

Benzene

Toxicological overview

Key Points

Kinetics and metabolism

- The primary route of entry is via inhalation. Dermal absorption is poor.
- Reactive metabolites such as benzene oxide have been implicated in the mechanism(s) of benzene toxicity.

Health effects of acute exposure

- Acute exposure may resemble solvent intoxication, clinically manifest as drowsiness, dizziness, delirium, loss of consciousness, respiratory arrest and death.

Health effects of chronic exposure

- Two, well documented adverse health effects of chronic benzene exposure are anaemia and leukaemia.
- Benzene is a known human carcinogen and clastogen but is not considered to be a reproductive toxicant.

Toxicological Overview

Summary of Health Effects

Acute exposure to relatively high concentrations of benzene (benzol) may result in CNS disturbances consistent with solvent exposure, *viz.*, drowsiness, dizziness, headache, tremor, delirium, ataxia, loss of consciousness, respiratory arrest and death [1].

A characteristic effect of chronic benzene exposure is aplastic anaemia, resulting from suppression of bone marrow tissue [2]. Benzene is a known human carcinogen, with a substantial number of case reports and epidemiological studies providing evidence of a causal relationship between occupational (chronic) exposure and various types of leukaemia [3]. It is currently hypothesised that the carcinogenic effects of benzene are predominantly mediated via metabolites such as benzene oxide [4]. It is mutagenic and a genotoxic carcinogen. The assumption is made that there is no threshold to such effects and that any exposure results in some increase in risk, albeit this may be very small.

Kinetics and metabolism

Benzene is well absorbed by inhalation [11]: systemic absorption of benzene from the lungs is greatest over the first few minutes of exposure (70 – 80% of inhaled dose) and decreases thereafter to approximately 50% of the inhaled dose after one hour [12].

Dermal absorption of benzene is generally considered to be poor. When applied as a discrete droplet, 99.9% of an applied dose may vaporise from the skin surface before being absorbed [13]. However, excessive dermal contamination may make a substantial contribution to the daily intake and so skin contact with benzene should be avoided [14].

Systemic absorption of benzene after ingestion is likely to be high, especially when dissolved in water and case reports of poisoning indicate that benzene is extensively absorbed by the oral route [11].

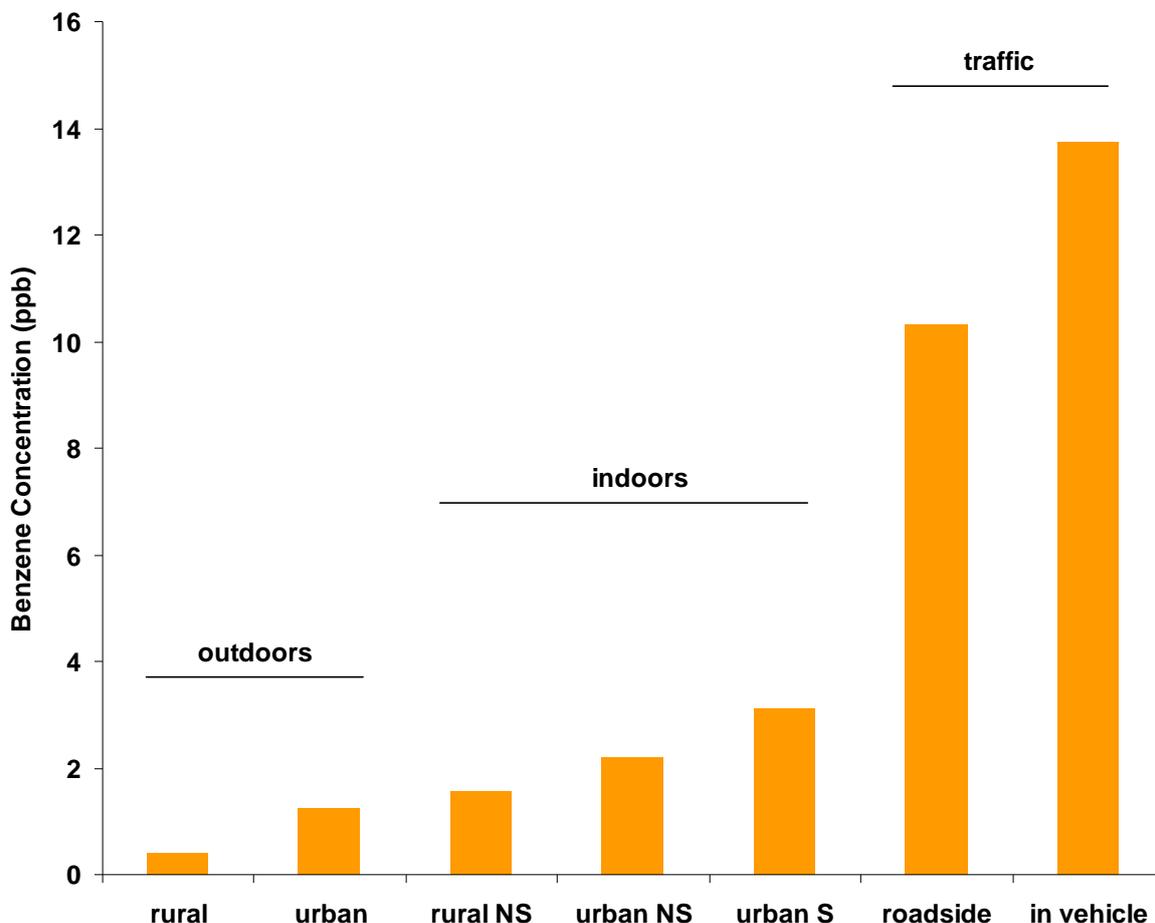
The metabolism of benzene has been widely studied in human and animal models due to its putative role in carcinogenesis (metabolic activation) [15, 16]. The metabolic pathways implicated in benzene toxicity are broadly comparable across species. However, there are significant species-specific differences in the extent to which benzene is metabolised by each pathway [17]. Furthermore, the proportion of benzene metabolised by each pathway appears to be dose-dependent, with hydroquinone and phenyl conjugation pathways predominating at lower (<10ppm) and higher (>10ppm) concentrations, respectively ([18, 19] as reviewed by [1]).

Two enzymes have been particularly implicated in the mechanism of benzene toxicity: cytochrome P450 2E1 (CYP2E1) and quinone oxidoreductase (NQO1). Absence of CYP2E1 leads to a reduction of the cytotoxic and genotoxic effects of benzene in transgenic mice [20]. Conversely, susceptibility to benzene toxicity is augmented in human individuals and animals lacking NQO1 [21, 22]. Although the actual metabolite that is responsible for the carcinogenic effects of benzene has not been definitively identified [16], there is evidence that this is mediated by benzene oxide, a reactive metabolite of CYP2E1 [4] which is sufficiently stable ($t_{1/2} \sim 7 - 9$ minutes) to ensure distribution throughout the body.

Sources and route of human exposure

Benzene is a ubiquitous air pollutant which can vary widely in concentration according to location (Figure 1). Historically, road traffic vehicles have represented the major source of benzene in the UK and accounted for ~ 60% of total emissions in 1990 [5]. Legislation to decrease the benzene content of engine fuels to less than 1% [6] and the compulsory introduction of catalytic converters on vehicle exhausts have significantly reduced this source of pollution; in 2004, road vehicles accounted for less than 20% of UK benzene emissions [5]. Domestic sources currently contribute the greatest proportion (33%) of benzene emissions, principally through the combustion of fuels for cooking and heating and the operation of garden appliances such as lawn mowers and patio heaters [5].

Figure 1: Approximate concentrations of benzene in ambient air; data from [7].
 “ppb” = parts per billion; “NS” = non-smoker; “S” = smoker.



Contributions to the daily intake of benzene from food and water are relatively low (less than 1½ to 2% of total; Table 1), although contaminated groundwater may potentially represent a significant source of benzene exposure [8]. For the majority of the population, smoking and proximity to road traffic are the predominant factors affecting daily exposure (Table 1). Ambient air concentrations of benzene within dwellings tend to be around twice as high as comparable outdoor concentrations (Figure 1) and smoking indoors can make a significant contribution to the concentration of benzene [9].

Table 1: Current estimated (average) daily intake of benzene in adults; data from [10].

Source		Total Benzene (µg day ⁻¹)
Diet	Food	1.5
	Water	< 0.1
Air	Rural (non smoker)	73
	Urban (non-smoker)	92
Smoking	20 cigarettes per day	400

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Benzene is not generally regarded as an acutely toxic material and there are correspondingly few reports pertaining to the (human) health effects of a single exposure. In general, acute exposure to concentrations of benzene in excess of 500 ppm may illicit signs and symptoms consistent with solvent intoxication (Table 2). Overt signs of exposure have previously been referred to as “benzol jag”, characterised by euphoria, unsteady gait and confusion [23]. Recovery from an acute exposure is dose-dependent, with breathlessness, nervous irritability and unsteadiness in gait persisting in severe cases for two to three weeks [24].

Table 2: Summary of acute benzene vapour toxicity [11].

Concentration		Duration of exposure (min)	Effect(s)
ppm	mg m ⁻³		
25	80	480	No observable effect
50-150	160-480	300	Headache, lassitude, weakness
500	1,600	60	Symptoms of illness
1500	4,800	60	Serious symptoms
3000	9,600	30	Endurable
7500	24,000	30	Dangerous to life
19000-20000	60,800-64,000	5-10	Fatal

Inhalation

The commonly quoted “lethal dose” of benzene (20,000 ppm) is an estimate based on a review of a single case report following 5 – 10 minutes’ exposure [25]. Fatal exposures have been associated with asphyxiation, respiratory arrest, central nervous system depression and possibly cardiac arrhythmias [26]. Death may be due to CNS depression, asphyxiation or respiratory or circulatory arrest. It has been observed that aspiration of benzene directly onto the lungs causes “immediate pulmonary oedema and haemorrhage at the site of contact with the pulmonary tissue” [24].

Benzene is irritating to the nose and respiratory tract at “high” concentrations [24].

Ingestion

The single, acute lethal dose of benzene in humans is estimated to be 125 mg kg⁻¹, equivalent to 10 ml per 70 kg man⁻¹. Signs of intoxication following ingestion include staggered gait, vomiting, shallow and rapid pulse, somnolence, delirium, pneumonia, central nervous system depression, coma and death [11].

Dermal / ocular exposure

Whilst benzene is poorly absorbed through the skin, prolonged or excessive contact may cause signs consistent with the defatting (delipidising) effects of organic solvents, viz., erythema, vesiculation and dermatitis [27].

Benzene vapour may cause a smarting effect on the eyes at high concentrations. Eye contamination with droplets of benzene may cause a moderate burning sensation with only slight, transient injury to the epithelial cells [28].

Delayed effects following an acute exposure

Most cases of acute benzene intoxication resolve spontaneously or with supportive care in the absence of long-term sequelae [29].

Health Effects of Chronic / Repeated Exposure

Human Data

General toxicity

The adverse health effects of chronic benzene exposure have been extensively documented and primarily relate to impairment of the haemopoietic system [23-34], with bone marrow depression leading to aplastic anaemia being the most common clinical manifestation (occurring in approximately 1% of individuals exposed to > 100 ppm benzene) [11, 30]. Other effects on the haemopoietic system include leukopenia, agranulocytosis, anaemia, pancytopenia and myelodysplastic syndrome [31]. Benzene is also established as being leukaemogenic in humans [3, 32-38]. Exposures to 1 ppm benzene for 40 working years has been considered not to be associated with any increase in leukaemia or any other haematological abnormality [11, 39]. However, since benzene is a genotoxic carcinogen (see below) the assumption is made that there is no threshold for its effect. I.e. any exposure is associated with some increase in risk, although this may be very small [4].

Susceptibility to benzene toxicity has been related to genetic polymorphisms [40-45]. For example, an excess of CYP2E1 [46-48] or deficiency of quinone oxidoreductase (NQO) [49-51] may enhance benzene toxicity. Indeed, one study has suggested that chronic benzene exposure to less than 1 ppm may induce haematotoxic effects in such genetically susceptible populations, although it was recognised that more data were required before any definite conclusions could be drawn [52].

Other factors that influence the toxicity of benzene include the systemic distribution rates of metabolites and consequent events within bone marrow tissue such as secondary metabolic activation, induction of apoptosis, altered differentiation of early progenitor cells and depletion of the stem cell pool [30].

In addition to effects on the haematopoietic system, benzene exposures have been implicated in neurological disorders [53], immune dysfunction [11] and cancer [3]. Further, detailed information on the general toxicity of benzene can be obtained from a number of comprehensive reviews [11, 26, 36, 54].

Genotoxicity

Benzene is a human clastogen [3]: chronic exposure results in consistent structural and numerical chromosomal aberrations in lymphocytes and bone marrow cells which may be observed for at least five years after cessation of (occupational) exposure [11].

Although the actual metabolite that is responsible for the carcinogenic effects of benzene has not been definitively identified [16], there is evidence that it is mediated by benzene oxide, a metabolite of CYP2E1 which is sufficiently stable ($t_{1/2} \sim 7 - 9$ minutes) to ensure distribution throughout the body [9].

Carcinogenicity

Benzene is classified by the IARC as Group 1 human carcinogen [3] and its role as a leukaemogen has been clearly established through a number of epidemiological studies (Table 3).

Table 3: Empirical summary of studies pertaining to chronic (occupational) benzene exposure and putative disease outcomes. Putative disease outcome = disease state associated/correlated with occupational benzene exposure. Data derived from IPCS [11].

Study Type [¶]	“n”	Putative disease outcome	Original Reference
Case	44	Leukaemia	[55]
	63	Leukaemia, multiple myeloma, malignant lymphoma	[56]
	94	Hodgkin's disease	[57]
	1	Subacute granulocytic leukaemia	[58]
	6	Haemocytoblastic leukaemia	[59]
	1	Acute myelogenous leukaemia	[60]
Epidemiology	28,500	Aplastic anaemia, acute leukaemia	[61]
		Myeloid and monocytic leukaemia	[62]
		Leukaemia, multiple myeloma	[63]
	956	Leukaemia, acute myelogenous leukaemia	[64]
	3636	Leukaemia	[65]
	259	Lymphatic and haemopoietic neoplasms	[66]
	2013	Aplastic anaemia, leukaemia	[67]
	28,460	Acute and chronic leukaemia	[68]
	391	Leukaemia	[69]
	Leukaemia	[70]	

Reproductive and developmental toxicity

Benzene diffuses across the placenta and is considered to be fetotoxic in the presence of maternal toxicity [27]. Benzene is not considered to be a teratogen and there is currently no evidence that it causes reproductive effects in humans [71].

Animal Data

Animal studies are largely in accordance with the known toxicity of benzene in humans. However, the carcinogenic effects of benzene in animals is primarily associated with epithelial tissue rather than leukaemia [11].

General toxicity

Numerous repeated dose studies in animals have shown that benzene produces bone marrow depression leading to a range of haematological effects including reduction in haematocrit, decreased haemoglobin and a reduction in RBC (red blood cell), WBC (white

blood cell) and platelet counts. Decreased proliferation of B and T lymphocytes and resistance to infection has also been demonstrated [11].

Genotoxicity

Although assays for the ability of benzene to induce gene mutations in bacteria were negative, benzene has consistently given positive results from *in-vitro* assays for clastogenicity [72]. Thus, benzene clearly has mutagenic potential. There is *in-vivo* evidence to demonstrate that benzene is both clastogenic and induces gene mutations in animals. For example, in studies with transgenic mice (using lac1 as a reporter gene), benzene induced gene mutations in the lung and spleen [11]. Benzene is clearly an *in-vivo* mutagen.

Carcinogenicity

Benzene has been shown to produce several types of neoplasms in both rats and mice after either oral dosing or inhalation exposure. These include various types of epithelial neoplasms and a few lymphomas and leukaemias [11].

Reproductive Toxicity

A number of studies have been carried out to investigate the effect of exposure to benzene during pregnancy. None has detected any teratogenic potential even at exposure levels that produced some evidence of toxicity in the maternal animals. Some adverse effects on the foetus (reduced birth weight and/or minor skeletal variants) were seen at relatively high exposure levels (~ 150 mg m⁻³ and above). Some haematopoietic changes were observed in offspring from adults exposed to lower levels (16 mg m⁻³ and above) [11].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.