. Genotoxicity/Mutagenicity

Benzoyl chloride was not mutagenic in the Bacterial Reverse Mutation Assay (Ames test) with *Salmonella* strains TA98, TA100, TA1535 and TA1537.[16] However, positive results have been reported in Salmonella strains TA100, TA98, and TA104 and E. coli strain WP2 UVRA in two studies.[17,18] Other studies[19,20] found no mutagenic activity in recombination deficient and reversion assays. Because *Salmonella* tests are conducted in an aqueous medium and benzoyl chloride is unstable in water, the value of these mutagenicity tests is questionable. The mutagenicity of benzoyl chloride was classified by the International Agency for Research on Cancer (IARC) as equivocal. (WHO 1999)

In an *in vivo* micronucleus assay, 0 or 175 mg/kg body weight of benzoyl chloride was administered to mice by gavage. The study was performed under GLP and was negative.[16]

G. Metabolism/Pharmacokinetics

Elimination and distribution of ^{14}C-labelled benzoyl chloride was similar in many respects to that of its hydrolysis product, benzoic acid, which is excreted primarily as urinary hippuric acid.[22] The absorption and excretion of ^{14}C-benzoyl chloride (BC) was studied in groups of male and female Holtzman albino rats (1-3/group) exposed by gavage to single doses of benzoyl chloride. Five groups of females were exposed to average concentrations ranging from 11.8–12.6 mg/kg. They were sacrificed 8 (1 group), 24 (3 groups), or 48 hrs (1 group) after dosing, respectively. One group of males was exposed to an average concentration of 8.8 mg/kg and sacrificed 48 hours after dosing. Benzoyl chloride was rapidly absorbed in the gastrointestinal tract and efficiently eliminated in the urine (90%) and feces (2%) in 48 hours. Radioactivity in the blood (as benzoyl chloride equivalents) peaked at 4 ppm by 4 hours after dosing and then rapidly decreased to 0.02 ppm by 24 hours. The elimination half-life of ^{14}C in the blood was 1.5 hours. Total radiocarbon residue in tissues was approximately 1.5% of the dose after 72 hours with fat, liver, and kidneys containing the highest residue levels. The pharmacokinetics of benzoyl chloride appeared to follow a one-compartment open model system. Benzoyl chloride was rapidly distributed in the body and the rate of elimination in the urine is proportional to the concentration of benzoyl chloride in the blood. At 8 hr, about 0.8% of the administered 14C was present in the tissues. The radiocarbon elimination half-lives in the tissues ranged from 2.9–16.0 hours (brain: 16.0 hours, ovary: 10.1 hours).[23]

H. Other

Pertinent relative hydrolysis information on hydrogen chloride, a very quick hydrolysis product for benzoyl chloride:

> In a 1-year exposure of rats to 10 ppm hydrogen chloride, histopathological examination of the respiratory tract demonstrated no tumors while rhinitis, squamous hyperplasia, and metaplasia were reported at an incidence that was very similar to control animals.[24,25] The rat study appears to indicate minimal, if

any, irritancy at a concentration of 10-ppm following chronic exposure. The RD_{50} in mice for hydrogen chloride is reported to be 309 ppm.[26,27] In addition, baboons exposed to 500, 5000, and 10,000 ppm of hydrogen chloride for 15 minutes demonstrated a concentration-dependant increase in respiratory rate and minute volume and a decrease in PaO_2[28] during exposure, a distinctly different response in respiratory rate than that observed in the standardized murine model, where irritation is linked to decreased respiratory rate.[26] No effects on baboons were reported on pulmonary function parameters for any exposure groups 3-days and 3-months post exposure.[28]

V. HUMAN USE AND EXPERIENCE

Benzoyl chloride vapor is a strong lachrimator and is irritating to the eyes and mucous membranes.[1,2] Severe irritation may result from hydrolysis of benzoyl chloride on contact with moist mucous membranes to hydrochloric acid and benzoic acid. Repeated exposures can cause central nervous system (CNS) depression.[1] Excessive exposure may cause pulmonary edema and CNS depression. Ingestion may cause severe irritation and burns to the mouth, throat, and stomach.[6]

A manufacturer of benzoyl chloride reported worker exposure monitoring results for nearly 100 air samples collected over an 8-year period. The mean exposure concentration was less than 0.1 ppm with only one sample exceeding 2 ppm. This manufacturer set their internal occupational exposure limit to 1 mg/m^3 (0.2 ppm), 8-hour TWA based on analogy to the similar, but more acutely toxic properties of benzyl chloride.[6] There were no worker complaints on the days that air samples were taken indicating that concentrations averaging about 0.1 ppm, 8-hour TWA (along with the peaks/excursions inherent in the TWA), are not expected to be irritating to the acclimatized worker.

In two small Japanese factories with poor industrial hygiene controls[29], six cases of malignant respiratory cancer[29,30] occurred among workers engaged in the manufacturer of benzoyl chloride and its chlorinated toluene derivatives. These cases involved relatively young workers, three of whom were non-smokers. Two of them subsequently died.[7,31] The death rate from lung cancer for all workers (147) was estimated to be an order of magnitude higher than expected.[29] Workers were exposed, however, to several other chemicals in the production process, including the suspected carcinogen, benzotrichloride.[29] Additional cases of chronic pharyngitis, chronic sinusitis, hyposmia or anosmia, and skin disorders such as parachroma and warts were reported among the approximately 20 workers in one of the Japanese factories.[29]

A cohort mortality study consisted of 697 male employees at a chlorination plant between 1943 and 1982, where a majority of the cohort was potentially exposed to benzotrichloride, benzylchloride, benzoyl chloride, and other related chemicals. The study found a statistically significant increase in lung cancer mortality among male employees with 15 or more years of employment. The animal data, as well as other epidemiologic studies, suggest an association between the chlorination process of toluene at the plant and an increased risk of respiratory cancer, most likely from the benzotrichloride.[32] A slight increase in lung cancer mortality incidence was found in a factory manufacturing chlorinated toluenes, including benzotrichloride and benzoyl chloride in Britain.[33]

Mortality rates were studied in British workers from a factory that manufactured chlorinated toluenes. The study population included 790 unexposed workers and 163 exposed workers between 1961 and 1970. The study concluded that exposed workers employed before 1951 had an increased lung and digestive cancer risk, but that the most likely causal agent was benzotrichloride. A follow-up study for the period 1961 to 1984 found statistically significant excesses of lung cancer and Hodgkin's disease, again attributed to benzotrichloride, not benzoyl chloride.[31]

Data for hydrogen chloride:

There are no data on human sensory irritation to benzoyl chloride. There is pertinent information for benzoyl chloride hydrolysis resulting in hydrogen chloride relating to expected sensory irritation:

> It has reported that subjects exposed to 100 ppm hydrogen chloride as "work yet undisturbed" and >500 ppm hydrogen chloride exposure as "work impossible."[34] An epidemiological investigation indicates a "hormesis" effect with respect to hydrogen chloride exposure, where subjects exposed to 1.4 ppm HCl with peaks up to 27 ppm demonstrated significant reductions in respiratory symptoms (chronic cough and phlegm, bronchitis episodes, etc.) with an Odds Ratio ranging from 0.2-0.7.[35] In another study, ten asthmatic subjects exposed to 0.8 and 1.8 ppm HCl for 45 minutes did not demonstrate any significant changes in pulmonary function.[36]

VI. RATIONALE

The primary basis for the OEL is protection against the severe irritation that benzoyl chloride causes to the eyes and mucous membranes. This occurs primarily as

a result of the rapid hydrolysis to hydrogen chloride in biological systems. The release of HCl by benzoyl chloride is a critical exposure aspect and an equivalent of 5 ppm as HCl would be appropriate as a ceiling exposure level.[24–28,34–36] Based upon the toxicity data reviewed to date, this value should be adequate to prevent short-term irritation. A skin notation is warranted to protect from systemic and chronic toxicity, as there was an increased incidence rate of tumors following multiple skin applications of 2.8 mg twice per week over 50 weeks[14] and a skin absorption LD_{50} of 790 mg/kg in rabbits.[8] A DSEN notation is appropriate for benzoyl chloride based on the positive sensitization response of about 90% in a guinea pig maximization test.[11]

VII. RECOMMENDED OEL GUIDE

5 ppm as HCl (7.2 mg/m^3 HCl) Ceiling, Skin, DSEN

VIII. REFERENCES

Literature searches performed: Computer searches according to the WEEL AOP "Literature Search Protocol" and of Toxicology Data Bank, MEDLINE, HAZARD- LINE, TOXLINE and CANCERLINE databases, MicroMedex/TOMES, MEDITEXT®, HAZARDTEXT®, CHRIS, Fisher/Acros MSDS, Dolphin MSDSs, HSDB®, LOLI®, ERG2000, New Jersey Hazardous Substance Fact Sheet, OHM/TADS, RTECS®, POISINDEX®.

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