HPA Compendium of Chemical Hazards

Benzene

Key Points

Fire

- Highly flammable volatile liquid
- Vapour/air mixtures may be explosive
- In the event of a fire involving benzene, use normal foam and wear liquid tight clothing and breathing apparatus

Health

- Toxic by inhalation and ingestion
- Harmful and irritant
- Carcinogen and possible mutagen
- Acute exposure to low levels can be irritating to eyes and can result in drowsiness, tachycardia, headaches, tremors, confusion and unconsciousness
- Chronic exposure to low levels can cause onset of a range of diseases including cancer
- Exposure to high levels may result in death
- Benzene can cause leukaemia
- It is not known if benzene can cause damage to the unborn child

Environment

- Avoid release into the environment
- Inform Environment Agency of substantial release incidents

Prepared by R P Chilcott
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2011
Version 4

Contents

Benzene

General information

Key Points

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- In the event of a fire involving benzene, use normal foam and wear liquid tight clothing and breathing apparatus

Health

- Toxic by inhalation and ingestion
- Harmful and irritant
- Carcinogen and possible mutagen
- Short term exposure to low levels can be irritating to eyes and can result in drowsiness, rapid heart rate, headaches, tremors, confusion and unconsciousness
- Long term exposure to low levels can cause onset of a range of diseases including cancer
- Exposure to high levels may result in death
- Benzene can cause leukaemia (a type of blood cancer)
- It is not known if benzene can cause damage to the unborn child

Environment

- Avoid release into the environment
- Inform Environment Agency of substantial release incidents

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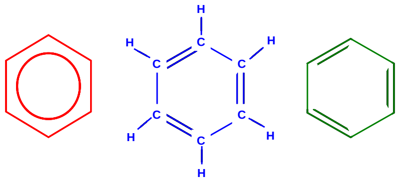
Version 2

Background

Benzene is mainly produced from crude oil and is a colourless, volatile liquid with a characteristic sweet odour.

Benzene is described as an "aromatic" hydrocarbon and is composed of a ring of six carbon atoms which can be represented by any one of three structures:

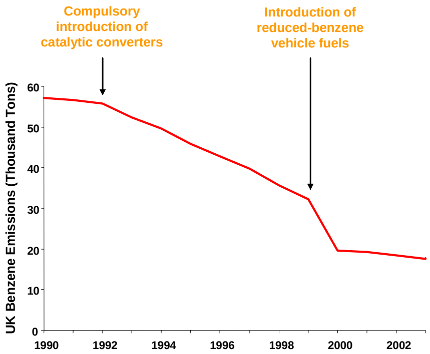


Benzene is normally present in the air at low concentrations, ranging from around 1 part per billion (ppb) in rural locations to 67 ppb at peak times in industrial areas. Nearly all airborne benzene is due to human activity, a proportion of which is due to road traffic emissions.

Benzene is also produced as a product of combustion and can be found in smoke arising from fires and tobacco products.

Around 640 thousand tons of benzene is used annually in the UK, mainly in the manufacture of other chemicals such as plastics, foams, dyes, detergents, solvents, drugs and insecticides. Before its toxic nature was realised, benzene was previously used in cosmetics (e.g. aftershaves), domestic (cleaning) solvents and in the process of decaffeinating coffee. Its use in such consumer products or processes is no longer permitted.

Two measures have substantially contributed to the reduction of benzene emissions in the UK; the compulsory introduction of catalytic converters on car exhausts and legislation to reduce benzene levels in car fuels:



Benzene is toxic, has mutagenic properties and can cause cancer in humans. Short term exposure to low levels can be irritating to eyes, cause drowsiness, dizziness, rapid heart rate, headaches, tremors, confusion and in some cases unconsciousness. Exposure to high concentrations can result in death.

In the past, occupational exposure has been shown to produce a range of diseases, including a decrease in white blood cells (which normally help fight infections), leukaemia (a type of blood cancer) and damage to DNA (mutagenicity). Therefore, exposures to benzene in the workplace are now subject to very strict limits.

Frequently Asked Questions

What is benzene?

Benzene is a colourless, volatile liquid with a characteristic sweet odour. Each molecule of benzene is composed of a ring of six carbon atoms (each connected to a hydrogen atom). Benzene is the starting material for a range of chemicals used in major industrial manufacturing processes.

How does benzene get into the environment?

The vast majority of benzene emissions are produced from internal combustion engines (i.e. from road traffic) and manufacturing processes, with smaller amounts being produced from fires and recycling processes.

How can I be exposed to benzene?

As a volatile liquid, benzene rapidly evaporates and is a common air pollutant, although generally present in very low concentrations. Therefore, most exposures are from inhalation. An additional (significant) source of benzene is from smoking tobacco products.

If there is benzene in the environment will I have any adverse health effects?

The presence of benzene in the environment does not always lead to exposure. Clearly, in order for it to cause any adverse health effects you must come into contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact. Following exposure to any chemical, the adverse health effects you may encounter depend on several factors, including the amount to which you are exposed (dose), the way you are exposed, the duration of exposure, the form of the chemical and if you were exposed to any other chemicals.

In general, the concentrations of benzene in the air are very low and are unlikely to contribute to ill health. Short term exposure to low levels of benzene by inhalation can cause irritation to eyes, also drowsiness, dizziness, an increase in heart rate, the onset of headaches, tremors, confusion and in some cases can result in unconsciousness. Exposure to high concentrations of benzene by inhalation can result in death. Long term exposure has been shown to result in a range of diseases such as aplastic anaemia and leukaemia (a type of blood cancer).

Can benzene cause cancer?

Yes. Benzene is known to produce leukaemia in humans.

Does benzene affect children or damage the unborn child?

There is little information on the effects of benzene on children. However, they may be more susceptible to the effects of benzene due to their smaller size. No definite association has been made between exposure during pregnancy and birth defects. However, exposure to benzene during pregnancy should be avoided.

What should I do if I am exposed to benzene?

You should remove yourself from the source of exposure.

If you have got benzene on your skin, remove soiled clothing, wash the affected area with lukewarm water and soap for at least 10 – 15 minutes and seek medical advice.

If you have got benzene in your eyes, remove contact lenses, irrigate the affected eye with lukewarm water for at least 10 – 15 minutes and seek medical advice.

If you have inhaled or ingested benzene, seek medical advice.

Benzene

Incident management

Key Points

Fire

- Highly flammable
- Vapour/air mixtures may be explosive
- Low flash point
- In the event of a fire involving benzene, use normal foam and liquid tight fire kit with breathing apparatus

Health

- Toxic by inhalation, ingestion and skin contact
- Harmful and irritant
- Carcinogen and possible mutagen
- Exposure by any route may lead to CNS depression, convulsions and coma (consistent with solvent intoxication)
- Casualties may develop ventricular arrhythmias

Environment

- Avoid release into environment
- Inform Environment Agency of substantial release incidents

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Hazard Identification

Standard (UK) Dangerous Goods Emergency Action Codes[a]

UN		**1114**	Benzene	
EAC		**3WE**	Use normal foam. Wear liquid-tight chemical protective clothing in combination with breathing apparatus*. Spillages and decontamination run-off should be prevented from entering drains and watercourses. Substance can be violently or explosively reactive. There may be a public safety hazard outside the immediate area of the incident**.	
APP		**A(fl)**	Gas-tight chemical protective suit with breathing apparatus ***	
Hazards	**Class**	**3**	Flammable liquid	
	Sub risks	**-**		
HIN		**33**	Highly flammable liquid (flash-point below 23°C)	

UN – United Nations number; EAC – Emergency Action Code; APP – Additional Personal Protection; HIN - Hazard Identification Number

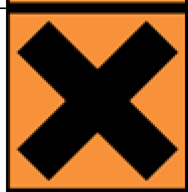
* Liquid-tight chemical protective clothing (BS 8428) in combination with self-contained open circuit positive pressure compressed air breathing apparatus (BS EN 137).

** People should stay indoors with windows and doors closed, ignition sources should be eliminated and ventilation stopped. Non-essential personnel should move at least 250 m away from the incident.

*** Gas-tight chemical protective clothing (BS EN 469 part 2) in combination with self-contained open circuit positive pressure compressed air breathing apparatus (BS EN 137).

[a] Dangerous Goods Emergency Action Code List, HM Fire Service Inspectorate, Publications Section, The Stationery Office, 2009.

Chemical Hazard Information and Packaging for Supply Classification[a]

Classification	**F**	Highly flammable	
	Carc. cat. 1	Category 1 carcinogen	
	Muta. Cat. 2	Category 2 mutagen	
	T	Toxic	
	Xn	Harmful	
	Xi	Irritant	
Risk phrases	**R45**	May cause cancer	
	R46	May cause heritable genetic damage	
	R11	Highly flammable	
	R36/38	Irritating to eyes and skin	
	R48/23/24/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed	
	R65	Harmful: may cause lung damage if swallowed	
Safety phrases	**S53**	Avoid exposure – obtain special instructions before use	
	S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)	

[a] Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures- Table 3.2.
http://esis.jrc.ec.europa.eu/index.php?PGM=cla (accessed 11/2011)

*Globally Harmonised System of Classification and Labelling of Chemicals (GHS)[(a)]**

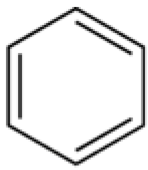
Hazard Class and Category	Flam. Liq. 2	Flammable liquids, category 2	
	Carc. 1A	Carcinogenicity, category 1A	
	Muta. 1B	Germ cell mutagenicity, category 1B	
	STOT RE 1	Specific target organ toxicity following repeated exposure, category 3	
	Asp. Tox. 1	Aspiration hazard, category 1	
	Eye Irrit. 2	Eye irritation, category 2A	
	Skin Irrit. 2	Skin irritation, category 2	

[a] Annex VI to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures- Table 3.1.
http://esis.jrc.ec.europa.eu/index.php?PGM=cla (accessed 11/2011)

Hazard Statement	**H225**	Highly flammable liquid and vapour
	H350	May cause cancer
	H340	May cause genetic defects
	H372**	Causes damage to organs through prolonged or repeated exposure
	H304	May be fatal if swallowed and enters airways
	H319	Causes serious eye irritation
	H315	Causes skin irritation
Signal Words	DANGER	

* Implemented in the EU on 20 January 2009.

Physicochemical Properties

CAS number	71-43-2
Molecular weight	78
Empirical formula	C_6H_6
Common synonyms	Benzol; Cyclohexatriene
State at room temperature	Liquid
Volatility	Highly volatile, vapour pressure: 102 mm Hg at 26°C
Specific gravity	0.9 at 15°C (water = 1)
Flammability	Flammable; flash point -11.1 °C
Lower explosive limit	1.3
Upper explosive limit	7.1
Water solubility	Low solubility in water; 0.2 % at 25 °C
Reactivity	May form explosive mixtures with air
Reaction or degradation products	-
Odour	Characteristic, sweet odour at lower concentrations with a disagreeable, irritating odour at higher concentrations.
Structure	

References[a,b,c]

[a] International Programme on Chemical Safety, Environmental Health Criteria 150: Benzene, 1993.
[b] The Merck Index (14th Edition). Entry 1066: Benzene, 2006.
[c] CIRUS Electronic Information System, London Fire Brigade, 2005 Edition.

Threshold Toxicity Values

EXPOSURE VIA INGESTION	
mg kg^{-1} bw	**SIGNS AND SYMPTOMS**
125	Lethal dose

EXPOSURE VIA INHALATION		
ppm	**mg m^{-3}**	**SIGNS AND SYMPTOMS**
25	**80**	No immediate clinical effects (8 hours)
50 – 150	**160 – 480**	Headache, lethargy, weakness (5 hours)
500	**1,600**	Symptoms of illness (60 minutes)
1,500	**4,800**	Serious symptoms (60 minutes)
7,500	**24,000**	Dangerous to life (30 minutes).
20,000	**64,000**	Central nervous system depression, cardiac arrhythmia, respiratory failure and death (5 – 10 minute exposure).

Reference[(a)]

[a] International Programme on Chemical Safety, Environmental Health Criteria 150: Benzene, 1993.

Published Emergency Response Guidelines

Emergency Response Planning Guideline (ERPG) Values[a]

	Listed value (ppm)	Calculated value (mg m^{-3})
ERPG-1*	50^	160
ERPG-2**	150	480
ERPG-3***	1000	3200

[Calculations based on 1 ppm = 3.2 mg m^{-3} at 20C°]

* Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odour.
** Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action.
*** Maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hr without experiencing or developing life-threatening health effects.
^ Odour should be detectable near ERPG-1.

Interim Acute Exposure Guideline Levels (AEGLs)[b]

	ppm				
	10 min	**30 min**	**60 min**	**4 hr**	**8 hr**
AEGL-1†	130	73	52	18	9
AEGL-2††	2,000*	1,100	800	400	200
AEGL-3†††	**	5,600*	4,000*	2,000*	990

* ≥ 10 % LEL LEL = 14000 ppm
** 3-10 mins = 9700 ppm
For values denoted as * safety consideration against hazards of explosions must be taken into account.
For values denoted as ** extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

† The level of the chemical in air at or above which the general population could experience notable discomfort.
†† The level of the chemical in air at or above which there may be irreversible or other serious long-lasting effects or impaired ability to escape.
††† The level of the chemical in air at or above which the general population could experience life-threatening health effects or death.

[a] American Industrial Hygiene Association (AIHA). 2010 Emergency Response Planning Guideline Values and Workplace Environmental Exposure Level Guides Handbook, Fairfax, VA (accessed 01/2011).
[b] U.S. Environmental Protection Agency. Acute Exposure Guideline Levels, http://www.epa.gov/oppt/aegl/pubs/chemlist.htm (accessed 01/2011).

Exposure Standards, Guidelines or Regulations

Occupational standards

WEL[a]	**LTEL(8 hour reference period):** 1 ppm (3.25 mg m^{-3})	
	STEL(15 min reference period): No guideline value specified	

Public health guidelines

DRINKING WATER QUALITY GUIDELINE[b]	1 µg L^{-1}
AIR QUALITY GUIDELINE[c]	17, 1.7 and 0.17 µg m^{-3} for an excess lifetime cancer risk of 1/10000, 1/100000, 1/1000000, respectively.
SOIL GUIDELINE VALUE AND HEALTH CRITERIA VALUES [d,e]	**Residential** 0.33 mg kg^{-1} dry weight soil
	Allotment 0.07 mg kg^{-1} dry weight soil
	Commercial 95 mg kg^{-1} dry weight soil
	Index Dose $_{oral}$ 0.29 µg kg^{-1} bw day^{-1}
	Mean Daily Intake $_{oral}$ 3 µg day^{-1}
	Index dose $_{inhalation}$ 1.4 µg kg^{-1} bw day^{-1}
	Mean Daily Intake $_{inhalation}$ 200 µg day^{-1}

WEL – Workplace exposure limit; LTEL - Long-term exposure limit; STEL – Short-term exposure limit

[a] List of approved workplace exposure limits (as consolidated with amendments October 2007). http://www.hse.gov.uk/coshh/table1.pdf (An update to EH40/2005: Workplace Exposure Limits 2005. The Stationery Office, London) (accessed 01/2011).
[b] The Water Supply (Water Quality) Regulations 2000 (England) and the Water Supply (Water Quality Regulations 2001 (Wales) (accessed 01/2011)..
[c] Air Quality Guidelines for Europe. World Health Organization Regional Office for Europe, Copenhagen WHO Regional Publications, European Series, No. 91, Second Edition, 2000 (accessed 01/2011).
[d] Environment Agency (EA). Soil Guideline Values for Benzene in soil. Science Report SC050021/Benzene SGV.2009. EA. Bristol, UK .
[e] Environment Agency (EA), Contaminants in soil: updated collation of toxicological data and intake values for humans. Benzene. Science Report SC050021. 2009, EA: Bristol, UK (accessed 01/2011).

Health Effects

Major routes of exposure[(a)]

- Toxic by ingestion, inhalation and skin contact.

Immediate signs or symptoms of acute exposure[(a)]

- Inhalation may cause tracheitis, laryngitis, bronchial irritation, pulmonary haemorrhage, cough and pulmonary oedema. Systemic features may also occur.
- Ingestion may cause nausea, vomiting and abdominal pain.
- Dermal exposure may cause irritation with erythema, blistering and dermatitis due to the defatting effect of benzene. Second-degree burns have occurred. These effects may follow dermal exposure to benzene liquid or vapour. Systemic features may also occur.
- Ocular exposure may cause Irritation and transient corneal damage.
- Systemic features include initial euphoria and excitation followed by dizziness, drowsiness, headache, incoordination, coma and convulsions. Cerebral oedema has been reported. Tachycardia and ventricular fibrillation may occur. There may be respiratory depression and respiratory arrest.

TOXBASE - http://www.toxbase.org (accessed 01/2011)
[a] TOXBASE: Benzene, 11/2006.

Decontamination and First Aid

Important Notes

- Ambulance staff, paramedics and emergency department staff treating chemically-contaminated casualties should be equipped with Department of Health approved, gas-tight (Respirex) decontamination suits based on EN466:1995, EN12941:1998 and prEN943-1:2001, where appropriate.
- Decontamination should be performed using local protocols in designated areas such as a decontamination cubicle with adequate ventilation.
- Flammability warning: prevent exposure to all sources of ignition such as naked flames, electrical equipment, oxidising chemicals and the smoking of tobacco products.

Dermal exposure[a,b]

- Remove patient from exposure.
- The patient should remove all clothing and personal effects.
- Double-bag soiled clothing and place in a sealed container clearly labelled as a biohazard.
- Gently blot away any adherent liquid from the patient.
- Wash hair and all contaminated skin with copious amounts of water (preferably warm) and soap for at least 10-15 minutes. Decontaminate open wounds first and avoid contamination of unexposed skin.
- Pay special attention to skin folds, axillae, ears, fingernails, genital areas and feet.
- Observe for at least 4 hours after exposure.
- Monitor pulse, blood pressure, cardiac rhythm, GCS and respiratory rate. Perform 12 lead ECG.
- Apply other measures according to the patient's clinical condition.

Ocular exposure[c]

- Remove patient from exposure.
- Remove contact lenses if necessary and immediately irrigate the affected eye thoroughly with water or 0.9% saline for at least 10-15 minutes.
- Patients with corneal damage or those whose symptoms do not resolve rapidly should seek urgent ophthalmological assessment.

Inhalation[d]

- Remove patient from exposure.
- Ensure a clear airway and adequate ventilation.
- Give oxygen to symptomatic patients.
- Observe for at least 4 hours after exposure.
- Monitor pulse, blood pressure, cardiac rhythm, GCS and respiratory rate. Perform 12 lead ECG.

TOXBASE - http://www.toxbase.org (accessed 01/2011)
[a] TOXBASE: Benzene, 11/2006.
[b] TOXBASE: Benzene – skin exposure, 11/2006.
[c] TOXBASE: Chemicals splashed or sprayed into the eyes, 07/2007.
[d] TOXBASE: Benzene – inhalation, 11/2006.

- If the patient has clinical features of bronchospasm treat conventionally with nebulised bronchodilators.
- Apply other measures as indicated by the patient's clinical condition.

Ingestion[(a)]

- Ensure a clear airway and adequate ventilation.
- Give oxygen to symptomatic patients.
- Gut decontamination is contraindicated because this may increase the risk of aspiration.
- Observe for at least 4 hours after exposure.
- Monitor pulse, blood pressure, cardiac rhythm, GCS and respiratory rate. Perform 12 lead ECG.
- Apply other measures as indicated by the patient's clinical condition.

TOXBASE - http://www.toxbase.org (accessed 01/2011)
[a] TOXBASE: Benzene – ingestion, 11/2006.

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.

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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].

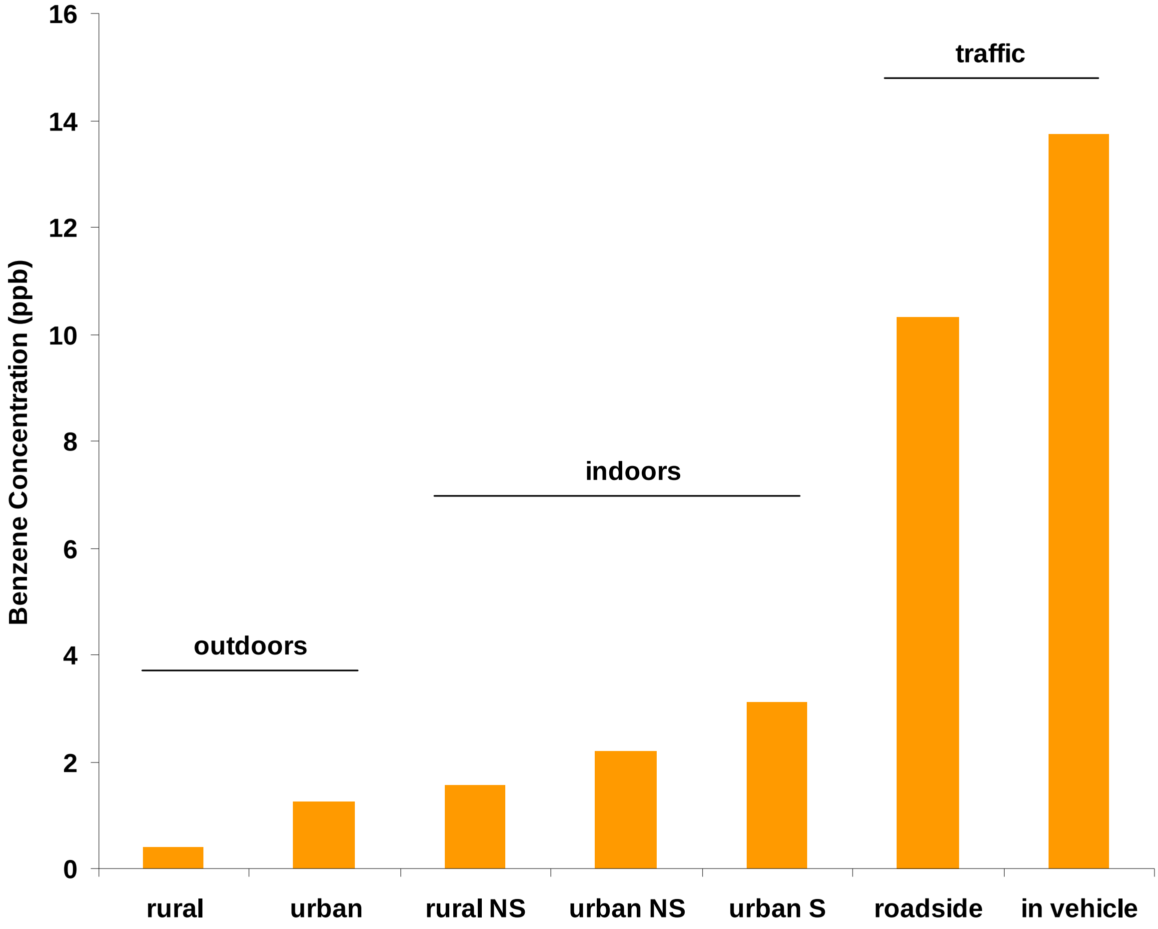
The metabolism of benzene has been widely studied in human and animal models due to its putative role in carcinogenesis (metabolic activation) [15, 16]. The metabolic pathways implicated in benzene toxicity are broadly comparable across species. However, there are significant species-specific differences 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 (NQ01). 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 NQ01 [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 ($t_{½}$ ~ 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 propinquity 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, pnuemonitis, 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 ($t_{½}$ ~ 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.