α-CHLORINATED TOLUENES AND BENZOYL CHLORIDE

Data were last reviewed in IARC (1982) and the compounds were classified in *IARC Monographs* Supplement 7 (1987a).

1. Exposure Data

Benzyl chloride

1.1 Chemical and physical data

1.1.1 *Nomenclature*

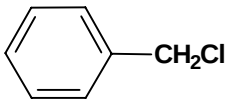
Chem. Abstr. Serv. Reg. No.: 100-44-7

Chem. Abstr. Name: (Chloromethyl)benzene

IUPAC Systematic Name: α-Chlorotoluene

Synonyms: Chloromethyl benzene; chlorophenylmethane; α-tolyl chloride

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_7H_7Cl Relative molecular mass: 126.6

1.1.3 *Chemical and physical properties of the pure substance*

From Lide (1997), unless otherwise specified

(*a*) *Description:* Colourless liquid with a pungent odour (Lewis, 1993)

(*b*) *Boiling-point:* 179°C

(*c*) *Melting-point:* –45°C

(*d*) *Density*: d_{10}^{20} 1.10

(*e*) *Solubility*: Insoluble in water; slightly soluble in carbon tetrachloride; miscible with chloroform, diethyl ether and ethanol (Budavari, 1996)

(*f*) *Vapour pressure*: 133 Pa at 22°C; relative vapour density (air = 1), 4.36 (Verschueren, 1996)

(*g*) *Stability*: Decomposes in hot water to benzyl alcohol (United States Environmental Protection Agency, 1980); decomposes rapidly when heated in the presence of iron (Budavari, 1996); combustible (Lewis, 1993)

(*h*) *Reactivity*: Undergoes reactions both at the side-chain containing the chlorine and at the aromatic ring (Gelfand, 1979)

(*i*) *Flash-point*: 67°C (closed cup); 74°C (open cup) (Lin & Bieron, 1993)
(*j*) *Explosive limit*: Lower, 1.1% by volume of air (Lin & Bieron, 1993)
(*k*) *Octanol/water partition coefficient (P)*: log *P*, 2.30 (Verschueren, 1996)
(*l*) *Conversion factor*: $mg/m^3 = 5.18 \times ppm$

1.2 Production and use

The chemical processes associated with the manufacture of chlorinated toluenes are summarized in Figure 1.

Plant capacities for the production of benzyl chloride in western countries totalled 144 thousand tonnes in 1989. Total production in these countries in 1988 was approximately 93 thousand tonnes, with production in the United States of 26 500 tonnes or 54% of capacity (Lin & Bieron, 1993). Information available in 1995 indicated that benzyl chloride was produced in 16 countries (Chemical Information Services, 1995).

More than two-thirds of the benzyl chloride produced is used in the manufacture of butyl benzyl phthalate, a plasticizer used extensively in vinyl flooring and other flexible poly(vinyl chloride) uses such as food packaging. Other significant uses are the manufacture of benzyl alcohol and benzyl chloride-derived quaternary ammonium compounds, each of which consumes more than 10% of the benzyl chloride produced. In the dye industry, benzyl chloride is used as an intermediate in the manufacture of triphenylmethane dyes. Derivatives of benzyl chloride are processed further to pharmaceutical, perfume and flavour products (Lin & Bieron, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 27 000 workers in the United States were potentially exposed to benzyl chloride (see General Remarks). Occupational exposures to benzyl chloride may occur in its production and use as a chemical intermediate.

1.3.2 *Environmental occurrence*

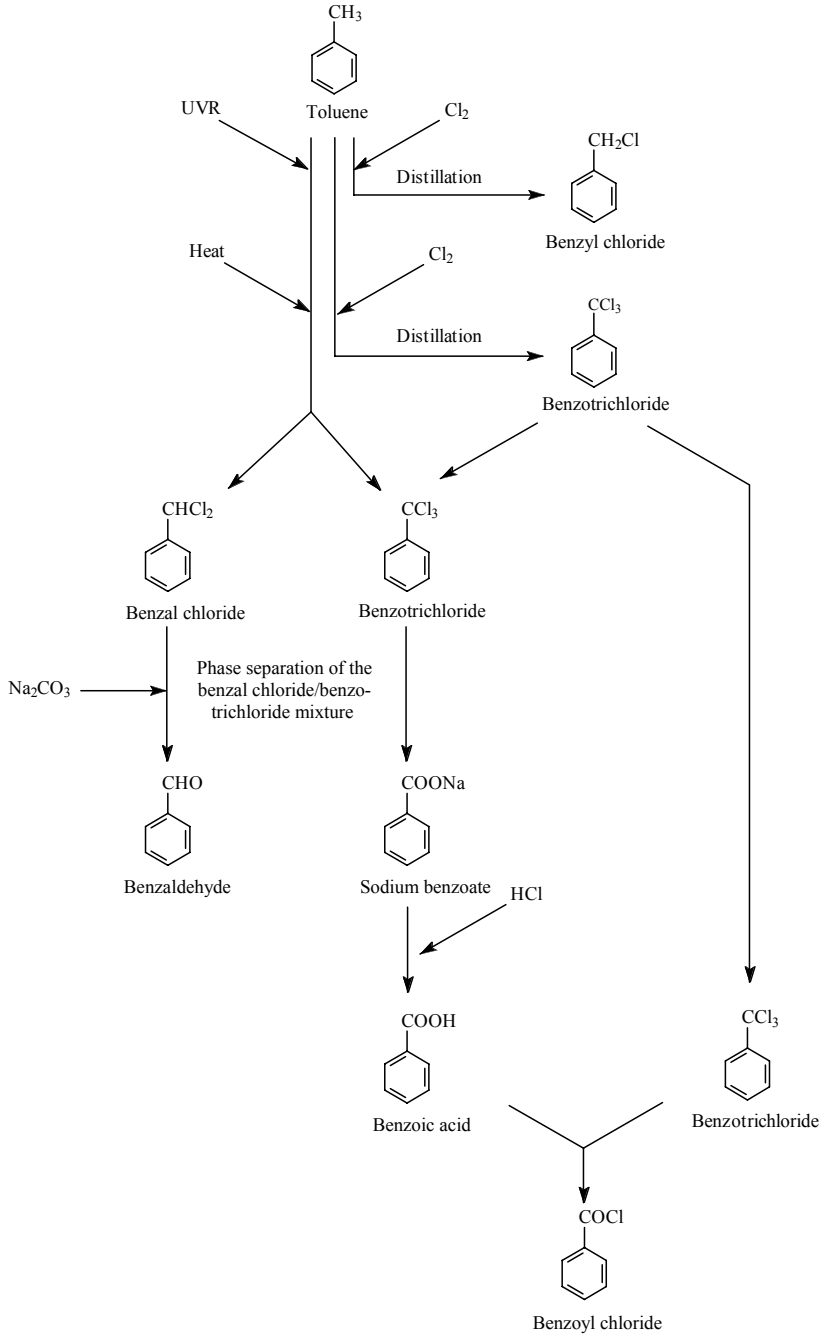
Benzyl chloride has been detected in surface water, industrial effluents and river water (Sheldon & Hites, 1978; Hushon *et al.*, 1980).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 5.2 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to benzyl chloride in workplace air.

No international guideline for benzyl chloride in drinking-water has been established (WHO, 1993).

Figure 1. Chemical processes associated with the manufacture of chlorinated toluenes and benzoyl chloride



From Sorahan *et al.* (1983)

Benzal chloride

1.1 Chemical and physical data

1.1.1 *Nomenclature*

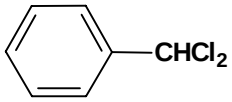
Chem. Abstr. Serv. Reg. No.: 98-87-3

Chem. Abstr. Name: (Dichloromethyl)benzene

IUPAC Systematic Name: α,α-Dichlorotoluene

Synonyms: Benzyl dichloride; benzylene chloride; benzylidine chloride; chlorobenzal; (dichloromethyl)benzene; dichlorophenylmethane; dichlorotoluene

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_7H_6Cl_2$ Relative molecular mass: 161.0

1.1.3 *Chemical and physical properties of the pure substance*

From Lide (1997), unless otherwise specified

(*a*) *Description*: Colourless liquid with a pungent odour (Lewis, 1993; Budavari, 1996)

(*b*) *Boiling*-point: 205°C

(*c*) *Melting*-point: –17°C

(*d*) *Density*: d_4^{14} 1.26

(*e*) *Solubility:* Insoluble in water; very soluble in diethyl ether and ethanol

(*f*) *Vapour pressure*: 133 Pa at 35.4°C (Lin & Bieron, 1993)

(g) *Stability*: Hydrolysed to benzaldehyde under both acid and alkaline conditions (Gelfand, 1979); fumes in air (Budavari, 1996)

(*h*) *Reactivity*: Undergoes reactions both at the side-chain containing the chlorine atoms and at the aromatic ring (Gelfand, 1979)

(*i*) *Conversion factor:* $mg/m^3 = 6.58 \times ppm$

1.2 Production and use

Information available in 1994 indicated that benzal chloride was produced in two countries (Belgium, Japan) (Chemical Information Services, 1994).

Benzal chloride is used almost exclusively for the manufacture of benzaldehyde and cinnamic acid (Lewis, 1993; Budavari, 1996).

1.3 Occurrence

1.3.1 *Occupational exposure*

No information on occupational exposure to benzal chloride was available to the Working Group.

1.3.2 *Environmental exposure*

Benzal chloride has been detected in surface waters (Hushon *et al.*, 1980).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not proposed any occupational exposure limit for benzal chloride in workplace air. Russia has a short-term exposure limit of 0.5 mg/m^3 for exposure in workplace air. Sweden lists benzal chloride as a probable human carcinogen and Finland and Germany list benzal chloride as suspected of having carcinogenic potential (International Labour Office, 1991).

No international guideline for benzal chloride in drinking-water has been established (WHO, 1993).

Benzotrichloride

1.1 Chemical and physical data

1.1.1 *Nomenclature*

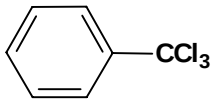
Chem. Abstr. Serv. Reg. No.: 98-07-7

Chem. Abstr. Name: (Trichloromethyl)benzene

IUPAC Systematic Name: α,α,α-Trichlorotoluene

Synonyms: Benzenyl chloride; benzenyl trichloride; benzylidyne chloride; benzyl trichloride; phenyl chloroform; phenyltrichloromethane; toluene trichloride; trichloromethylbenzene

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_7H_5Cl_3$ Relative molecular mass: 195.5

1.1.3 *Chemical and physical properties of the pure substance*

From Lide (1997), unless otherwise specified

(*a*) *Description*: Colourless to yellowish oily liquid with a pungent odour (Lewis, 1993; Budavari, 1996)

(*b*) *Boiling point*: 221°C

(*c*) *Melting-point*: –5°C

(*d*) *Density*: d_4^{20} 1.37

(*e*) *Solubility*: Insoluble in water; soluble in benzene, diethyl ether and ethanol

(*f*) *Vapour pressure*: 20 Pa at 20°C (Verschueren, 1996); relative vapour density (air = 1), 6.77 (Lin & Bieron, 1993)

(*g*) *Stability*: Unstable; hydrolyses in the presence of moisture; fumes in air (Budavari, 1996)

(*h*) *Reactivity*: Undergoes reactions both at the side-chain containing the chlorine atoms and at the aromatic ring (Gelfand, 1979)
(*i*) *Flash-point*: 127°C (open cup) (Budavari, 1996)
(*j*) *Octanol/water partition coefficient (P)*: log *P*, 4.1 (Verschueren, 1996)
(*k*) *Conversion factor*: mg/m^3 = 8.00 × ppm

1.2 Production and use

Total production capacity in the western countries in 1988 for benzotrichloride was 68 thousand tonnes; production in 1988 was approximately 31 500 tonnes (Lin & Bieron, 1993). Information available in 1994 indicated that benzotrichloride was produced in eight countries (Chemical Information Services, 1994).

Benzotrichloride is mostly used as a chemical intermediate, primarily for benzoyl chloride. Lesser amounts are used in the manufacture of benzotrifluoride, as a dyestuff intermediate, and in producing hydroxybenzophenone ultraviolet light stabilizers (Lin & Bieron, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

No information on occupational exposure to benzotrichloride was available to the Working Group.

1.3.2 *Environmental occurrence*

Benzotrichloride has been detected in surface waters (Hushon *et al.*, 1980).

1.4 Regulations

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not recommended an 8-h time-weighted average threshold limit value but has recommended 0.8 mg/m^3 as the ceiling value for occupational exposures to benzotrichloride in workplace air. Russia has a short-term exposure limit of 0.2 mg/m^3 for exposure in workplace air. Sweden lists benzotrichloride as a probable human carcinogen and Finland and Germany list benzotrichloride as suspected of having carcinogenic potential (International Labour Office, 1991).

No international guideline for benzotrichloride in drinking-water has been established (WHO, 1993).

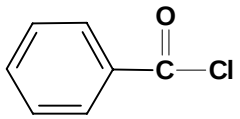
Benzoyl chloride

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 98-88-4
Chem. Abstr. Name: Benzoyl chloride
IUPAC Systematic Name: Benzoyl chloride
Synonym: Benzene carbonyl chloride

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_7H_5ClO Relative molecular mass: 140.6

1.1.3 *Chemical and physical properties of the pure substance*

From Lide (1997), unless otherwise specified

(*a*) *Description*: Colourless liquid with a pungent odour (Lewis, 1993)
(*b*) *Boiling point*: 197.2°C
(*c*) *Melting-point*: 0°C
(*d*) *Density*: d_4^{20} 1.21
(*e*) *Solubility*: Decomposes in water and ethanol; soluble in benzene, carbon disulfide and carbon tetrachloride; miscible with diethyl ether (Budavari, 1996)
(*f*) *Vapour pressure*: 53 Pa at 20°C; relative vapour density (air = 1), 4.88 (Verschueren, 1996)
(*g*) *Flash-point*: 72.2°C (Lewis, 1993)
(*h*) *Conversion factor*: $mg/m^3 = 5.75 \times ppm$

1.2 Production and use

Information available in 1995 indicated that benzoyl chloride was produced in 11 countries (Chemical Information Services, 1995).

Benzoyl chloride is used in the manufacture of benzoyl peroxide and dye intermediates, for acylation (introduction of the benzoyl group into alcohols, phenols and amines), and as an analytical reagent (Lewis, 1993; Budavari, 1996).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 6900 workers in the United States were potentially exposed to benzoyl chloride (see General Remarks). Occupational exposures to benzoyl chloride may occur in its production and use as a chemical intermediate.

1.3.2 *Environmental occurrence*

No information on environmental occurrence of benzoyl chloride was available to the Working Group.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not recommended an 8-h time-weighted average threshold limit value but has

recommended 2.8 mg/m^3 as the ceiling value for occupational exposures to benzoyl chloride in workplace air. Hungary has an 8-h time-weighted average exposure limit of 5 mg/m^3 and Russia has a short-term exposure limit of 5 mg/m^3 for occupational exposure in workplace air (International Labour Office, 1991).

No international guideline for benzoyl chloride in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

Six cases of respiratory tract cancer were reported among benzoyl chloride production workers in two small plants in Japan. The cases occurred in people aged ≤ 44 years, three of whom were nonsmokers (IARC, 1982, 1987a).

A mortality study of 953 workers potentially exposed to various chlorinated toluenes and benzoyl chloride was conducted in a factory in England (Sorahan *et al*., 1983). Included were workers employed for six or more months between 1961 and 1970 and followed through 1976 for vital status. Standardized mortality ratios (SMR) were calculated using mortality rates from England and Wales as the referent. Although workers with exposures to specific chlorinated toluenes could not be evaluated, groups with low (n = 153) and high (n = 163) exposures to chlorinated toluenes were identified from job titles. Significant excesses occurred for all deaths combined for the high-exposure (SMR, 1.6; 25 obs./15.4 exp.) but not the low-exposure (SMR, 1.2; 66 obs./56.1 exp.) groups. The high-exposure group also had significant excesses for all cancers (SMR, 2.5; 10/4.0), cancer of the digestive system (SMR, 4.0; 5/1.2) and cancer of the respiratory system (SMR, 2.8; 5/1.8). Among the low-exposure group, a significant excess occurred for mouth and throat cancer (SMR, 5.7; 2/0.35).

Sorahan and Cathcart (1989) extended the follow-up of their cohort through 1984 and conducted a nested case–control study of lung cancer to obtain more detailed information on occupational risks and to control for possible confounding by smoking. Twenty-six lung cancers were each matched to three controls by age and year of starting employment. A significant excess for lung cancer occurred among the high-exposure group (SMR, 3.3; 10/3.0), but not among the low-exposure group (SMR, 1.4; 16/11.5). Conditional logistic regression of the case–control data revealed relative risks of 1.4 (95% confidence interval (CI), 0.4–4.2) for benzotrichloride, 1.1 (95% CI, 0.3–4.2) for other chlorinated toluenes and 3.0 (95% CI, 0.3–25.8) for smoking. The relative risks for chemicals are expressed per 10 years of exposed employment.

A mortality study was conducted among 697 male employees (610 whites and 11 assumed to be white) at a chlorination plant in Tennessee (United States) (Wong, 1988). The cohort consisted of all employees at the plant between 1943 and 1980. Almost all of the cohort held jobs with potential exposure to benzotrichloride, benzyl chloride or benzoyl chloride, there being substantial overlap between these groups. The mortality data were compared with the United States national age- and cause-specific rates for five-

year time periods from 1940 to 1982. Respiratory tract cancer mortality was elevated for the entire cohort (7, including 6 lung cancers observed, 2.8 expected; SMR, 2.5; 95% CI, 1.0–5.0) and the white employees alone (7 observed, 2.7 expected; SMR, 2.7; 95% CI, 1.1–5.5). The respiratory cancer mortality was similarly elevated for the three specific chemical exposure subgroups. The values were: benzotrichloride SMR, 2.6 ($p < 0.05$); benzyl chloride or benzoyl chloride SMR, 2.6 ($p < 0.05$). The cohort was also divided according to length of employment (< 15 years and 15+ years). The respiratory tract cancer SMRs were 1.3 and 3.8 ($p < 0.05$), respectively. The author concluded that the data suggest an association between the process of toluene chlorination at the plant and an increased risk of respiratory cancer. [The Working Group noted that more precise identification of a single causative exposure is not possible from this study.]

3. Studies of Cancer in Experimental Animals

Benzyl chloride was tested in mice by skin application and in rats by subcutaneous injection. Sarcomas at the injection site in rats were observed in 6/8 high-dose and 3/14 low-dose compared with none in controls. Skin carcinomas were observed in 3/20 exposed mice whereas none was observed in the vehicle (benzene) control mice. When benzyl chloride was administered to mice and rats in corn oil by gavage, increased incidences of papillomas and carcinomas of the forestomach were observed in mice of each sex, and the incidence of thyroid C-cell tumours was increased in female rats but decreased in male rats; a few neoplasms of the forestomach were observed in male rats (IARC, 1982, 1987a).

Benzal chloride was tested in two experiments in mice by skin application, the results of which were reported together. In the first experiment, the total dose of benzal chloride was about 289 mg per mouse during a 50-week dosing period, after which all mice were killed at week 82. No skin tumours developed in 20 controls, while, in the treated group of 19 (14 of which had died by the end of the experiment), nine mice had squamous cell carcinomas of the skin and two had skin fibrosarcomas. In the other experiment in which the total benzal chloride dose was about 1109 mg per mouse, but which was terminated after just 43 weeks, 2/10 mice developed skin papillomas compared with 0/10 in the controls (IARC, 1982).

Benzotrichloride was tested in three studies by skin application to female mice. It produced squamous cell carcinomas of the skin and lung tumours in all three experiments; upper digestive tract tumours were also observed in two of the three experiments. Increases in the incidence of tumours at other sites were reported. In a strain A mouse lung tumour bioassay, benzotrichloride increased the incidence of lung adenomas (IARC, 1982, 1987a).

Benzoyl chloride was tested in two experiments by skin application to female mice. A few skin carcinomas and lung adenomas were observed, but their incidence was not significant. However, no skin tumours occurred in controls of either experiment or lung tumours in controls of one of them (IARC, 1982).

3.1 Oral administration

Mouse: Groups of 40 female ICR mice, nine weeks of age, were administered benzotrichloride (reagent grade) by gavage at doses of 0, 0.0315, 0.125, 0.5 and 2 μL/mouse twice per week for 25 weeks and the experiment was terminated at 18 months. The mortality of exposed mice increased dose-dependently. The 0.5 and 2 μL doses induced forestomach papillomas and carcinomas in 23/40 ($p < 0.01$; Fisher's exact test) and 25/38 ($p < 0.01$) mice, respectively, compared with 0/39 controls. Higher incidences of lung adenomas and carcinomas were also found: 7/39 [not significant] at 0.0315 μL, 26/39 ($p < 0.01$) at 0.125 μL, 35/40 ($p < 0.01$) at 0.5 μL and 24/38 ($p < 0.01$) at 2 μL compared with 1/39 controls. The highest dose also induced thymic lymphomas in 8/38 ($p < 0.01$) mice compared with 1/39 controls (Fukuda *et al*., 1993).

3.2 Inhalation exposure

Mouse: Groups of female ICR-Jcl mice were exposed to air or benzotrichloride vaporized at either 50°C (6.7 ± 1.66 ppm [54 ± 13 mg/m^3]) for five months or 20 ± 5°C (1.62 ± 0.43 ppm [13 ± 3.4 mg/m^3]) for 12 months, for 30 min per day on two days per week. Afterwards, they were observed for a further five months (50°C vaporization) or three months (20°C vaporization). In the control, exposed (50°C) and exposed (20°C) groups, respectively, lung tumours were observed in 3/30 (3 adenomas), 17/32 (16 adenomas, 1 adenocarcinoma) and 30/37 (17 adenomas, 13 adenocarcinomas) mice; skin tumours were observed in 0/30, 8/32 (4 papillomas, 4 carcinomas; $p < 0.02$) and 10/37 (6 papillomas, 4 carcinomas) mice; and malignant lymphomas were observed in 0/30, 8/32 ($p < 0.02$) and 4/37 mice. The differences in incidence were significant (Yoshimura *et al*., 1986).

Groups of female ICR-Jc1 mice were exposed to air or to benzoyl chloride vaporized at 50°C [concentration not stated] for 30 min per day on two days per week for five months. They were then observed for a further seven to nine months (12–14 months total). In the control and exposed groups, respectively, lung tumours were observed in 3/30 (3 adenomas) and 3/28 (1 adenoma and 2 adenocarcinomas) mice and skin papillomas in 0/30 and 2/28 mice. The differences in incidence were not significant (Yoshimura *et al.*, 1986). [The Working Group noted the short duration of exposure and observation time, allowing only comparison with mice simultaneously exposed to benzotrichloride.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Benzyl chloride is absorbed through lung and gastrointestinal tract. It can react with tissue proteins and is metabolized in rodents and rabbits to *N*-acetyl-*S*-benzylcysteine (benzyl mercapturic acid) through side-chain conjugation and to benzoic acid and the glycine conjugate of benzoic acid (hippuric acid). The percentages of the dose excreted in the urine as benzyl mercapturic acid in rats, guinea-pigs and rabbits, respectively, were 27%, 4% and 49%. Rabbits also excrete about 37% as benzoic acid (17% free acid and 20% conjugated). In rats, 30% of the dose was recovered as the hippuric acid derivative (IARC, 1982).

In rats receiving [^{14}C]benzyl chloride in corn oil by gavage, the peak plasma level was reached after 30 min. The distribution half-life was 1.3 h, while the elimination half-life was 58.5 h. After 48 h, the higher concentrations were found in the stomach, gastric contents, ileum and duodenum, followed by liver, adrenal, bone marrow and blood. After 72 h, approximately 76% was excreted in urine and, in expired air, 7% as $^{14}CO_2$ and less than 1.3% as benzyl chloride or its metabolites. Urinary metabolites were identified as *S*-benzyl-*N*-acetyl cysteine, benzyl alcohol and benzaldehyde (Saxena & Abdel-Rahman, 1989).

No data were available on the disposition of benzotrichloride, benzal chloride or benzoyl chloride.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride are irritant to the eyes, skin and respiratory tract of mice exposed by skin application (IARC, 1982).

In rats and mice, benzyl chloride, benzotrichloride and benzal chloride produce signs of central nervous system toxicity and hyperaemia of the extremities (IARC, 1982).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Oral administration to rats of 0.006 mg/kg bw benzyl chloride per day on days 1–19 of gestation increased embryolethality, but doses of 0.0006 or 0.00006 mg/kg bw per day did not produce any malformations (IARC, 1982).

No data were available on the reproductive and developmental effects of benzotrichloride, benzal chloride or benzoyl chloride.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Benzyl chloride was the subject of a large, multilaboratory investigation, as a consequence of which there are numerous data that were tabulated in a previous volume (IARC, 1987b). A few additional data have become available (see Table 1). Benzyl chloride induced DNA damage and mutations in bacteria. It induced somatic and sex-linked recessive lethal mutations in *Drosophila melanogaster* and mitotic recombination, gene conversion, mutation and DNA damage in fungi. Benzyl chloride induced sister chromatid exchanges, chromosomal aberrations, mutations and DNA strand breaks in cultured rodent cells. In cultured human cells, it induced DNA strand breaks, but not chromosomal aberrations; conflicting results were obtained for induction of sister chromatid exchanges. Benzyl chloride did not induce micronuclei in mice *in vivo*. [^{14}C]Benzyl chloride injected intravenously into mice arylated DNA in various organs, the higher concentrations one hour after injection being found in brain and testis, followed by liver and lung. The principal adduct cochromatographed with *N7*-benzylguanine (Solveig Walles, 1981).

Benzal chloride induced DNA damage and mutations in bacteria.

Benzotrichloride induced DNA damage and mutations in bacteria.

No activity of benzoyl chloride was observed in single bacterial tests for either differential toxicity or mutation induction.

Lung adenomas derived from control and benzotrichloride-treated strain A/J mice (Stoner *et al*., 1986) were examined for the presence of activated K-*ras* proto-oncogenes. DNA segments were amplified using the polymerase chain reaction and sequenced to identify the mutations. An activated K-*ras* protooncogene was detected in all of the lung tumours tested. In the control mouse lung tumours (described in an earlier publication, You *et al*., 1989), activating mutations were in both codon 12 (6/10, 60%) and codon 61 (3/10, 30%) with several types of nucleotide substitution. In contrast, all of the activating mutations in tumours from benzotrichloride-treated mice (24/24) were in codon 12 and were exclusively GC→AT transitions, whereas only 27% of the K-*ras* mutations in spontaneous tumours were GC→AT transitions. The authors conclude that this result may indicate a direct genotoxic effect of benzotrichloride, although selective promotion of the GC→AT transition during tumorigenesis induced by benzotrichloride cannot be excluded (You *et al*., 1993).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Little information on occupational or environmental exposures to these chemicals was available to the Working Group.

5.2 Human carcinogenicity data

Small cohort studies of occupational exposures to α-chlorinated toluenes and benzoyl chloride in the United States and England each noted an approximately three-fold excess of lung cancer.

Table 1. Genetic and related effects of chlorinated toluenes and benzoyl chloride

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Benzyl chloride				
ECD, *Escherichia coli pol* A, differential toxicity (spot test)	+	NT	275 000	Fluck *et al*. (1976)
ECD, *Escherichia coli pol* A, differential toxicity (spot test)	–	NT	10 000	Rosenkranz & Poirier (1979)
ECL, *Escherichia coli pol* A, differential toxicity (liquid suspension test)	+	+	10	Rosenkranz & Poirier (1979)
BSD, *Bacillus subtilis rec*, differential toxicity	(+)	NT	10 000 µg/disk	Yasuo *et al* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	500	Yasuo *et al*. (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	125	Simmon (1979a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	–	31.5	Neudecker *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	+	50	Ashby *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	(+)	500	Brooks & Gonzalez (1982a)
SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test)	?	?	2000 µg/disk	Hyldig-Nielsen & Hartley-Asp (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	125	Jones & Richold (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	25	Kirkland *et al.* (1982a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	200	Ladner (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	112	Moore & Chatfield (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	NT	150	Pour *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation (fluctuation test)	NT	–	250	Sargent & Regnier (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	1250	Trueman & Callander (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	250	Varley (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	250	Venitt *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	250	Watkins & Rickard (1982)

Table 1 (contd)

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	5	Booth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	40	Hemminki *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	–	5000	Rosenkranz & Poirier (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	125	Simmon (1979a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2000	Brooks & Gonzalez (1982a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	125	Jones & Richold (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	500	Kirkland *et al*. (1982a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	200	Ladner (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	1250	Trueman & Callander (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Varley (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Watkins & Rickard (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Booth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	125	Simmon (1979a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2000	Brooks & Gonzalez (1982a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	125	Jones & Richold (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	NT	500	Kirkland *et al*. (1982a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	200	Ladner (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	NT	1250	Trueman & Callander (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Varley (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Watkins & Rickard (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Booth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000	Rosenkranz & Poirier (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	125	Simmon (1979a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2000	Brooks & Gonzalez (1982a)

Table 1 (contd)

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation (spot test)	–	–	2000 µg/disk	Hyldig-Nielsen & Hartley-Asp (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	125	Jones & Richold (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	500	Kirkland *et al*. (1982a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	200	Ladner (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	1250	Trueman & Callander (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Varley (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Watkins & Rickard (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Booth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	125	Simmon (1979a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2000	Brooks & Gonzalez (1982a)
SA9, *Salmonella typhimurium* TA98, reverse mutation (spot test)	–	–	2000 µg/disk	Hyldig-Nielsen & Hartley-Asp (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	125	Jones & Richold (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	500	Kirkland *et al*. (1982a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	200	Ladner (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	250	Pour *et al*. (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Sargent & Regnier (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation (fluctuation test)	+	+	10	Styles & Pritchard (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	1250	Trueman & Callander (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Varley (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Venitt *et al*. (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Watkins & Rickard (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Booth *et al*. (1983)

Table 1 (contd)

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	40	Hemminki *et al*. (1983)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	–	125	Simmon (1979a)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	NT	250	Kirkland *et al*. (1982a)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	+	100	Venitt *et al*. (1982)
EC2, *Escherichia coli* WP2, reverse mutation	+	–	400	Yasuo *et al*. (1978)
EC2, *Escherichia coli* WP2, reverse mutation	+	NT	25	Kirkland *et al*. (1982a)
SSB, *Saccharomyces cerevisiae* D6, strand breaks, cross-links	+	NT	100	Tippins (1982)
SSD, *Saccharomyces cerevisiae rad* mutants, differential toxicity	+	NT	100	North & Parry (1982)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	+	+	250	Brooks & Gonzalez (1982b)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	+	NT	125	Goodwin & Parry (1982)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	+	NT	220	Mitchell & Gilbert (1982)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	+	+	0.5	Parry (1982a)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	+	+	125	Wilcox & Parry (1982)
SCH, *Saccharomyces cerevisiae* D3, homozygosis	(+)	(+)	400	Simmon (1979b)
SCH, *Saccharomyces cerevisiae* D7, homozygosis	+	NT	50	Kelly & Parry (1982)
SCH, *Saccharomyces cerevisiae* D6, homozygosis	+	+	25	Parry (1982b)
ANG, *Aspergillus nidulans*, genetic crossing-over	+	NT	100	Igwe & Cohn (1982)
ANG, *Aspergillus nidulans*, genetic crossing-over	+	+	500	Watkins (1982)
SCF, *Saccharomyces cerevisiae* D7, forward mutation	–	NT	500	Goodwin & Parry (1982)
SCF, *Saccharomyces cerevisiae* D4, forward mutation	+	NT	330	Mitchell & Gilbert (1982)
ANR, *Aspergillus nidulans*, reverse mutation	+	NT	100	Igwe & Cohn (1982)
NCR, *Neurospora crassa*, reverse mutation	+	NT	50	Luker (1982)
SCN, *Saccharomyces cerevisiae* D6, aneuploidy	–	–	200	Parry (1982b)
ANN, *Aspergillus nidulans*, aneuploidy	–	–	2500	Watkins (1982)

Table 1 (contd)

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMM, *Drosophila melanogaster*, somatic mutation and recombination	+		126 feed	Fahmy & Fahmy (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		252 feed	Fahmy & Fahmy (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		504 feed	MacDonald & Telford (1982)
DIA, DNA strand breaks, cross-links, Chinese hamster lung V79 cells *in vitro*	+	NT	126	Swenberg (1981)
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*	+	NT	18	Phillips & James (1982)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	NT	+	11	Lee & Webber (1982)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	18	Mirzayans *et al*. (1982a)
G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance *in vitro*	–	NT	25	Mirzayans *et al*. (1982a)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	10	Ross & McGregor (1982)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	8	McGregor *et al*. (1988)
G51, Gene mutation, mouse lymphoma L5178Y cells, ouabain resistance *in vitro*	–	NT	NG	Booth *et al*. (1983)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	10	Phillips & James (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	12.7	Hemminki *et al*. (1983)

Table 1 (contd)

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	14	Phillips & James (1982)
CIC, Chromosomal aberrations, Chinese hamster lung cells *in vitro*	(+)	+	30	JETOC (1997)
CIR, Chromosomal aberrations, rat cells *in vitro*	+	NT	15	Malallah *et al*. (1982)
TCM, Cell transformation, C3H 10T½ mouse cells *in vitro*	–	–	20	Poole & McGregor (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*	+	NT	0.1	Pienta *et al* (1977)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*	–	NT	5	Poiley *et al*. (1980)
DIH, DNA strand breaks, cross-links, human alveolar tumour cells *in vitro*	+	NT	125	Mirzayans *et al*. (1982b)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	10	Hartley-Asp (1982a)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	5	Kirkland *et al*. (1982b)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	10	Hartley-Asp (1982a)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	10	Kirkland *et al*. (1982b)
BFA, Urine of mice, *Salmonella typhimurium* TA100, TA98, TA1535, TA1537, TA1538 mutagenicity	–		550 ip × 2	Jones & Richold (1982)
HMM, Host-mediated assay, *Salmonella typhimurium* TA1530, TA1538 and *Saccharomyces cerevisiae* D3 in Swiss-Webster mice	–		4400 im × 1	Simmon *et al*. (1979)
MVM, Micronucleus test, male TuckTO mice *in vivo*	–		300 ip × 2	Danford & Parry (1982)
MVM, Micronucleus test, NMRI mice *in vivo*	–		400 po × 2	Hartley-Asp (1982b)
MVM, Micronucleus test, CD-1 mice *in vivo*	–		876 po × 2	Holmstrom *et al*. (1982)
MVM, Micronucleus test, CD-1 mice *in vivo*	–		550 ip × 2	Richardson *et al*. (1982)

Table 1 (contd)

	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVM, Micronucleus test, (CBA × BALB/c)F_1 mice *in vivo*	–		2000 sc × 1	Scott & Topham (1982)
Benzal chloride				
BSD, *Bacillus subtilis rec*, differential toxicity	+	NT	5000 µg/disk	Yasuo *et al*. (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	100	Yasuo *et al*. (1978)
EC2, *Escherichia coli* WP2, reverse mutation	–	+	100	Yasuo *et al*. (1978)
Benzotrichloride				
BSD, *Bacillus subtilis rec*, differential toxicity	+	NT	500 µg/disk	Yasuo *et al*. (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	195	Yasuo *et al*. (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	100	Yasuo *et al*. (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	100	Yasuo *et al*. (1978)
EC2, *Escherichia coli* WP2, reverse mutation	–	+	100	Yasuo *et al*. (1978)
Benzoyl chloride				
BSD, *Bacillus subtilis rec*, differential toxicity	+	NT	100 µg/disk	Yasuo *et al*. (1978)
EC2, *Escherichia coli* WP2, reverse mutation	–	+	500	Yasuo *et al*. (1978)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; ip, intraperitoneal; im, intramuscular; po, oral; sc, subcutaneous

5.3 Animal carcinogenicity data

Benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride have been studied by skin application to mice. Small numbers of skin tumours were produced by benzyl chloride and benzoyl chloride, while clear increases in skin tumours were produced by benzal chloride and benzotrichloride. Following subcutaneous injections to rats, benzyl chloride produced some injection site tumours. Administration by gavage of benzyl chloride to mice and rats produced forestomach tumours in mice and a few neoplasms of the forestomach were observed in male rats. Benzotrichloride administered by gavage to mice produced tumours of the forestomach and lungs. In addition, benzotrichloride and benzoyl chloride were administered by inhalation to mice: benzotrichloride produced increases in the incidences of tumours of the lung and skin, whereas no significant increase in tumour incidence was observed after benzoyl chloride administration.

5.4 Other relevant data

No studies were available on the disposition of benzotrichloride, benzal chloride or benzoyl chloride. Benzyl chloride is rapidly absorbed and distributed from the gastrointestinal tract. Excretion is mainly in urine as *S*-benzyl-*N*-acetylcysteine, benzyl alcohol and benzaldehyde.

All of the compounds are irritant to the skin and mucous membranes.

Benzyl chloride, benzal chloride and benzotrichloride, but not benzoyl chloride, are bacterial mutagens. Only benzyl chloride has been more extensively tested. It is genotoxic to fungi, *Drosophila melanogaster* and cultured mammalian cells, but did not increase the frequency of micronuclei in mice.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of α-chlorinated toluenes and benzoyl chloride.

There is *sufficient evidence* in experimental animals for the carcinogenicity of benzyl chloride.

There is *limited evidence* in experimental animals for the carcinogenicity of benzal chloride.

There is *sufficient evidence* in experimental animals for the carcinogenicity of benzotrichloride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of benzoyl chloride.

Overall evaluation

Combined exposures to α-chlorinated toluenes and benzoyl chloride are *probably carcinogenic to humans (Group 2A)*.

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