Benzyl chloride; CASRN 100-44-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Benzyl chloride

File First On-Line 08/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	message	01/01/1992
Carcinogenicity Assessment (II.)	yes	08/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Benzyl chloride
CASRN — 100-44-7
Primary Synonym — Chloromethylbenzene

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Benzyl chloride
CASRN — 100-44-7
Primary Synonym — Chloromethylbenzene

The health effects data for benzyl chloride were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC.

Agency Work Group Review — 11/07/1991

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Benzyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Benzyl chloride
CASRN — 100-44-7
Primary Synonym — Chloromethylbenzene
Last Revised — 08/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk

Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Based on inadequate human data and sufficient evidence of carcinogenicity in animals; namely significantly increased incidences of benign and malignant tumors at multiple sites in both sexes of mice and a significant increase in thyroid tumors in female rats. There was evidence of mutagenicity in a variety of test systems.

II.A.2. Human Carcinogenicity Data

Inadequate. Studies have shown that occupational exposure to the process of benzoyl chloride production, in which benzyl chloride is a minor reaction by-product, may increase the risk of cancer-induced mortality. The available human data for benzyl chloride alone are considered inadequate because the studies included small numbers of cancer deaths and were based on exposure to mixtures of chlorinated compounds. In addition, data on cigarette smoking were incomplete.

Sakabe et al. (1976) reported three cancer deaths among 41 workers employed in a benzoyl chloride production plant in Japan between 1954 and 1972. Two of the deaths were from lung cancer, both in smokers who were in their forties. The third cancer death was from maxillary malignant lymphoma in a 50 year-old worker with and unspecified smoking status. The fourth cancer case, diagnosed as squamous cell carcinoma of the lung, was identified in a nonsmoker still living in 1973. These four workers were employed in benzoyl chloride production from 6 to 15 years. The number of deaths from lung cancer (2) was significantly higher than the number expected (0.06), based on the Japanese national rate for death from lung cancer in males.

In addition to benzyl chloride, these workers were exposed to benzotrichloride, benzoyl chloride, toluene, chlorine gas, hydrogen chloride, benzal chloride, other chlorinated toluenes and polymerized products from the process. The authors considered it unlikely that the four cases of cancer were produced by exposure to benzyl chloride because this was a very minor reaction product in the production process.

In a subsequent case report, two lung cancer deaths were identified among workers engaged in benzoyl peroxide and benzoyl chloride production at another plant, in which the total number of workers ranged from 13 in 1952 to 40 in 1963 (Sakabe and Fukuda, 1977). The two individuals, one of whom was a smoker, were in their forties and had worked in benzoyl chloride production for 6 to 18 years. The number of deaths expected among these workers was not reported.

Sorahan et al. (1983) carried out a study of cancer mortality among 953 workers at a British factory engaged in production of chlorinated toluenes. As in the Japanese plants, there was exposure to toluene (the starting material), benzotrichloride and benzoyl chloride (the major reaction products), as well as to benzyl chloride, benzal chloride and other materials. The cohort of exposed workers consisted of 163 males employed for at least six months between 1961 and 1970. Some of these individuals started employment as early as 1923. Of the 10 deaths from cancer (25 total deaths) reported in this group, 5 were due to digestive system cancers and 5 to respiratory cancers, compared with the expected values of 1.24 and 1.78, respectively. The standardized mortality ratio for each of these sites was significantly higher than expected, based on mortality rates for England and Wales. A survival analysis using the Cox Proportional Hazard Model, adjusted for age at entry to the survey and the time period when employment began, was also conducted. This analysis showed a statistically significant association between estimated cumulative exposure and deaths from cancer at all sites (but not for digestive or respiratory cancers individually) for persons first employed before 1951. The association was not significant for all entry cohorts combined. Interpretation of this study is limited by several factors including possible bias in assignment of exposure categories, exposure to multiple compounds and lack of data on smoking.

A retrospective mortality study was reported on a cohort of 697 male workers who were exposed to benzyl chloride, benzoyl chloride and benzotrichloride at a chlorination plant in Tennessee (Wong and Morgan, 1984). The length of employment at the plant ranged from 1 year to >35 years. Seven deaths from respiratory cancer were found in the total cohort compared with 2.84 deaths expected, based on U.S. mortality rates for males. Five of these deaths occurred in workers employed for at least 15 years. This was significantly greater than the 1.32 deaths expected for this subgroup. The results of this study were confounded by exposures to several chemicals and lack of data on smoking.

In summary, because of small sample sizes, lack of data on cigarette smoking and the fact that exposure was to a mixture of halogenated intermediates, the available human data are insufficient to determine the potential carcinogenicity of benzyl chloride.

II.A.3. Animal Carcinogenicity Data

Sufficient. In a NCI carcinogenicity bioassay (Lijinsky, 1986), Fischer F344 rats (52/sex/dose) and B6C3F1 mice (52/sex/dose) were administered benzyl chloride in corn oil by gavage 3 times/week for 104 weeks. They were sacrificed for comprehensive histological analysis 3 to 4 weeks after the last dose. Rats received either 0, 15, or 30 mg/kg per dose; mice received either 0, 50, or 100 mg/kg per dose. No significant differences in survival were seen between treated and control groups. In rats, the only statistically significant increase in tumor incidence attributed to treatment was thyroid C- cell adenoma/carcinoma in the female high-dose group (4/52, 8/51, 14/52 for low, medium and high doses, respectively). In male mice, statistically significant increases in the following tumor incidences were observed: hemangioma/hemangiosarcoma in the high-dose group (0/52, 0/52, 5/52) hepatic carcinoma/adenoma in the low-dose group (17/52, 28/52, 20/51) forestomach carcinoma in the high-dose group (0/51, 2/52, 8/52), and forestomach carcinoma/papilloma in the high-dose group (0/51, 4/52, 32/52). In female mice, a statistically significant increase in the incidence of forestomach carcinoma/papilloma was reported (0/52, 5/50, 19/51). Also, a slightly increased incidence of lung alveolar-bronchiolar adenoma/carcinoma (1/52, 2/51, 6/51) was observed in the high-dose group of female mice.

Fukuda et al. (1981) conducted two skin-painting studies on specific- pathogen-free ICR mice, using benzyl chloride dissolved in benzene. Benzene- only controls were included for vehicle comparison. In the first study, no tumors were observed in 11 mice treated with 10 uL benzyl chloride 3 times/week for 4 weeks, followed by 2 times/week until termination at 40 weeks. In the second study, 2.3 uL benzyl chloride was diluted to a final volume of 25 uL with benzene and applied to the skin of 7-week-old mice 2 times/week for 50 weeks. Two of 20 control animals developed lung adenomas, while 5/20 treated mice developed tumors, including 2 lung adenomas and 3 skin carcinomas. Two of the skin carcinomas metastasized to the primary lymphatic organs, liver, or kidneys. Although these tumor incidences are not statistically significantly greater than controls, the authors considered benzyl chloride to be a weak carcinogen when applied topically. The short duration of the studies limited their sensitivity.

Efforts to assess the potency of benzyl chloride as a carcinogen and skin tumor initiator provided predominantly negative results. Coombs (1982a) applied 1.0 mg benzyl chloride in toluene to the backs of 40 T.O. (Swiss- Webster derived Theiler's Original) mice, followed by twice weekly treatments of croton oil in toluene for 10 months. While 8/19 positive controls treated with 0.4 mg benzo[a]pyrene developed skin tumors, none (0/37) of the benzyl chloride-treated mice did. In a second initiation-promotion test, Coombs (1982b) topically applied 10, 100, or 1000 ug benzyl chloride in acetone, followed by twice weekly applications of the promotor 12-O-tetra-'3-decanoyl- phorbol-'3-acetate. At the end of 11 weeks, all of the positive controls treated with (7,12-dimethylbenz[a]anthracene) had skin tumors, whereas at 6 months (approximately 12 weeks later), only 20% of the mice treated with benzyl chloride showed similar changes. Ashby et al. (1982) topically treated groups of 20 Swiss mice with 100 ug benzyl chloride in toluene

twice weekly. After 7.5 months, none of the treated mice had skin tumors compared with 18/20 of the positive controls treated with benzo[a]pyrene.

Druckrey et al. (1970) administered benzyl chloride in peanut oil via weekly subcutaneous injection to BD-strain rats for 51 weeks. Local sarcomas were produced in 3/14 rats given 40 mg/kg/week and in 6/8 rats given 80 mg/kg/week. The average induction time was 500 days and metastases to the lung occurred in the high-dose group only.

Groups of 20 strain A/H mice were injected intraperitoneally over a 24- week period with benzyl chloride in tricaprylin (total doses of 4.7, 11.8, or 15.8 mmol/kg). No differences in pulmonary adenoma formation between treated and vehicle control mice were observed (Poirier et al., 1975).

II.A.4. Supporting Data for Carcinogenicity

Benzyl chloride was weakly mutagenic to Salmonella typhimurium strain TA100 and Eschericia coli WP2 uvr A(p), which are sensitive to the induction of point mutations (Venitt, 1982). It was also positive for genotoxicity in repair-deficient strains (Fluck et al., 1976; Rosenkranz and Leifer, 1980). Parry and Wilcox (1982) reported that benzyl chloride affects the replication and repair mechanisms in fungi. In Drosophila melanogaster, benzyl chloride was found to induce somatic mutations more readily than sex-linked alterations (Fahmy and Fahmy, 1982). In mammalian cultured cells, benzyl chloride was slightly mutagenic to DNA excision-repair deficient strains of CHO cells (Hoy et al., 1984), but was generally ineffective in increasing unscheduled DNA synthesis (Mitchell, 1976; Booth et al., 1983). Scott and Topham (1982) concluded that benzyl chloride was generally not mutagenic in in vivo mammalian systems, including the mouse micronucleus and sperm head abnormality tests.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.7E-1 per (mg/kg)/day

Drinking Water Unit Risk — 4.9E-6 per ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+1 ug/L
E-5 (1 in 100,000)	2 ug/L
E-6 (1 in 1,000,000)	2E-1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — thyroid, C-cell adenoma/carcinoma
Test animals — rat/Fischer 344, female
Route — gavage, corn oil
Reference — Lijinsky, 1986

Administered Dose (mg/kg, 3 times/week)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	4/52
15	1.06	8/51
30	2.12	14/52

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The human equivalent doses were calculated by multiplying the experimental dose by 3 days/7 days and by 104 weeks/107.5 weeks. Because body weight gain data were not provided, a reference weight of 0.35 kg for rats was assumed.

Using the data from Lijinsky (1986), slope factors were derived for the incidence of forestomach papilloma and carcinoma in male mice [5.6E-2 per (mg/kg)/day] and in female mice [1.2E-1 per

(mg/kg)/day]. The rat C-cell adenoma/carcinoma data were used because they resulted in the highest slope factor.

The unit risk should not be used if the water concentration exceeds 2E+3 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

A sufficent number of animals were used for analysis of late-developing tumors. Benzyl chloride was administered by a relevant route of exposure at two doses in both sexes of two species for the animals' lifespan. Histological examination was comprehensive. Slope factors derived from tumor data at another site in another species were within a factor of 3.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The 1986 Health and Environmental Effects Profile for Benzyl Chloride has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 03/01/1989

Verification Date — 03/01/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Benzyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Benzyl chloride
CASRN — 100-44-7
Primary Synonym — Chloromethylbenzene

VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

None available

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Benzyl chloride
CASRN — 100-44-7
Primary Synonym — Chloromethylbenzene

Date	Section	Description
08/01/1989	II.	Carcinogen summary on-line
01/01/1992	I.B.	Inhalation RfC message on-line
10/28/2003	I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Benzyl chloride
CASRN — 100-44-7
Primary Synonym — Chloromethylbenzene
Last Revised — 08/01/1989

- 100-44-7
- BENZENE, (CHLOROMETHYL)-
- BENZILE (CLORURO DI) (Italian)
- BENZYL CHLORIDE
- BENZYLE (CHLORURE DE) (French)
- BENZYLCHLORID (German)
- CHLOROMETHYLBENZENE
- CHLOROPHENYLMETHANE
- alpha-CHLOROTOLUENE
- omega-CHLOROTOLUENE
- alpha-CHLORTOLUOL (German)
- CHLORURE DE BENZYLE (French)

- NCI-C06360
- RCRA WASTE NUMBER P028
- TOLUENE, alpha-CHLORO-
- TOLYL CHLORIDE
- UN 1738