NICNAS

National Industrial Chemicals Notification and Assessment Scheme

Benzene

Priority Existing Chemical Assessment Report No. 21

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with Environment Australia (EA) and the Therapeutic Goods Administration (TGA), which carry out the environmental and public health assessments, respectively.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals.

This Priority Existing Chemical report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with the Act. Under the Act manufacturers and importers of Priority Existing Chemicals are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the *Commonwealth Chemical Gazette*.

In accordance with the Act, publication of this report revokes the declaration of this chemical as a Priority Existing Chemical, therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under section 64 of the Act.

Copies of this and other Priority Existing Chemical reports are available from NICNAS either by using the prescribed application form at the back of this report, the website www.nicnas.gov.au or ordering directly from the following address:

GPO Box 58
Sydney
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AUSTRALIA

Overview

Benzene (CAS No. 71-43-2) was declared a Priority Existing Chemical on 7 April 1998 in response to occupational and public health concerns.

Benzene occurs naturally in fossil fuels and is produced incidentally in the course of natural processes and human activities that involve the combustion of organic matter such as wood, coal and petroleum products. The main industrial use of benzene is as a starting material for the synthesis of other chemicals. Most benzene feedstock is imported, but some is manufactured at an Australian steelworks as a by-product of coal coking. Large quantities of benzene are produced during the refining of petroleum and retained as a component of petrol. Petrol vehicle emissions are the predominant source of benzene in the environment.

Benzene is volatile and water-soluble and is considered biodegradable. Its major release is to the atmosphere, where it will break down in a matter of weeks. Direct release to the aquatic compartment is expected to be minor and significant removal will occur from volatilisation. Benzene release to soil is likely to be marginal. Concentrations in aquatic systems are expected to be far lower than of concern and a low aquatic risk is predicted. Due to the low expected exposure, a low environmental risk to terrestrial organisms is predicted. The short atmospheric lifetime of benzene indicates concentrations will not occur at levels harmful to the atmosphere. While widespread transport within the troposphere is possible, the chemical is not expected to reach the stratosphere and therefore would not have an influence on global warming or ozone depletion.

In animals and humans, benzene is absorbed by all routes of exposure, although dermal absorption is limited by its rapid evaporation from the skin. It is metabolised in the liver and several other organs, including the bone marrow. The parent molecule is eliminated with exhaled air. The metabolites are excreted in the urine.

In animals, benzene is not highly acutely toxic. Chronic exposure can result in central nervous system depression, immunosuppression, bone marrow depression, degenerative lesions of the gonads, foetal growth retardation, damage to genetic material and solid tumours in several organs.

In humans, acute exposure to high concentrations of benzene vapours can result in irritation of the skin, eyes and respiratory system and in central nervous system depression. Chronic exposure can result in bone marrow depression and leukaemia, particularly acute myeloid leukaemia, and possibly an increased risk of non-Hodgkin's lymphoma and multiple myeloma. Structural and numerical chromosome aberrations have been detected in peripheral blood cells of workers exposed to high levels of benzene. For bone marrow depression, the lowest observed adverse effect level in humans is 7.6 parts per million (ppm), based on minimal blood count changes in otherwise healthy workers. No threshold has been established for the genotoxic and carcinogenic effects of benzene. Epidemiological evidence indicates that the risk of leukaemia increases with exposure and is significantly elevated at cumulative exposures above 50 ppm-years, corresponding to an 8-hour time-weighted average exposure above 1.25 ppm over a working life of 40 years.

Chronic benzene toxicity has been attributed to the formation of reactive metabolites that appear to exert their toxic effect in combination, with no one metabolite accounting for all of the observed effects.

Benzene is currently listed in the NOHSC *List of Designated Hazardous Substances* with the following classification: 'Flammable', 'Carcinogen, Category 1' and 'Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed'. Category 1 carcinogens are those substances known to be carcinogenic to humans. Based on the assessment of health effects, this report has concluded that benzene also meets the NOHSC *Approved Criteria for Classifying Hazardous Substances* for classification as a skin, eye and respiratory system irritant and as a mutagenic substance in Category 3.

The public is exposed to benzene through the inhalation of indoor, in-vehicle and outdoor air contaminated with the chemical through releases that predominantly derive from vehicle exhaust, petrol evaporation and tobacco smoke. The 24-hour average lifetime exposure in the Australian urban population is estimated at 5.2 parts per billion (ppb). It is one-fifth higher in passive smokers exposed to tobacco smoke at home, at work and in their cars (6.1 ppb) and almost three times as high (15.2 ppb) in the average smoker.

Benzene-induced bone marrow depression is not expected to present a significant public health risk. Based upon low-dose extrapolation of relevant quantitative risk estimates and the above-mentioned exposure estimate, the excess lifetime risk of benzene-induced leukaemia in the Australian urban population is estimated to be in the order of one case per 10,000 with increased risk in sensitive subpopulations or at higher exposure levels. However, the estimated excess risk is based on substantial uncertainties in the exposure assessment which should be validated through collection of monitoring data.

As benzene is an established human carcinogen for which no safe level of exposure has been established, it is recommended that any increase in public exposure be avoided and that measures be taken to reduce exposure where this is practicable. The establishment of a national ambient air benzene level would facilitate these objectives.

Occupational exposure to benzene is predominantly by the inhalation route. It occurs primarily in the petroleum, steel, chemical and associated industries and in laboratories using the chemical for research or analysis. Occupational exposure to benzene can also result from the contamination of workplace environments with petrol vapours, engine exhaust or tobacco smoke, for example, in vehicle mechanics, professional drivers and hospitality workers. It is estimated that current long-term occupational exposures to benzene are less than or equal to 0.7 ppm in the steel and associated industries and during maintenance of phenol plants; less than 0.1 ppm in the upstream petroleum industry (oil and gas production); less than 0.5 ppm in the chemical industry and in laboratory workers; less than 0.2 ppm in vehicle mechanics; less than 0.7 ppm in the downstream petroleum industry (refining, distribution and marketing of petroleum products); and less than 0.05 ppm in people who work in roadside or in-vehicle environments contaminated with vehicle exhaust or in indoor environments contaminated with tobacco smoke.

The occupational risk characterisation found no cause for concern about acute health effects or bone marrow depression, given the control measures which are already in place in Australian workplaces. However, there is cause for concern about the risk for leukaemia in all workers with repeated occupational exposure to benzene. There is no known threshold for the carcinogenic effects of benzene, but because the risk for leukaemia increases with exposure, it can be reduced by controlling exposure to the highest practicable standard.

With regard to occupational health and safety, it is recommended that the national exposure standard for benzene be revised. It is recommended that an eight-hour time-weighted average of 0.5 ppm be adopted. It is further recommended that the current hazard classification be amended to include classification as 'Irritating to eyes, respiratory system and skin' (risk phrase R36/37/38) and as a mutagenic substance in Category 3 (risk phrase

R40: ‘Possible risks of irreversible effects, Mutagen Category 3’). Occupational exposures to benzene should be minimised by improving workplace control measures and by using the best available technology.

This report has identified the need to reduce public exposure to air benzene levels as much as practicable. Public health recommendations include measures to reduce indoor benzene levels, such as proper sealing of attached garages and minimising environmental tobacco smoke. In order to better characterise the risk to the public from benzene exposure, personal and ambient air monitoring is recommended and a national ambient air standard should be set.

Contents

Abbreviations and Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ADG	Australian Dangerous Goods
AIP	Australian Institute of Petroleum
ALC	absolute lymphocyte count
ALL	acute lymphatic leukaemia
AML	acute myeloid leukaemia
ANLL	acute non-lymphocytic leukaemia
atm	atmosphere
Avgas	light aircraft gasoline
BCF	bioconcentration factor
BP	benzene poisoning
BTX	benzene/toluene/xylenes
BW	body weight
C	centigrade
CAS	Chemical Abstracts Service
CFU-E	colony forming units of erythrocyte progenitor cells
CFU-M	colony forming units of granulocyte/macrophage progenitor cells
CI	confidence interval
CLL	chronic lymphatic leukaemia
cm	centimetre
cm^2	square centimetre
cm^3	cubic centimetre
CMA	Chemical Manufacturers Association
CML	chronic myeloid leukaemia
CNS	central nervous system
CSF	colony stimulating factor
CYP	cytochrome-P450
DNA	deoxyribonucleic acid
EA	Environment Australia
EC_{50}	median effective concentration
EINECS	European Inventory of Existing Chemical Substances
EPA	Environment Protection Authority
ETS	environmental tobacco smoke
g	gram
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
GD	gestation day
GLP	Good Laboratory Practices
GM-CSF	granulocyte/macrophage colony stimulating factor
GSH	glutathione
GST	glutathione-S-transferase
h	hour
ha	hectare
Hb	haemoglobin
Hct	haematocrit

IARC	International Agency for Research on Cancer
IL-1	interleukin-1
IPCS	International Programme on Chemical Safety
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union for Pure and Applied Chemistry
K	Kelvin
kg	kilogram
K_m	Michaelis-Menten constant
km	kilometre
km^2	square kilometre
K_{oc}	sorption coefficient
kPa	kilopascal
kt	kilotonne
L	litre
LC	lymphocyte
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest observed adverse effect level
LP	leaded petrol
LPG	liquid pressurised gas
m^3	cubic meter
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
mg	milligram
mL	millilitre
ML	megalitre
mM	millimolar
MM	multiple myeloma
MN	micronucleus
mol	mole
MSDS	material safety data sheet
NADPH	nicotinamide adenine dinucleotide phosphate
NEPC	National Environment Protection Council
NEPM	National Environment Protection Measures
ng	nanogram
NHIS	National Health Interview Survey
NHL	non-Hodgkin's lymphoma
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute of Occupational Safety and Health
nm	nanometre
nmol	nanomole
nM	nanomolar
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOHSC	National Occupational Health and Safety Commission
NPI	National Pollutant Inventory
NQO1	NAD(P)H:quinone oxidoreductase
NSAID	non-steroidal anti-inflammatory drug
OECD	Organisation for Economic Co-Operation and Development
OR	odds ratio

OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbon
PGE_2	prostaglandin E_2
PKC	protein kinase C
Plt	blood platelet
PNEC	predicted no-effect concentration
$P_{o/w}$	octanol/water partition coefficient
POP	persistent organic pollutant
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PULP	premium unleaded petrol
RBC	red blood cell (erythrocyte)
RNA	ribonucleic acid
RR	relative risk
s	second
SAb	spontaneous abortion
s-AML	secondary acute myeloid leukaemia
SC	subcutaneous
SCE	sister chromatid exchange
SGA	small-for-gestational age
SIR	standardised incidence rate
SMA	State marketing area
SMR	standardised mortality rate
STP	sewage treatment plant
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
t	tonne
TGD	Technical Guidance Document
TWA	time-weighted average
TWA_8	8-h time-weighted average
ULP	unleaded petrol
UN	United Nations
USEPA	United States Environmental Protection Agency
$UTL_{95\%,95\%}$	upper tolerance limit of a distribution's 95th percentile
v/v	volume/volume
VOC	volatile organic chemical
w/w	weight/weight
WBC	white blood cell (leukocyte)
WHO	World Health Organization
y	year
µg	microgram
µL	microlitre
µM	micromolar
µmol	micromole
8-OHdG	8-hydroxydeoxyguanosine

1. Introduction

1.1 Declaration

The chemical benzene (CAS No. 71-43-2) was declared a Priority Existing Chemical for full assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* on 7 April 1998. It was nominated by the public because of concerns about its human health effects and the adequacy of the current Australian occupational exposure standard.

1.2 Objectives

The objectives of this assessment were to:

- characterise the properties of benzene;
- determine the uses of benzene in Australia;
- determine the extent of occupational, public and environmental exposure to benzene;
- characterise the intrinsic capacity of benzene to cause adverse effects on persons or the environment;
- characterise the risks to humans and the environment resulting from exposure to benzene; and
- determine the extent to which any risk is capable of being reduced.

1.3 Sources of information

Consistent with the objectives, this report presents a summary and critical evaluation of relevant information relating to the potential health and environmental hazards from exposure to benzene. Relevant scientific data were submitted by the applicants listed in Section 3, obtained from published papers identified in a comprehensive literature search of several online databases up to December 2000, or retrieved from other sources such as the reports and resource documents prepared for the health surveillance program of the Australian Institute of Petroleum (AIP) and the Illawarra leukaemia cluster investigation. Due to the availability of several peer-reviewed overseas assessment reports, not all primary sources of data were evaluated. However, relevant studies published since the cited reviews were assessed on an individual basis.

The characterisation of health and environmental risks in Australia was based upon information on use patterns, product specifications, occupational exposure and emissions to the environment made available by applicants and relevant State authorities. Information to assist in the assessment was also obtained through site visits and telephone interviews. The site visits included two petroleum refineries, two petrol terminals, a steelworks, a coal tar distillery, a bulk liquid storage facility and three chemical plants.

1.4 Peer review

During all stages of preparation, the report has been subject to internal peer review by NICNAS, Environment Australia (EA) and the Therapeutic Goods Administration (TGA). Selected parts of the report were also peer reviewed by Professor Tom Beer, CSIRO Atmospheric Research (Sections 8 and 15); Dr Stephen Corbett, New South Wales Department of Health (Section 11); Dr Andrea Hinwood, Department of Environmental Protection, Western Australia (Sections 9, 11 and 13); and Professor Martyn T. Smith, University of California (Sections 9 and 12).

2. Background

2.1 Introduction

Benzene is a naturally occurring, hazardous, volatile organic compound which is ubiquitous in the environment. It is formed from biomass under the impact of heat, pressure and geological time. As such, it is present in fossil fuels which may release it to air when unearthed and, in particular, when heated to combustion. Benzene is also a product of natural processes and human activities that involve the instantaneous thermal degradation of organic matter. These sources of entry include bush fires, crop residue and forest management burning, petroleum refining, petrol combustion, wood and charcoal fires, fumes from heated cooking oils, tobacco smoke, incense, and waste incineration. In addition, benzene enters the environment in emissions and waste streams from industrial processes and waste disposal facilities.

2.2 International perspective

Benzene was first isolated in 1825 and gradually became widely used as a solvent and starting material for the synthesis of a number of organic chemicals (Folkins, 1984). Benzene also became recognised as a valuable constituent of petrol because of its antiknock properties and ability to increase the octane rating of automotive fuels.

Until World War II, benzene was isolated from light oil, which is a by-product of the carbonisation of coal to produce gas for heating or coke for the blast furnaces of the steel industry. Beginning in the 1930s, new catalytic and thermal processes for the production of aromatic hydrocarbons from crude oil were discovered and commercialised in the petroleum industry. With the advent of natural gas in the 1960s, worldwide coal gas production started to diminish. Simultaneously, the introduction of modern steel processing methods decreased coke production and made it attractive to burn the light oil as fuel rather than segregate it into benzene and other products. In consequence, the petroleum industry is now the predominant source of benzene.

In recent years, the use of benzene-containing solvents has been practically eliminated because of the toxicity of the chemical. Current worldwide consumption of benzene is 30-35 million metric tonnes (t) per annum, primarily as chemical feedstock in the production of large-scale intermediates such as ethyl benzene, cumene and cyclohexane (Chemistry & Industry News, 1996). This figure does not include benzene produced by the petroleum industry and retained as a petrol component.

Commercial low-grade qualities are sometimes referred to as benzol. Benzene is not to be confused with benzine, which is a mixture of several low-boiling hydrocarbons obtained in the distillation of petroleum.

2.3 Australian perspective

Developments in Australia have followed the general pattern outlined above, albeit with a delay of 1-2 decades. The recovery of benzene from coal gas is now limited

to the steelworks at Port Kembla in New South Wales and Whyalla in South Australia.

There are eight petroleum refineries in Australia: two in Brisbane and Sydney and one in Adelaide, Geelong, Melbourne and Perth. Since the 1970s, close to 100% of local demand for petrol has been met from crude which is low in aromatic fractions (Tresider, 1998). As such, all Australian petroleum refineries have processes in place to increase the content of aromatic hydrocarbons including benzene in their petrol blendstock. Petroleum-derived benzene feedstock for the chemical industry is not produced in Australia.

As of 1986, new petrol-driven cars had to be fitted with catalytic converters and use unleaded fuel. An Australian Standard for petrol for motor vehicles was established in 1990 and limited the benzene content to a maximum of 5% v/v (Standards Australia, 1990). In 1998, the average benzene content in Australian petrol was 2.9, 2.6 and 3.3% v/v in leaded petrol (LP), unleaded petrol (ULP) and premium unleaded petrol (PULP) respectively (AIP, 1998b). The *Fuel Quality Standards Act 2000* enables the Commonwealth to make mandatory national quality standards for fuel supplied in Australia. Among others, these will include a maximum content of benzene in petrol of 1% v/v from January 1 2006. Meanwhile, Western Australia and Queensland have introduced regulations limiting the benzene content in petrol to 1% and 3.5% respectively (EA, 2000b).

In 1980, AIP contracted The University of Melbourne to set up an epidemiological health surveillance program called Health Watch. The program covers about 95% of the industry's 18,000 employees in refineries, natural gas plants, distribution terminals and production sites. It consists of a prospective cohort study of all-cause mortality and cancer incidence, in addition to a case-control study of lympho-haematopoietic cancers and benzene exposure established in 1988 (Glass et al., 1998, 2000; Health Watch, 1998).

Air pollution became a major concern in the 1990s and prompted environment and health authorities from the Commonwealth, States and Territories to initiate several research projects into ambient air quality. Early results of this research resulted in the inclusion of benzene in the National Pollutant Inventory (NPI), which was established by the National Environment Protection Council (NEPC) in 1998. The NPI currently comprises 36 chemicals of health and environmental concern which must be reported to EA if the quantity used or handled per site exceeds a threshold limit, which for benzene is 10 t per year (EA, 1999b). More recently, the Australian and New Zealand Environment and Conservation Council contracted the Victorian Environment Protection Authority (EPA) to assess the available air level data and derive a risk-based rank order of hazardous air pollutants according to their priorities for further research (EPA Victoria, 1999). Based on a scoring system as well as on professional judgement, benzene came first among 15 chemicals recommended for general urban air monitoring. Benzene is also the subject of a publication in the series of National Environmental Health Forum Monographs, which are intended to provide plain language information about important, topical environmental health matters (Wadge & Salisbury, 1997). Current EA initiatives such as the Fuel Quality Review and Living Cities – Air Toxics Program both address a number of environmental aspects relating to benzene (EA, 2000a, 2000b).

Public concern about exposure to benzene reached a peak in 1996, when a cluster of leukaemia cases was identified in people living in the suburbs adjacent to the coke ovens and coal gas by-product plant at the Port Kembla steelworks. A committee reporting to the New South Wales Department of Health was set up to

investigate the matter. It concluded that based on the available data, it was not possible to ascribe the cluster to a particular exposure (including benzene). The investigation produced several useful publications relating to benzene and the risk of leukaemia (ILISC, 1997; Westley-Wise et al, 1999).

2.4 Assessments by other national or international bodies

Although there have been restrictions on the manufacture, handling, storage and use of benzene in Australia since 1978, this report represents the first comprehensive risk assessment by a national agency.

Benzene has been assessed by several overseas or international bodies involved in the review or evaluation of data pertaining to the health and/or environmental hazards posed by chemicals. Of these, the most noteworthy are:

- The Advisory Committee to the German Chemical Society on Existing Chemicals of Environmental Relevance (GDCh, 1988);
- The Agency for Toxic Substances and Disease Registry under the US Department of Health and Human Services (ATSDR, 1997);
- The Commission of the European Communities (EC, 1989, 2000);
- Environment and Health Canada (Government of Canada, 1993);
- The International Agency for Research on Cancer (IARC, 1982a, 1987);
- The International Programme on Chemical Safety (IPCS, 1993);
- The UK Department of the Environment (DoE, 1994);
- The US Environmental Protection Agency (USEPA, 1985, 1998a, 1998c); and
- The OECD SIDS International Assessment Report (draft) (OECD, 2000).

3. Applicants

Following the declaration of benzene as a Priority Existing Chemical, 21 companies or organisations applied for assessment of the chemical. The applicants supplied information on the properties, import and manufacturing quantities and uses of benzene and, in some cases, on occupational exposures and releases to the environment. In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, NICNAS provided the applicants with a draft copy of the report for comments during the corrections/variation phase of the assessment. The applicants were as follows:

Alltech Associates (Australia) Pty Ltd
PO Box 6005
Baulkham Hills NSW 2153

Australian Institute of Petroleum
GPO Box 279
Canberra ACT 2601

Australian Council of Trade Unions
393 Swanston Street
Melbourne VIC 3000

Australian Manufactures Workers Union
3/440 Elizabeth Street
Melbourne VIC 3000

Bio-Scientific Pty Ltd
PO Box 78
Gymea NSW 2227

BP Australia Holding Limited
360 Elizabeth St
Melbourne VIC 3000

Caltex Petroleum Australia Pty Ltd
19-29 Martin Pl
Sydney NSW 2000

Crown Scientific Pty Ltd
Private Mail Bag 4
Moorebank NSW 2170

Huntsman Chemical Company Australia Pty Ltd
PO Box 62
West Footscray VIC 3012

ICN Biomedicals Australasia
PO Box 187
Seven Hills NSW 2147

Whyalla Steelworks (OneSteel Manufacturing)
PO Box 21
Whyalla SA 5600

Koppers Coal Tar Products Pty Ltd
PO Box 23
Mayfield NSW 2304

Merck Pty Ltd
207 Colchester Rd
Kilsyth VIC 3137

Mobil Oil Australia Pty Ltd
417 St Kilda Rd
Melbourne VIC 3004

BHP Steel – Flat Products
PO Box 1854
Wollongong NSW 2505

Qenos Pty Ltd
Private Bag 3
Altona VIC 3018

Selby-Biolab
Private Bag 24
Mulgrave North VIC 3170

Sigma-Aldrich Pty Ltd
PO Box 970
Castle Hill NSW 2154

Terminals Pty Ltd
PO Box 268
Footscray VIC 3011

3M Australia Pty Ltd
PO Box 144
St Marys NSW 2760

Trafigura Fuels Australia Pty Ltd
Unit 2, 47 Epping Rd
North Ryde NSW 2113

4. Chemical Identity and Composition

4.1 Chemical name (IUPAC)

Benzene

4.2 Registry numbers

Benzene is listed on the Australian Inventory of Chemical Substances (AICS) as *benzene.*

CAS number	71-43-2
EINECS number	200-753-7
UN number	1144

4.3 Other names

Annulene

Benzol(e)

Bicarburet of hydrogen

Carbon oil

Coal naphtha

Cyclohexatriene

Mineral naphtha

Motor benzol

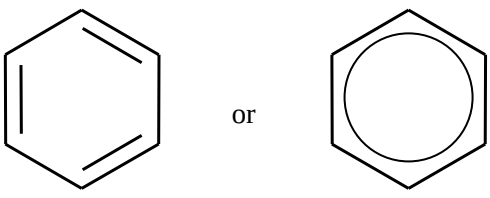
Phenyl hydride

Pyrobenzol(e)

4.4 Molecular formula

C_6H_6

4.5 Structural formula



4.6 Molecular weight

78.11

4.7 Composition of commercial grade product

Several different grades of benzene are commercially available. The principal impurities are toluene, xylenes and other hydrocarbons with boiling points similar to that of benzene. The higher the grade, the lower the content of thiophene (thiofuran) and other sulfur compounds, which foul many catalysts used in reactions of benzene (Fruscella, 1992). The specifications for two typical import grades and the benzene/toluene/xylenes (BTX) mixture produced at the Port Kembla steelworks are shown in Table 4.1.

Table 4.1: Raw material specifications for some commercially available benzene grades

Test	Pure benzene	Crude benzene	BTX
Benzene (% v/v)	>99	≥95	≥80
C_9 & higher (% v/v)	-	<1.5	<1.6
Carbon disulfide (ppm)	-	<50	<4000
H_2S & SO_2	None	-	-
Non-aromatic C_5-C_6 (% v/v)	<0.15	<0.7	<1.5
Styrene (% v/v)	-	-	<1.8
Thiophene (ppm)	<1	<6000	<6000
Toluene (% v/v)	-	-	<12.5
Total sulfur (ppm)	-	-	<6000
Xylenes & styrene (% v/v)	-	-	<3.8

5. Physical and Chemical Properties

5.1 Physical state

Benzene is a volatile, colourless and flammable liquid with a characteristic, sweet aromatic odour (Budavari, 1996). The odour threshold ranges from 0.8-160 ppm (AIHA, 1989); 50% of the population can identify the odour at 2 ppm and 100% at 5ppm (Verscheuren, 1996). The physical properties of benzene are summarised in Table 5.1.

Conversion factors (at 25°C):

1 mg/m^3 = 0.31 ppm *and* 1 ppm = 3.2 mg/m^3 (Cavender, 1994).

5.2 Physical properties

Table 5.1: Physical properties

Property	Value	Reference
Melting point	5.53ºC	Folkins (1984)
Boiling point	80.1ºC	Folkins (1984)
Density • at 15ºC • at 20ºC • at 25ºC	 0.885 kg/L 0.879 kg/L 0.874 kg/L	 Fruscella (1992)
Vapour density	2.8 (relative to air = 1)	Cavender (1994)
Vapour pressure • at 0ºC • at 20ºC • at 25ºC • at 40ºC • at 50ºC	 3.47 kPa 9.97 kPa 12.6 kPa 24.2 kPa 35.8 kPa	 Folkins (1984), Fruscella (1992)
Water solubility (at 25ºC)	1.80 g/L	IPCS (1993)
Henry's Law constant (at 20ºC)	0.56 kPa.m^3/mol	Mackay & Leinonen (1975)
Partition coefficient (log $P_{o/w}$)	1.56-2.15	IPCS (1993)
Sorption coefficient (log K_{oc})	1.8-1.9	IPCS (1993)
Flash point (closed cup)	– 11ºC	Fruscella (1992)
Autoignition temperature	560ºC	Fruscella (1992)
Explosive limits • lower • upper	 1.4% v/v (45 g/m^3) 7.9% v/v (250 g/m^3)	 Cavender (1994)

5.3 Chemical properties

The six carbon atoms of benzene form a regular hexagon and all 12 atoms lie in a single plane, with all bond angles being exactly 120° (Fruscella, 1992). The molecule is traditionally depicted as having alternating single and double bonds (see structure (1) in Section 4). However, as the six carbon-carbon bonds are

physically and chemically identical and intermediate in length between single and double bonds (as indicated by structure (2) in Section 4), benzene does not react as a typical unsaturated compound.

Benzene has great thermal stability and elevated temperatures are required for its decomposition. It undergoes substitution and addition reactions and ring cleavage. For industrial applications, the most important reactions are alkylation with ethylene or propylene to produce ethyl benzene or cumene, hydrogenation to cyclohexane, nitration and sulfonation to form nitrobenzene and benzenesulfonic acid, and halogenations. Benzene cannot be hydrolysed.

Benzene is miscible with numerous other organic solvents including alcohol, acetone, diethyl ether, ethyl acetate, chloroform, carbon disulfide, glacial acetic acid and oils (Budavari, 1996). Its solubility in water ranges from 1.13% v/v at 25°C to 5.07% v/v at 107°C (Folkins, 1984). Benzene forms binary and tertiary azeotropes with water and a large number of organic substances (for examples, see Folkins (1984)).

Benzene is highly flammable and potentially explosive. Combustion products include carbon dioxide, water vapour and carbon monoxide. With a deficiency of air or oxygen, partial decomposition and soot deposition occur (Folkins, 1984). Vapours burn with a sooty flame.

6. Methods of Detection and Analysis

6.1 Characterisation

Benzene can be characterised by infrared, ultraviolet and mass spectrometry and nuclear magnetic resonance techniques (Fruscella, 1992).

6.2 Detection and analysis

A time-honoured spot test for benzene in the workplace or surroundings involves the treatment of a sample with nitric acid followed by ether extraction and dissolution in a mixture of alcohol and methyl ethyl ketone. Benzene is converted to *m*-dinitrobenzene which imparts a persistent red colour to the solution (Dolin, 1943, cited in Fruscella, 1992).

Standard analytical methods for benzene in air, water, soil, foods, smoke, biological samples, petroleum products etc. rely on gas chromatography (GC) with flame or photo ionisation detection, or on gas chromatography-mass spectrometry (GC-MS) (Fruscella, 1992; IPCS, 1993). Benzene in water, soil and food is usually measured by a purge and trap method by bubbling an inert gas through the sample and collecting the chemical on an absorbent. Benzene is then desorbed and determined. The best available GC methods are able to detect benzene at 0.1 ppb in air or 1 ng/kg in liquid or solid media, although 3 ppb in air and 1μg/L in water are the limits of detection in routine analysis (IPCS, 1993; NHMRC, 1996). The GC-MS method is not quite as sensitive, but more reliable in the case of samples with multiple components with retention times similar to that of benzene (IPCS, 1993).

6.3 Atmospheric monitoring methods

In the environment

The methods commonly used for measuring the concentration of benzene in ambient air fall into the following two categories (EPA Victoria, 1999):

(1) discrete air sampling with subsequent laboratory analysis; or

(2) continuous or semi-continuous in-field analysis.

Among the former, the most widely used method involves the collection of air into a stainless steel canister over a predetermined period of time such as 24 h, followed by analysis of a concentrate of the air sample by GC or GC-MS. This method is described in more detail by DEP Western Australia (2000).

A commonly used continuous method for in-field analysis utilises an optical remote sensing system to determine the concentration of the chemical by means of the differential absorption of transmitted light by gaseous compounds along the light path. The system consists of a light transmitter and sensor placed at a given distance apart at the monitoring site.

Alternatively, the concentration in air can be analysed by semi-continuous gas chromatography. Samples of air are collected directly onto solid absorbents,

desorbed thermally onto the GC column and analysed while the next sample is collected.

The analytical limit of detection of the above methods typically ranges from 0.003-0.1 ppb. All of the methods allow for the simultaneous determination of several other gaseous air pollutants in the same sample. Discrete sampling methods determine average pollutant levels over the sample collection time. Continuous or semi-continuous methods enable more detailed information about concentration variations to be obtained.

In the workplace

This section summarises the methods commonly used for the measurement of benzene in the workplace. Other past and present techniques are described in a recent review by Verma & des Tombe (1999a, 1999b).

For personal monitoring during full shifts or tasks, workers are equipped with a charcoal tube or badge placed in the breathing zone. For area monitoring, the tube or badge is placed at a fixed location in the workplace environment. Tubes are connected with a portable metering pump, whereas badges sample the air by diffusion. At the end of the sampling period, the tube or badge is sealed and transferred to a laboratory, where the chemical is liberated from the absorbent by elution or thermal desorption and quantified by GC (NIOSH, 1994). The result is expressed as a time-weighted average (TWA) concentration in ppm or mg/m^3 over the duration of the sampling period. The analytical detection limit depends on the airflow across the absorbent and the duration of the sampling period. The detection limit using charcoal tube sampling and analysis according to the NIOSH method is 0.02 ppm.L, or 0.004 ppm for a sample collected over 60 min at a pump speed of 80 mL/min (IPCS, 1993). The agreement between the tube and badge methods is not perfect, but the differences are generally of little importance (Hotz et al., 1997; Purdham et al., 1994).

'Grab sampling' or instantaneous measurement of the concentration of airborne benzene is conducted with colorimetric detector tubes. These are glass tubes sealed at both ends with a graduated concentration scale etched into the outer surface. The tubes contain a carrier material covered with chemical reagents that react with benzene to produce a colour change whose end-point is read against the scale. Prior to use, the seals are broken, the tube is connected to a hand pump and the pump is operated to draw a defined amount of air through the tube. A colorimetric detector has become available which can measure benzene at 0.2 ppm in the presence of other hydrocarbons, with a measuring time of 8 minutes. Non-selective photoionisation detectors can be used for instantaneous measurement of benzene concentrations with a detection limit of approximately 0.1 ppm but, because the detector also responds to volatile organic chemicals, they are limited to situations where the vapour is known to be pure benzene. Recently, a benzene-selective photoionisation detector has become available which is claimed to be able to measure benzene at concentrations of 0.1 ppm – 200 ppm in the presence of other hydrocarbons within approximately 1 minute. The detector uses a single use pre-treat tube to filter out interfering hydrocarbons except for $\leq C_3$ alkanes and must be calibrated against 5 ppm benzene prior to use.

A less widely used method is continuous area monitoring, which is performed by pumping air collected at one or more fixed locations through an auto analyser equipped with an ultraviolet spectrometer. This method delivers readings for TWA

as well as peak concentrations and has a limit of detection of approximately 0.2 ppm (IPCS, 1993).

6.4 Biological monitoring methods

Biological monitoring for benzene exposure involves the measurement of unmetabolised benzene in blood, urine or breath samples, of benzene metabolites in the urine, or of protein adducts with the benzene oxide metabolite.

The concentration of benzene in venous blood and urine can be determined by GC, with a detection limit of around 0.5 µg/L (IPCS, 1993). For the determination of benzene in breath air, an end-exhaled sample is collected and analysed by GC-MS, with a detection limit of 3-6 ppb (Money & Gray, 1989). However, these methods are only suitable for research purposes, as great care must be exercised to avoid contamination of the samples with ambient benzene.

Various metabolites are excreted in the urine, including phenol, hydroquinone and catechol conjugates, S-phenylmercapturic acid and *trans,trans*-muconic acid (see Section 9.3), although none of them is formed exclusively from benzene. These metabolites can be quantified by GC, GC-MS or high-performance liquid chromatography as described by Ducos et al. (1990), Hotz et al. (1997), Lee et al. (1993), Popp et al. (1994) and others. Whereas the urinary concentration of phenol has been widely used as an index of benzene exposure, the background levels make it unreliable at exposures <5-10 ppm. The concentration of S-phenylmercapturic acid or muconic acid relative to creatinine in an end-of-shift urine sample has been shown to be a fairly good indicator of exposure in the 0.25-1 ppm range, even in smokers (Ghittori et al, 1995; Hotz et al, 1997; Ong et al, 1996).

The metabolite benzene oxide binds to nucleophilic sites and forms phenyl cysteine residues with proteins such as haemoglobin and albumin (see Section 9.3.1). The concentration of such adducts in blood correlates with benzene exposure. However, high background levels severely limit the practical use of the S-phenyl cysteine adduct as a biological marker for benzene uptake (Yeowell-O'Connell et al, 1998).

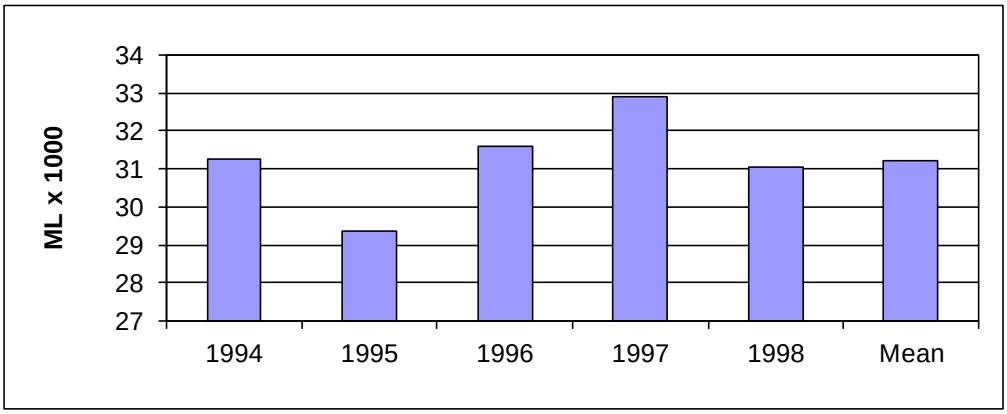
7. Manufacture, Importation and Use

7.1 Manufacture and importation

Benzene is introduced into Australia through extraction, importation and manufacture.

The total Australian production of crude in 1994-98 is shown in Figure 7.1. Crude includes unrefined oil as well as condensate, which is a liquid mixture of hydrocarbons recovered from gas wells. The mean annual and 1998 volumes are both approximately 31,000 ML. Australian crude is reported to have a low benzene content, estimated at about 0.1% v/v (Glass et al, 1998). As such, the annual extraction of benzene from Australian oil and gas fields can be estimated at approximately 31 ML. As the density of benzene is around 0.88 kg/L, this corresponds to a quantity of 27 kilotonnes (kt) pure benzene.

Figure 7.1: Australian production of crude oil and condensate 1994-98 (AIP, 1999b)



The throughput of crude at Australian refineries in 1998 was 44,678 ML, of which 62% was of non-Australian origin (AIP, 1999a). Most of the imports come from oil fields in the Pacific basin and contain approximately the same concentration of benzene as Australian crude, that is, about 0.1% v/v (Glass et al, 1998). This corresponds to a total input of 45 ML or 39 kt pure benzene.

From these figures, it can be concluded that Australia is a net importer of benzene in crude to the tune of approximately 12 kt per annum.

Table 7.1 shows the throughput of benzene-containing gasoline products, that is, leaded petrol (LP), unleaded petrol (ULP), premium unleaded petrol (PULP) and light aircraft gasoline (Avgas), at Australian refineries in 1998. The table also gives the average content of benzene and the corresponding quantities of pure benzene. Data for Avgas are estimates, but have little impact on the total. Other petroleum products such as liquefied petroleum gas, kerosene, civil aviation jet fuel, diesel oil, fuel and heating oils and lubricants contain no or practically no (<0.02% v/v) benzene (AIP, 1999a; IARC, 1989; Potter & Simmons, 1998).

The volume of pure benzene in petrol produced at Australian refineries in 1998 was 484 ML, corresponding to 426 kt pure benzene. As the throughput crude contained

approximately 39 kt pure benzene, it can be concluded that the production of benzene in the Australian petroleum industry amounted to 387 kt in 1998.

Table 7.1: Throughput of LP, ULP, PULP and Avgas at Australian refineries in 1998 (AIP, 1998b, 1999b)

	LP	ULP	PULP	Avgas	Total
Petrol (ML)	4965	12,218	640	100	17,923
Benzene (% v/v)	2.9	2.6	3.3	1.0	-
Pure benzene (ML)	144	318	21	1	484

Petrol is also imported in finished form. From January 1994 through August 1999, petrol imports averaged 680 ML per annum (DISR, 1999). There is no information on the benzene content of imported petrol, but it is unlikely to differ much from that of Australian ULP, which averages 2.6% v/v. As such, annual imports of benzene as an ingredient in petrol purchased overseas is estimated at 18 ML corresponding to approximately 15 kt pure benzene.

The Port Kembla steelworks produces 20-22 ML per annum of a commercial low-grade benzene product called BTX. As the specifications stipulate a benzene content of ≥80% v/v (Table 4.1), this corresponds to approximately 14.0-15.5 kt pure benzene per annum. The Whyalla steelworks no longer produce BTX, however, 0.12kt of benzene per annum, from the naphthalene still, is reinjected into the fuel gas stream.

Benzene is also produced as a by-product stream component at two olefins (pyrolysis) plants belonging to Qenos Pty Ltd. The total quantity amounts to approximately 15 kt per annum, all of which is exported for use or further processing overseas.

The only importer of benzene feedstock is Huntsman Chemical Company, whose annual imports are stable at about 50 kt pure benzene and 30 kt crude benzene (≥95% v/v), that is, approximately 80 kt pure benzene per annum.

Minor quantities not exceeding 1 t in the aggregate are imported for laboratory and other small-scale uses, as described below.

7.2 Manufacturing processes and end use

7.2.1 Petroleum industry

Table 7.2 provides an overview of the location and ownership of the currently operating oil refineries in Australia, as well as a summary of the processes employed to produce benzene, their capacity, and the benzene content of locally produced petrol. The latter is taken from a 1994 survey, which reported the concentration in % w/w (Tresider, 1998). As such, it is not directly comparable to the data provided in Table 7.1[1]. The process technologies and end use of the benzene produced are described below.

[1] The factor needed to convert % w/w to % v/v varies with the density of the petrol. Based on the average density of Australian petrol in 1999, multiplication of the concentration in % w/w with 0.84 will give an approximate concentration in % v/v (Exxonmobile personal communication, 2001).

Table 7.2: Benzene processes at Australian oil refineries (AIP, 1997; Mobil, 2000; Tresider, 1998)

State	Location	Owner	Benzene technology	Capacity (kt/y)*	Benzene in LP/ULP/PULP (% w/w)
NSW	Clyde	Shell	Reforming Cracking	890 1558	2.7/ 2.4/3.6
	Kurnell	Caltex	Reforming Cracking	1344 2024	2.3/2.3/4.7
QLD	Bulwer Island	BP	Reforming Cracking	588 912	2.5/3.7/5.0
	Lytton	Caltex	Reforming Cracking	1157 1469	2.4/2.5/4.4
SA	Port Stanvac	Mobil	Reforming	1157	2.3/2.0/2.5
VIC	Altona	Mobil	Reforming Cracking	1380 1246	4.8/4.5/5.5
	Geelong	Shell	Reforming Cracking	1380 1780	3.6/3.6/5.4
WA	Kwinana	BP	Reforming Cracking	979 1456	1.9/2.0/2.2

***** The capacity is calculated on the basis of 350 stream days per year and refers to the quantity of raw material processed, not benzene produced.

Based on more recent information (AIP average data for 1999), ULP contains approximately 3.01% (w/w) benzene, PULP contains 4.02% (w/w) and LP contains 3.46 (w/w) (Exxonmobile Personal Communication, 2001).

Petroleum refining

Petroleum refining involves a series of continuous, enclosed processes designed to convert crude oil and condensate into end products such as liquefied petroleum gas, Avgas, petrol, jet fuel, diesel, heating oil, lubricants and bitumen. The main processes designed to augment the content of aromatics such as benzene in petrol are shown in the flowchart in Figure 7.2 and summarised below.

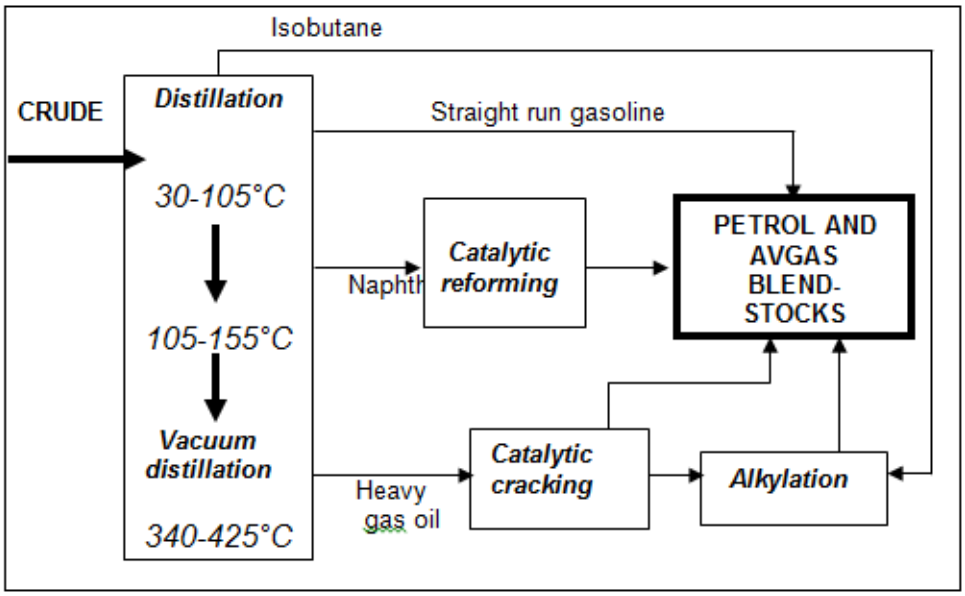


Figure 7.2: Benzene production in petroleum refineries

At all refineries, crude oil is first separated into a number of fractions by atmospheric and vacuum distillation. Petrol is a blend of butane, refined naphthas, isomerate, reformate, cracked gasoline and alkylate. Avgas is primarily made from alkylate although reformate can also be used.

The straight run gasoline fraction contains a 5- to 10-fold concentrate of all the benzene that was present in the crude, corresponding to a benzene concentration of 0.5-1% v/v.

The naphtha fraction, which contains many cyclic, saturated hydrocarbons, undergoes catalytic reforming in a process using heat, pressure and a platinum catalyst to convert a portion of the feedstock to aromatic compounds. The resulting reformate typically contains 4-8% v/v of benzene (Audrey, 1994).

At the Mobil Altona refinery, part of the heavy gas oil fraction is piped to a nearby petrochemical plant for steam cracking, as described below. This process gives rise to a by-product known as steam cracked naphtha or pyrolysis gasoline, which contains 6-8% benzene. This by-product stream is piped back to the oil refinery where it is stored in floating-roof tanks and eventually exported to overseas customers by shipping tanker.

The heavy gas oil fraction, which contains large, high boiling hydrocarbon molecules, is cracked to a mixture of lower molecular weight compounds by means of heat, pressure and a silica/aluminium oxide or zeolite catalyst. The benzene content of cracked gasoline rarely exceeds 1-2% v/v, but varies depending on the composition of the feedstock, the nature of the catalyst and the temperature and pressure conditions. As shown in Figure 7.2, some of the output from the cracking process is reacted with isobutane to form larger branched-chain molecules (isoparaffins) that increase the octane rating of the final petrol blend. The alkylation process does not augment benzene content.

Eventually, the various petrol feedstock qualities are blended to produce end products with the desired specifications. These vary according to the likely ambient temperatures in the area and season in question and generally require higher concentrations of aromatic components such as benzene in colder climates.

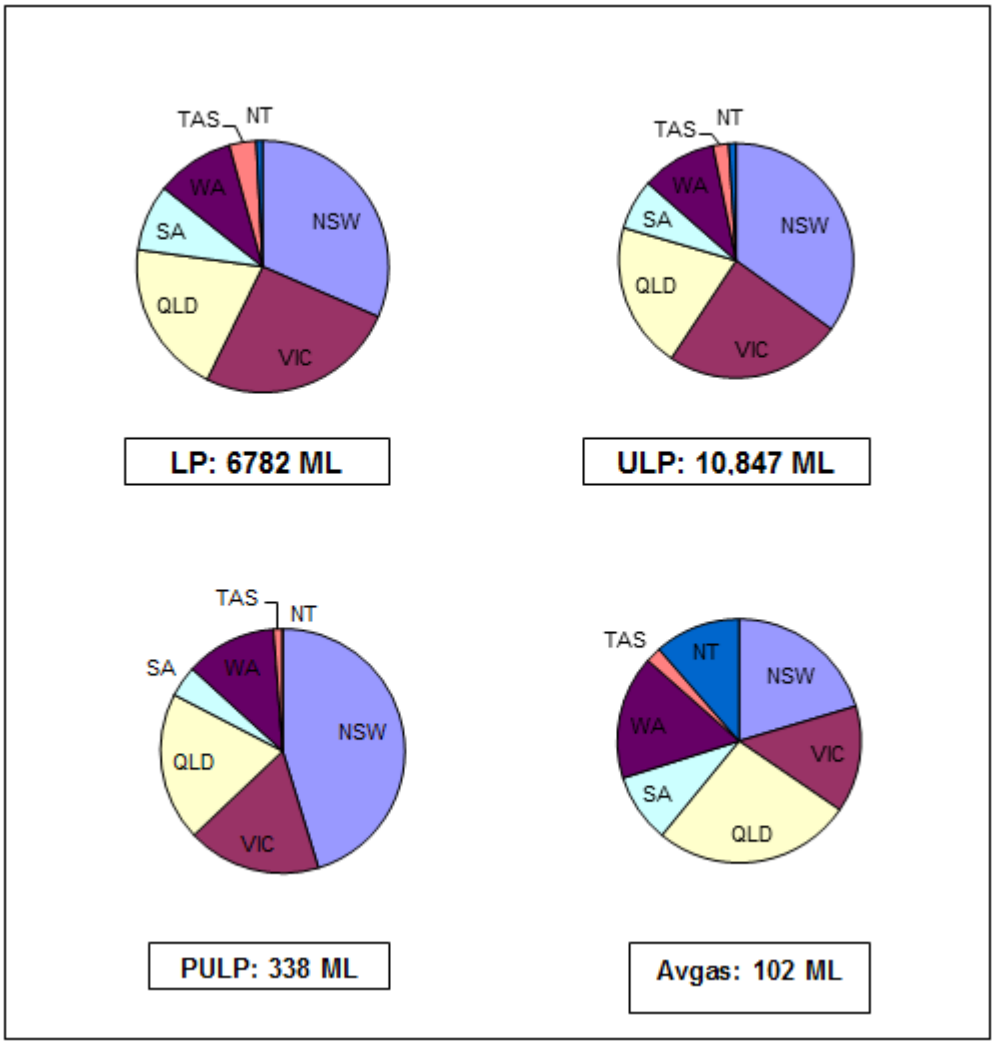
Feedstock and end product are stored in tanks equipped with floating roofs or connected to vapour recovery systems. The end products are distributed to larger terminals by pipeline, in coastal tankers or bottom-loaded rail tankers and/or to local depots and service stations in road tankers, the majority of which are bottom loaded. In rural areas not all road tankers are bottom loaded. Terminals in Sydney, Melbourne and Perth have vapour recovery systems to minimise vapour emissions during truck filling operations. There were 8233 petrol retail outlets in Australia at the end of 1998 (AIP, 2000).

End use

In Australia, all benzene produced by petroleum refiners is retained as one of several aromatic components in automotive petrol and Avgas; most of this benzene is burnt during normal engine operation. Figure 7.3 shows the total demand for benzene-containing petroleum products in 1996, and its breakdown by State marketing area[2].

[2] The State marketing area (SMA) of Queensland includes the Murwillumbah district of NSW, which is supplied from the refineries in Brisbane. The SMA of South Australia includes the Broken Hill-

Figure 7.3: Demand for petrol in 1996 (AIP, 1997)



As expected, the demand for petrol is highest in the most populous States of New South Wales and Victoria. Queensland, Western Australia and the Northern Territory account for more than one-half of the total demand for Avgas.

Since catalytic converters became mandatory on new cars in 1986, there has been a steady increase in the demand for ULP and a corresponding decline in the demand for LP. However, although LP contains more benzene than ULP, the corresponding fall in benzene consumption has been counterbalanced by an overall growth in petrol demand. PULP, which was first produced in significant quantities in 1989 and has the highest concentration of benzene (Table 7.1), accounted for only 2% of total petrol sales in 1996, almost half of which was generated in New South Wales. However, PULP demand is expected to grow as LP is phased out nationally by 2002 and pre-1986 cars will need to run on either PULP or lead replacement petrol, that is, PULP pre-blended with an anti-valve seat recession additive.

Wilcannia district of NSW and the Murrayville district of Victoria, which are supplied from the refinery at Port Stanvac. The SMA of Victoria includes the Riverina district of New South Wales, which is supplied from the refineries at Altona and Geelong. The SMA of New South Wales includes the Australian Commonwealth Territory.

The likely impact of the predicted changes in demand on the use of benzene in petrol can be estimated on the basis of AIP's petrol sales forecasts for the decade 1998-2007 (AIP, 1998a). If current benzene concentrations are assumed to remain unchanged throughout the period, total benzene use in petrol is estimated to increase from 434 kt/y in 1998 to 461 kt/y in 2007. However, if a nationwide standard is introduced limiting the maximum content in petrol to 1%, total benzene use in petrol is estimated to fall to 176 kt/y in 2007.

Independent petrol retailers

The main imports of petrol are marketed by independent chains or supermarkets such as Trafigura (formerly Burmah) Fuels, Liberty and Woolworths, who had 564 service stations between them at the end of 1998 (AIP, 2000). Their imports pass through the terminals of Vopak (formerly Van Ommeren) at Port Botany in Sydney and Hastings Point near Melbourne, Gull at Kwinana in Western Australia, and Fletcher Challenge in Brisbane. These terminals have a petrol storage capacity of 95, 70, 53 and 13 ML respectively (DISR, 1999; Vopak, 2000).

7.2.2 Steel and associated industries

BTX

In the steel industry, BTX is a by-product from volatile fractions produced in the coking ovens. It contains ≥80% v/v benzene (see Table 4.1) and is recovered in an enclosed process which yields from 3-5 kg pure benzene per t coke produced.

The coking ovens are arranged in batteries, each of which may contain in the region of 60 units. The ovens are sequentially charged by means of mechanical hopper systems through special lidded holes that are closed and sealed to keep out air during the coking cycle. This cycle takes place at 900-1100°C for 12-24 h. On completion of the cycle, the hot coke is removed mechanically through doors on the sides of the oven and sprayed with flushing liquor (a dilute solution of ammonia in water) to quench combustion upon exposure to air.

The coke oven gas contains hydrogen, methane, carbon monoxide and light oil, which is a mixture of various aliphatic and aromatic hydrocarbons, including benzene. The overhead gas is collected into a pipe that runs along the length of each battery and propelled to the by-product plant. At emission, it has a temperature of approximately 600°C which is brought down to 80°C by spraying with flushing liquor. It is further cooled to 38°C, passed through an electrostatic precipitator and an acid scrubber where tar and ammonia are removed and cooled to a final temperature of 20°C. The gas then passes to a system of light oil scrubbers, where most of the C_5 and higher hydrocarbons are recovered by counter-current absorption using a high-boiling (300-400°C) petroleum fraction. BTX is recovered from the absorbent oil by steam stripping and separated from the water by distillation. At Port Kembla, the distillation process is continuous and BTX is collected and piped to a storage tank. At the smaller Whyalla steelworks, BTX is separated by batch distillation and returned directly to the gas system. At both sites, the refined coke oven gas is stored in a gasholder and used for heating.

Process waste water, which is mainly from the flushing liquor circuit and contains a number of contaminants, including benzene, is passed through a water/oil separator and discharged to a biological treatment plant. All storage tanks are eventually vented to the atmosphere, but may be connected to a vent header with a sealpot

arrangement to prevent emission unless there is a build-up of pressure. Excess gas is flared off.

All BTX produced at Port Kembla is transported by road to Huntsman Chemical Company in Melbourne for use as chemical feedstock.

Coal tar

Tar condensed from the coke oven gas and flushing liquor circuit is collected in a system of decanting tanks and pumped to a wet tar storage tank. This tank decants excess liquor back to the liquor circuit and transfers the tar sediment to a dry tar tank farm. The residue from the BTX distillation, which is known as naphthalene oil, is also pumped to the dry tar tank farm. The dry tar, which contains ≤0.16% residual benzene, is shipped to Koppers Coal and Tar Products at Mayfield, Newcastle, New South Wales, in splash top loaded rail or road tankers, or by sea tanker.

The Newcastle plant receives in the order of 125 kt crude tar per annum containing about 145 t residual benzene. The plant comprises two interconnected, fully enclosed systems which separate the tar in a series of continuous distillation processes. The distillation products include solvent naphtha (4% benzene), distilled tar (0.5% benzene), creosote oil (0.2% benzene), naphthalene (no measurable benzene) and coal tar pitch (no measurable benzene). Most of the solvent naphtha representing about 80% of the benzene received is burnt as fuel. The remainder is blended into creosote oil which is used in solvent-based industrial timber preservatives or as feedstock in the manufacture of carbon black. Distilled tar is used in the coatings industry. Naphthalene is exported and coal tar pitch onsold to the aluminium industry for the manufacture of carbon electrodes.

Process waste water from the Koppers coal tar plant is passed through a water/oil separator and discharged to a biological treatment plant. All storage tanks are connected to fume scrubbing systems. Off-gases from the stills are burnt as fuel.

7.2.3 Chemical industry

Qenos

Ethane and naphtha (gas oil) cracking

The olefins plant at the Qenos site at Altona in Melbourne produces 10-12 kt benzene per year as a by-product of the steam cracking of ethane and naphtha (gas oil) to ethylene, propylene and butadiene, which are then converted into plastics and rubbers. The Qenos (formerly Orica) olefins plant at Botany in Sydney produces 2-3 kt benzene per year as a by-product of the steam cracking of ethane to ethylene.

Steam cracking is a continuous, fully enclosed process which produces a variety of products by free radical reactions. Steam and hydrocarbon feedstock are mixed and subjected to a brief surge of extreme heat (750-900°C). The effluent is rapidly cooled, compressed, purified in a caustic washer, dried, chilled and fractionated in a train of distillation columns.

At the Altona plant, the by-product streams from the ethane and naphtha steam cracking processes are combined and purified by distillation to produce a pyrolysis

gasoline containing 6-8% benzene, which is piped to the Mobil Altona refinery and eventually exported for use overseas (Section 7.2.1).

At the Botany plant, the heavier molecules produced in the cracking process are collected in a feed tank and further processed in a fully enclosed system which is on stream for approximately 60 days per annum. In the process, the by-product stream is hydrogenated and then distilled to remove light ends, which are returned to the ethane cracking system. The end product is a pyrolysis gasoline containing approximately 55% aromatics including 35-36% benzene. This is stored on site in a floating-roof tank. At intervals of 5-6 months, it is piped to the bulk liquid terminal at Port Botany and shipped overseas for further processing.

Butadiene rubber manufacture

Qenos' Altona facility also uses about 40 t benzene per year as a solvent component in the manufacture of butadiene rubber. The benzene is purchased from Huntsman (see below) and supplied by dedicated road tanker. It is stored in a nitrogen-blanketed tank and pumped to the butadiene rubber plant via sealed pipes.

In the plant, butadiene is polymerised in solution in a fully enclosed batch process. The solvent contains cyclohexane and benzene in a ratio of about 2:1 and is not consumed in the reaction. The polymerisation process is strongly exothermic and the reactor temperature is kept at approximately 20°C by ammonia cooling. The reaction is stopped with an antioxidant. The solvent is removed from the rubber-solvent solution by steam stripping and is then condensed, purified and recycled to the beginning of the process for feedstock blending. Waste water is steam stripped to remove dissolved benzene prior to discharge to sewer. Off-gases containing benzene are sent to a thermal oxidiser for destruction.

Huntsman Chemical Company

The Huntsman (formerly Chemplex) plant at West Footscray in Melbourne converts about 80 kt benzene per annum to ethyl benzene and 10-15 kt to cumene (isopropyl benzene). Ethyl benzene is further processed to styrene, which is used in the production of polystyrene polymers and unsaturated polyester and vinyl ester resin solutions. Cumene is oxidised to acetone and phenol. The phenol is used on site in the production of phenol-formaldehyde resins. The acetone is onsold in bulk to other manufacturers.

Huntsman purchases about 15% of their requirements for benzene in the form of BTX produced at the Port Kembla steelworks. The remainder is imported from Indonesia, Japan, Korea and Singapore in chemical tankers. The bulk chemical is unloaded at Terminals Pty Ltd on Coode Island on Melbourne's waterfront where it is kept in storage before being transported to Huntsman by dedicated road tanker. A small part is trucked to Qenos' Altona facility for use as a solvent component in the manufacture of butadiene rubber.

Styrene manufacture

The styrene plant was commissioned in 1977 and operates a series of four continuous, fully enclosed processes, namely, ethylene, Litol, alkylation and dehydrogenation. The principal feedstocks are ethane, pure benzene and BTX.

In the Litol plant, BTX is vaporised with hot hydrogen and passed through fixed bed catalytic reactors to hydro-dealkylate toluene and xylenes to benzene and destroy heterocyclic compounds. Pure benzene is recovered by fractional

distillation. By-product hydrocarbon gases, excess hydrogen and heavy distillation residues are used as fuel. A waste stream rich in hydrogen sulfide is incinerated.

The alkylation plant makes ethyl benzene from benzene and ethylene produced on site by the cracking of ethane. In the first of two reactors, the alkylation is carried out in the presence of a homogenous acidic catalyst prepared separately from aluminium chloride. In the second reactor, recycled polyethyl benzene is trans-alkylated to ethyl benzene. The remaining undesired components from the dilute ethylene benzene stream are recovered, neutralised and used as fuel. Catalyst is removed from the alkylated liquor in a 3-stage wash system. The aqueous wash liquors containing aluminium and sodium chlorides and some hydrocarbon contaminants are treated aerobically at the site effluent treatment plant before discharge to sewer. The alkylation liquor is then refined in a 3-column distillation train. Pure ethyl benzene is recovered for subsequent use in the dehydrogenation plant. Excess benzene and the polyethyl benzene are recovered and recycled to the reactors. The heavy distillation residue is utilised elsewhere in the complex to lower the viscosity of other residue streams and ultimately utilised as fuel.

In the dehydrogenation plant, ethyl benzene is dehydrogenated to styrene at high temperature and low pressure in the presence of steam. The dehydrogenated mixture is condensed and cooled, the water is separated out, and the stream is refined in a 3-column distillation train. Hydrogen and other gases produced in the reactor are used as fuel. By-product benzene and toluene are recovered and sent to the Litol plant for conversion to pure benzene. Unreacted ethyl benzene is recovered and returned to the dehydrogenation reactor. Pure styrene is distilled and dosed with a polymerisation inhibitor prior to storage.

Tanks containing benzene are vented to a carbon bed vapour emission control system that recovers about 60 t of benzene per annum and returns it to the styrene plant.

Phenol manufacture

The phenol plant was commissioned in 1968. It produces phenol and acetone in a continuous, fully enclosed process. Cumene is formed by the reaction of pure benzene and propylene in a fixed-bed reactor using a phosphoric acid catalyst on a solid support. The pure benzene feedstock is either imported or produced in the styrene plant and piped to the phenol plant. A 3-column refining section recovers gaseous components from the cumene stream. Unreacted benzene is recycled into the process, and cumene is sent on to the oxidation reactor. Heavy distillation residue is utilised as fuel or as an aromatic feedstock in the Litol plant. The purified cumene stream is partially oxidised with air to cumene hydroperoxide, which is cleaved by acid to a mixture of crude phenol and acetone. The mixture is split into phenol and acetone, which are purified by distillation in a 7-column refining train.

Heavy distillation residue is subjected to a 2-column system, where some additional phenol is recovered via pyrolysis and distillation for recycling to the refining train. Residue from this system is utilised as fuel. Spent air from the oxidation reactor is chilled to remove most of the organic substances and then passed through activated carbon beds before release to the atmosphere. A combined aqueous waste stream is treated in the site effluent treatment plant prior to discharge to sewer.

7.2.4 Laboratory uses

Seven of the applicants listed in Section 3 identified themselves as occasional importers of reagent grade benzene. Between them, they imported approximately 500 kg benzene in 1999, which was onsold to a total of 55 end users. Of these, 27 were commercial enterprises such as contract and company in-house analytical laboratories. Twenty-one belonged to the science or medical faculties of 15 different universities. Seven were State or Commonwealth laboratories. The quantities purchased by individual laboratories in 1999 ranged from 0.1-150 L (0.88-130 kg), with a mean of 10 L (8.8 kg) and a median of 2.5 L (2.2 kg).

Benzene is also present in some ready-made liquid or gaseous standards for the calibration of gas chromatographs and other analytical instruments. The quantity of benzene consumed through the use of such standards is estimated at less than 1 kg per annum.

7.2.5 Coincidental production

Benzene is formed coincidentally during the burning of aromatic and non-aromatic organic compounds contained in biomass such as crops, wood and humus, in fossil fuels such as black and brown coal, and in petroleum products including diesel and jet engine fuel which have a negligible benzene content prior to combustion. These processes are important sources of entry into the environment and will be considered in detail in subsequent sections.

7.3 Summary

Table 7.3 summarises the industrial mass balance of benzene in Australia and the available information on its major manufacturers, importers and users, and most significant end uses. These figures are approximate and give a general indication of industrial use of benzene in Australia. Benzene produced coincidentally in the course of human activities or natural processes and products containing benzene as an impurity are not accounted for.

Table 7.3: Benzene mass balance and major manufacturers, importers and end users in Australia in 1998-99

	Kilotonnes/year (rounded)						
Industry or company	Extrac-tion	Manu-facture	Import	Total	Export	Con-sumption	End use
Petroleum	30	385	25	440	-	440	Petrol
Huntsman	-	-	80	80	-	95	Feedstock
Steel	15	-	-	15	-	0.2	Fuel
Qenos	-	15	-	15	15	0.040	Solvent
Others	-	-	0.0005	0.0005	-	0.0005	Reagent
TOTAL	45	400	105	550	15	535	-

In 1998-99, total benzene consumption in Australia was in the order of 535 kt per year. Of this quantity, 105 kt were imported, 45 kt were extracted from crude oil and coal gas, and the remainder produced at eight oil refineries. Petrol accounted for approximately 82%, chemical synthesis for 18% and all other uses combined for less than 1% of total consumption.

8. Environmental Release, Fate and Effects

As no environmental fate and toxicity studies were submitted for assessment, this section is based on international, peer-reviewed reports such as GDCh (1988), Government of Canada (1993) and IPCS (1993), the International Uniform Chemical Information Database (IUCLID) and the USEPA's ECOTOX database (USEPA, 2000). Data within these three reports are largely the same and also appear in the databases.

IUCLID contains non-confidential data supplied by industry to the European Commission. They have not undergone peer review and are therefore only reported where they are not described elsewhere but nonetheless give guidance to the fate and effects of benzene in the environment. Results in the ECOTOX database have been published and are generally considered reliable.

8.1 Environmental release

Benzene is ubiquitous in the environment, with numerous sources of entry including bush fires, crop residue and forest management burning, petrol combustion, wood fires, tobacco smoking and emissions and waste streams from various industries. Due to the nature of benzene being produced incidentally during natural processes and human activities, it is not possible to obtain accurate figures in estimating national releases. However, several point source releases provided in NPI reports for the first reporting year of 1998/99 are described in Section 15, which also gives an estimation of diffuse releases in a model urban environment.

Overall, release of benzene will primarily be to the atmosphere through emissions in exhaust during petrol combustion in motor vehicles, followed by releases to air from point sources in the petroleum, steel, aluminium, chemical and other industries. By contrast, releases to water and soil are expected to be relatively minor, as borne out in NPI reports where the highest annual release from a single point source to water and soil was 1100 kg and 45 kg respectively, compared with 130,000 kg to air from an oil and gas extraction plant.

8.2 Environmental fate

The Trent University (1999) Level 1 Fugacity Based Environmental Equilibrium Model indicates that in the order of 99% of benzene will partition to air, with 0.88% and 0.05% partitioning to water and soil respectively. Negligible amounts are expected to partition to sediments, suspended sediments, biota and aerosols.

8.2.1 Atmospheric fate

The water solubility of benzene suggests that one removal mechanism from the atmosphere is through returning to the terrestrial and aquatic compartments in rainwater. However, the Henry's Law constant and volatility of benzene indicate that the chemical would rapidly volatilise back into the atmosphere where it would be available for abiotic breakdown.

Direct photolysis

IPCS (1993) reports that direct photolysis of benzene in the troposphere is unlikely since the UV-visible spectrum of benzene shows no appreciable absorbance at wavelengths >260 nm. According to GDCh (1988), direct photolysis is of minor importance for the same reason.

IUCLID provides test results for a smog chamber experiment in which light with a wavelength >290 nm corresponding to tropospheric sunlight was used with benzene at a concentration of 100 ppm (0.32 mg/L). Although the validity of this test cannot be judged due to insufficient documentation, the outcome showed no evidence of benzene degradation. After the addition of chemicals producing active species, benzene half-lives were between 4-5 h. Using light with a higher intensity (wavelengths >230 nm), a half-life of 6.5 h was detected. These findings indicate that direct photolysis is minimal at environmentally significant wavelengths, stated by Howard et al. (1991) to be >290 nm, and thus confirm that this process will not be a major removal process for benzene in the troposphere.

Indirect photolysis

IUCLID provides details for several studies on indirect photolysis. The results of those where a half-life was determined are presented in Table 8.1. In all tests, hydroxyl radicals were used as the reactant, with air as the medium. Not all studies had temperature reported. However, where available, it was 25ºC. While the validity of these studies is uncertain, it is well accepted that indirect photolysis through reaction with hydroxyl radicals is the major degradation pathway for benzene in air (GDCh, 1988; Government of Canada, 1993; IPCS, 1993).

Table 8.1: Half-life of benzene in the atmosphere where degraded by hydroxyl radicals

Light source	Hydroxyl concentration (radicals/cm^3)	Rate constant (cm^3/(molecule.s)	Half-life (days)
Sun light	5 x 10^5	1.2 x 10^{-12}	13.4
Other*	5 x 10^5	1.2 x 10^{-12}	13.4
Sun light	7.5 x 10^6	1.3 x 10^{-12}	19
Sun light	1.1 x 10^6	1.3 x 10^{-12}	5.6
Sun light	1.2 x 10^6	1.2-1.6 x 10^{-12}	5.3

* Hydroxyl radicals produced by flash photolysis and using a resonance fluorescence method.

The Dutch Environment Ministry calculated a half-life of benzene in the atmosphere of 5.3 days assuming an average hydroxyl radical concentration of 1.25 x 10^6 molecules/cm^3 over the Netherlands with a rate constant of 1.3 x 10^{-12} cm^3/(molecule.s). This is reported in both IPCS (1993) and GDCh (1988), although neither report describes the basis for the assumed hydroxyl radical concentration. The global 24-h average hydroxyl radical concentration has been reported to be around 5 x 10^5 molecules/cm^3 (Calamari, 1993; GDCh, 1988). Additionally, using the OECD Environment Monograph No. 61 (OECD, 1993), a rate constant for benzene can be calculated at 2 x 10^{-12} cm^3/(molecule.s) (contrary to the range of 0.8-1.4 x 10^{-12} cm^3/(molecule.s) quoted in GDCh (1988)). Applying the global average hydroxyl radical concentration and rate constant from the OECD monograph and following the methodology in this monograph, gives an estimated half-life of 8 days. This is more in agreement with the Canadian authorities where a half-life attributable to reactions with hydroxyl radicals was calculated to be 9 days

under typical urban atmospheric conditions, although the hydroxyl radical concentration and rate constant were not reported (Government of Canada, 1993).

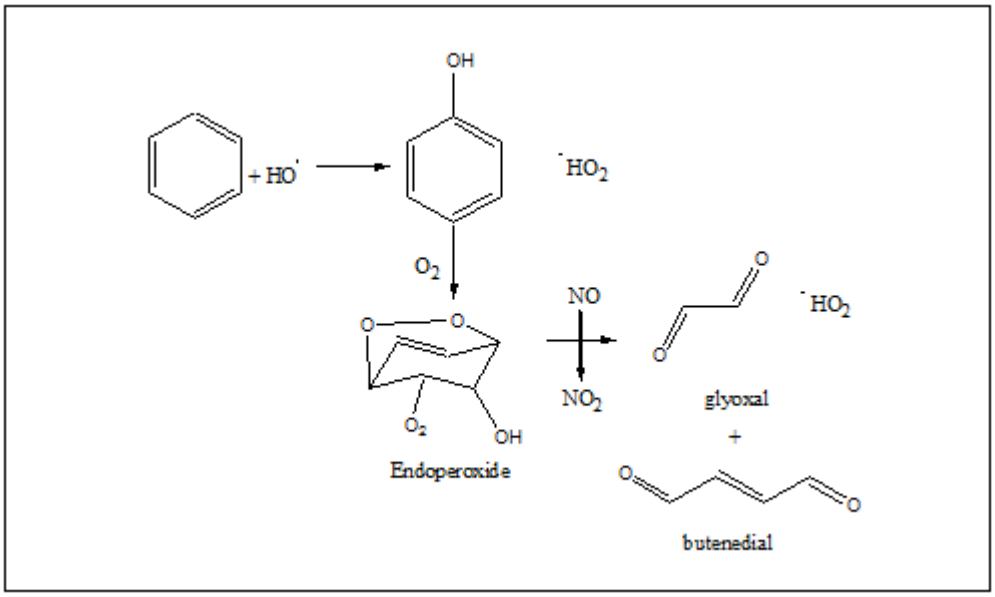
The global concentration used above applies to the average for the whole troposphere. In the lower troposphere where benzene and hydroxyl radicals occur at higher concentrations, the benzene half-life would be expected to be lower, and is reported as 3-10 days (GDCh, 1988). Additionally, in districts with high traffic density, where there is a higher concentration of hydroxyl radicals because of higher concentrations of precursors, a lower atmospheric half-life can be expected, and again 3-10 days is reported (GDCh, 1988).

For the purposes of this assessment, an atmospheric half-life of 8 days will be used based on the globally accepted tropospheric average for the concentration of hydroxyl radicals and the methodology and rate constant prescribed in the OECD monograph.

These results given above are all within the range predicted in Howard et al. (1991) where the photooxidation half-life in air has been calculated to fall between 50.1 h (2.09 days) and 501 h (20.9 days).

The proposed degradation pathway through reaction with hydroxyl radicals is shown in Figure 8.1 (Verscheuren, 1996).

Figure 8.1: Proposed degradation pathway of benzene in the atmosphere



In the IUCLID database one study is described where ozone was used as a reactant. In this test, air was the medium and the light source was chemiluminescence. A sensitiser concentration of 3 x 10^{12} molecules/cm^3 and a rate constant of 1 x 10^{-22} cm^3/(molecule.s) were used. In an urban atmosphere, the half-life for the reaction of benzene with ozone was calculated to be 105 years. In a rural atmosphere, the half-life would be 327 years, using an atmospheric concentration for ozone of 9.6 x 10^{11} molecules/cm^3. Therefore, photolysis through reaction with ozone is not expected to be a major removal process for benzene in the atmosphere.

One test is described where atomic oxygen was used as the reactant at a concentration of 7.2 x 10^4 molecules/cm^3 with a rate constant of 2.8 x 10^{-14} cm^3/(molecule.s). The half-life for this reaction between benzene and atomic oxygen was calculated to be 10.9 years, indicating that this reaction will not be a major removal process of benzene from the atmosphere.

One test describes the photodegradation using sulphur dioxide as the reactant. The test was performed in air with sunlight as the light source (light spectrum >290 nm). Benzene was present at a concentration of 100 ppm (0.32 mg/L). No further information is available on the method, so the validity of this test is unknown. However, sulphur dioxide was present at a concentration of 10-110 ppm (0.026-0.288 mg/L). Photodegradation was observed. IUCLID states that approximately 2 days was required for 50% degradation to CO_2, although the half-life for photodegradation of benzene is stated as 6 h.

8.2.2 Aquatic fate

Photolysis in water

Direct photolysis of benzene in aqueous solution was investigated with half-lives observed varying from 9-673 days. However, the authors concluded that the test method was not suitable for poorly soluble, volatile substances (GDCh, 1988).

Two direct photolysis studies are reported in IUCLID where benzene was tested adsorbed on silica gel. In both tests the concentration of benzene was 0.32 mg/L and the light source was not stated. Few details are reported and the validity of the tests is unknown. However, one was irradiated at >230 nm (not environmentally significant), and resulted in a half-life of 6.5 h. The other was irradiated at tropospheric wavelengths (>290 nm) and showed that 5% had photomineralised to CO_2 after 17 h.

Hydrolysis

IUCLID provides two reports for abiotic degradation of benzene, both concluding that hydrolysis is not expected to be a significant process for removing benzene. Few details are available for these tests and validity cannot be assumed. However, degradation by this route is not expected, as benzene has no hydrolysable groups.

Volatilisation

Volatility from water to air is summarised in several reports in IUCLID.

Based on a reported Henry's Law constant of 0.0053 atm.m^3/mol and a model river 1 m deep flowing at 1 m/s with a wind velocity of 3 m/s, the half-life of benzene was 2.7 h at 20°C.

The half-life for the evaporation of benzene from seawater was investigated in a mesocosm containing planktonic and microbial communities. Half lives for summer, spring and winter were reported as 3.1, 23 and 13 days respectively.

The half-life for evaporation of benzene from a 1 m thick still water column was 4.8 and 5 h at 25 and 10°C respectively by thermodynamic calculations. The residence half-time for well-mixed water was 37 min. This half-life of 4.8 h is also included in the IPCS (1993) and Government of Canada (1993) reports.

An experiment in a wind-wave tank 6 m long, 0.61 m deep and 0.6 m wide with wind velocities of around 6-13 m/s at a temperature of 20.7°C is described. The testing period was >50 h so that an approximate 10-fold change of solute concentration (which was measured by gas chromatography) would occur. The mass transfer coefficients of benzene at the water-air interface were 11.4-34 cm/h dependent on wind velocity. The volatilisation is of first order kinetics. For a wind speed of 7.09 m/s, a half-life of 5.2 h can be calculated.

While the reliability of these results is unclear, they support that rapid volatilisation from water will occur.

8.2.3 Terrestrial fate

Adsorption

Documentation on the adsorption of benzene to soil is limited as the exposure of the terrestrial compartment is likely to be low.

The Government of Canada (1993) report cites K_{oc} values for benzene ranging from 12-213, indicating the chemical to be moderately to highly mobile in soil.

IUCLID reports a calculated soil absorption coefficient of 71, using equations developed by Kenaga & Goring and published by the American Society for Testing and Materials. While this reference has not been obtained, an experimental soil absorption coefficient value of 83 is reported in IUCLID as well as in IPCS (1993).

IPCS (1993) cites a rounded log K_{oc} range of 1.8-1.9 (K_{oc} = 60-83), indicating fair mobility in soil, and states that benzene is not expected to adsorb to bottom sediments based on its K_{oc}, solubility and volatility.

K_{oc} values provided in IUCLID indicate that benzene may exhibit high mobility in soils and may migrate to groundwater. Several tests are reported and are generally described as valid, or valid with restrictions. They can be used to provide a guide as to the adsorptive behaviour of benzene.

One report gave the results of adsorption tests using radioactive labelled test substance on aquifer material. This test is described as valid with IUCLID noting that the test procedure was in accordance with generally accepted scientific standards and described in sufficient detail. The results provided log K_{oc} values between 2.09 and 3.01 (K_{oc} 123-1023). Experiments were carried out in capped glass centrifuge tubes on two American groundwater aquifer materials with the following characteristics:

Material:	Sand (%):	Silt (%):	Clay (%):	Organic matter (%):	pH:
A	90	8.0	2.0	4.4	3.8
B	70.4	24.0	5.6	2.2	5.5

Both these materials were acidic, with material A being quite acidic. It cannot be concluded from the IUCLID summary whether K_{oc} was a function of pH, although this is not expected to be the case since benzene is a neutral molecule. These results suggest that benzene is moderately mobile.

A water-soil adsorption coefficient of 18.2 provided in IUCLID was measured in soil-solution mixtures which were equilibrated for 24 h at 20°C in capped centrifuge tubes. Losses by volatilisation were avoided by sampling through the septum of the caps. The substance amounts were corrected by the airspace of the tubes under consideration of air volume and Henry's Law constant. Soil characteristics were reported as 9% sand; 68% silt; 21% clay and 1.9% organic matter. pH was not stated.

While IUCLID also provides some calculated results, these are not reported here as measured values are considered more reliable and the terrestrial compartment is not expected to be a significant sink for benzene.

Volatilisation

The primary mechanisms responsible for loss of benzene from soil are volatilisation to the atmosphere and runoff to surface water. Benzene released below the soil surface may leach to groundwater (Government of Canada, 1993).

The volatility of benzene from soil to air is summarised in two reports in IUCLID. In one report, the half-lives of volatilisation, without water evaporation, of benzene uniformly distributed at a rate of 1 kg/ha to 1 and 10 cm in soil with an organic carbon content of 1.25% were 7.2 and 38.4 days respectively. The second report is from a model developed to predict the environmental fate of benzene following leakage of gasoline from an underground storage tank. It estimated that some 67% of the benzene would volatilise from the soil within 17 months, with 29% leaching to groundwater and the remainder associating with the soil.

8.2.4 Biodegradation

IPCS (1993) provides the following insight into the biodegradation of benzene:

- In surface and ground water benzene is biodegradable by microorganisms under both aerobic and anaerobic conditions with the mechanism of biodegradation seeming to involve the formation of catechol via *cis*-1,2-dihydroxy-1,2-dihydrobenzene followed by ring cleavage.
- One study on the aerobic biodegradation of benzene in groundwater utilised a mixed bacterial culture from groundwater and soil bacteria capable of using gasoline as a sole carbon source. Under closed agitated conditions without added nutrients the half-life appeared to be <48 h with benzene levels falling from 480 to 218 μg/L in this time. When ammonium nitrate was added, the reaction was much faster, with benzene levels decreasing to 35 μg/L in 20 h.
- The biodegradation of benzene in ground and river waters appears to follow first-order rate kinetics with reported half-lives of 28 and 16 days respectively.

IUCLID provides results from several biodegradation studies which generally agree that a significant degree of biodegradation occurs under aerobic conditions. Some tests classify the substance as readily biodegradable. However, many of the tests are not ready biodegradation tests and the results do not indicate degradation that would be fast enough for benzene to be classed as readily biodegradable. While validity cannot be assumed, they may be used to provide guidance as to the biodegradability of benzene. As such, for the purposes of this assessment, the chemical will be considered at least inherently biodegradable.

The majority of tests summarised in IUCLID for anaerobic degradation indicate degradation is very slow to non-existent. This is supported in the GDCh (1988) report where it is stated that degradation of benzene has not yet been detected in anaerobic conditions. However, IPCS (1993) describes a report where samples of landfill leachate incubated under methogenic conditions in an anaerobic glove box showed a 72% reduction in benzene concentrations after 40 weeks, although no significant benzene biodegradation occurred during the first 20 weeks of incubation. In another study using anaerobic digesting sludge under methano-trophic conditions, benzene was undegraded after 11 weeks. It is also reported that no toxic effects of benzene on the anaerobic digestion of sewage sludges were observed until levels of 50-200 mg/L had been reached.

8.2.5 Bioaccumulation

Benzene is not expected to bioconcentrate to any significant degree in aquatic or terrestrial organisms given the reported values for log $P_{o/w}$ of 1.56-2.15 (GDCh, 1988; ICPS, 1993). IPCS (1993) also reports a bioconcentration factor (BCF) for freshwater algae of 30, for water fleas of 153-225 depending on the concentration of benzene in their food, and for goldfish of 4.3.

GDCh (1988) reports measured BCF values in *Clupea harengus* (herring) of 2-6 in most organs, and 31 in the gall bladder. One study outlined in this document claims no significant biological accumulation in algae or fish. For fish, the BCF was in the range of 1-10 after 3 days.

These conclusions are largely supported by data available from USEPA (2000) and IUCLID. Results are available for several species of fish including *Anguilla japonica* (Japanese eel), *Leuciscus idus melanotus* (golden orfe), *Morone saxatilis* (striped bass), *Salmo gairdneri* (rainbow trout) and *Engraulis mordax* (Northern anchovy). BCF values were all under 100, with the exception of the Northern anchovy. This species provided BCF values of 113-505, with an outlying result of 8450. There is not enough detail to determine whether these factors are for specific organs or the whole organism, which would impact on the analysis.

Nonetheless, based on the scale provided in Mensink et al. (1995), benzene can be classed as slightly to moderately concentrating in fish. No data are available on depuration rates.

Benzene appears to be more concentrating in invertebrates with results generally indicative of a moderately concentrating chemical. Several species of invertebrates have test results reported by USEPA (2000). An 8-day static and 9-day flow through test on *Brachionus plicatilis* (rotifer) showed BCF values of 100-1000 under static conditions and 10,000 under flow through conditions. The maximum concentration tested was 900 µg/L, well within the limit of solubility. Three results are available for *Daphnia pulex* with BCF values ranging from 153-225.

Several results in IUCLID were also reported by USEPA and have not been duplicated here. IUCLID provides information on depuration from *Daphnia pulex*. Daphnids were exposed to water dosed with 10 µg/L benzene, water containing algae preloaded by incubation with 50 µg/L benzene, or both dosed water and preloaded algae. The reported BCF values were 225 for exposure to just dosed water, 203 for feeding on preloaded algae and 153 after incubation in dosed water with preloaded algae. Where exposure was through dosed water only, clearance was 88% after 72 h. Where daphnids were exposed to dosed water and preloaded algae, 83% clearance was reported when moved to fresh water with unloaded algae, although the time involved in this depuration was not stated.

Limited data are available for algae, but suggest bioaccumulation will be slight, with the ECOTOX database (USEPA, 2000) reporting BCF values of 30 for the green algae *Chlorella fusca* and *Chlorella fusca vacuolata*.

8.3 Effects on organisms in the environment

Of the three assessments listed at the beginning of this section, only GDCh (1988) has any detailed discussion of the effects of benzene on organisms in the environment. As this publication is relatively old, the USEPA's ECOTOX database

was interrogated for more recent results (USEPA, 2000). In addition, IUCLID was consulted where limited data were reported in the other two sources, but as this is largely unvalidated, is used for guidance only. Not all available information is reported here due to its volume. However, the range for each trophic level will be given with an indication of where the majority of results fall.

8.3.1 Aquatic organisms

Fish

The majority of reported results come from tests performed under static conditions. GDCh (1988) provides 96-h results for 7 freshwater species including *Leuciscus idus melanotus* (golden orfe), *Lepomis macrochirus* (sun perch), *Pimephales promelas* (fathead minnow), *Lebistes reticulatus* (guppy), *Carassius auratus* (goldfish), *Gambusia affinis* (mosquito fish) and *Ictalurus punctatus* (channel catfish), with LC_{50} values ranging from 15-430 mg/L. Most of these fall in the 10-100 mg/L range, indicating slight toxicity to fish. This is largely supported by more recent data from USEPA (2000) where a 48-h LC_{50} to *Mugil curema* (white mullet) of 22 mg/L, 96-h LC_{50} to fathead minnow of 12.6-24.6 mg/L and 96-h LC_{50} to *Poecilia reticulata* (guppy) of 28.6 are reported. These results are all indicative of slight toxicity.

Flow through tests provide more sensitive results. All flow through results are for rainbow trout. Two tests reported in GDCh (1988) give 96-h LC_{50} values of 5.3 and 9.2 mg/L, while one more recent result gives a 96-h LC_{50} of 5.9 mg/L (USEPA, 2000). These results are indicative of moderate toxicity.

GDCh (1988) reports a 96-h LC_{50} of 5.8 mg/L in the saltwater species *Morone saxatilis* (striped bass), which is indicative of moderate toxicity. The test conditions are not known.

As such, benzene can be considered moderately to slightly toxic to fish under acute exposure.

Chronic and sub-chronic data for fish appear limited with only one study reported in GDCh (1988). Following 14 days exposure of *Lebistes reticulatus* (guppy) under static conditions, a LC_{50} of 63 mg/L was determined.

The Government of Canada (1993) report highlights an investigation into the chronic toxicity of benzene to the early life stages of rainbow trout, leopard frog and the Northeastern salamander. Eggs of each species were exposed continuously to benzene from within 30 minutes of fertilisation (embryos) through to 4 days post-hatch (larvae). This resulted in continuous exposures of 27 days for rainbow trout, 9 days for leopard frog and 9.5 days for Northeastern salamander. The corresponding LC_{50} values were 8.3, 3.7 and 5.2 mg/L respectively.

IUCLID provides results of tests in *Pimephales promelas* (fathead minnow), *Morone saxatilis* (striped bass) and *Clupea harengus* (pacific herring) for 7-day, 28-day and 17-day exposure periods respectively. The striped bass was exposed under flow through conditions. A no observed effect concentration (NOEC) of 10.2, 3.1 and 0.49-0.88 mg/L was reported for fathead minnow, striped bass and pacific herring respectively, although those for pacific herring were the highest concentrations tested on these fish so no real conclusions can be drawn from the results.

Overall, these results indicate that benzene is of very low toxicity to fish from chronic exposure.

GDCh (1988) lists some toxic effects of benzene on developmental stages and behaviour of fish. Pacific herring demonstrated a decrease of survival time of eggs after 48-h exposure of sexually mature females at 0.7 mg/L. However, this study was conducted in a polluted region so other chemicals may have been responsible. Other tests on pacific herring showed unspecified developmental abnormalities at 31-40 mg/L. Also, 24-h exposure of embryos to sublethal concentrations (up to 1.85 mg/L) under static conditions showed an effect on metabolism. Significantly less growth of the embryos, altered oxygen consumption and greater food intake in larvae were reported.

Sublethal effects were reported in the coho salmon at 1.8 mg/L and an increase in the respiratory rate of chinook salmon was found at 4.4 mg/L. This effect was also observed at the same concentration in striped bass.

Invertebrates

Invertebrates appear to be the largest group tested. GDCh (1988) provides results for four freshwater species, of which *Daphnia magna, Daphnia pulex* and *Daphnia cucullata* all had 48-h EC_{50} values >100 mg/L. One freshwater invertebrate, *Aedes aegypti* (mosquito larva) had a 24-h LC_{50} of 59 mg/L. Of the saltwater species reported in GDCh (1988), benzene could be considered moderately toxic to four species: *Artemia salina* (salt water shrimp), *Crango franciscorum* (bay shrimp), *Nitroca spinepes* and *Palaemonetes pugio* (grass shrimp), with 24- to 96-h LC_{50} values ranging from 20-82 mg/L. Two salt water species, *Cancer magister* (Dungeness crab) and *Crassostrea gigas* (oyster), had 96-h LC_{50} values >100 mg/L.

More recently published data from the ECOTOX database (USEPA, 2000) largely confirm the moderate to slight toxicity of benzene to aquatic invertebrates outlined above. Moderate toxicity is reported for *Ceriodaphnia dubia* (water flea; 24-h EC_{50} = 18.4 mg/L), *Gammarus fossarum* (scud; 96-h LC_{50} = 53 mg/L) and *Corixa punctata* (water boatman; 48-h LC_{50} = 48 mg/L), with LC_{50} values >100 mg/L reported for a further three species: *Daphnia magna, Lymnaea stagnalis* (great pond snail) and *Viviparus bengalensis* (snail).

However, one crab species (*Scylla serrata*) was relatively sensitive to benzene, with three 96-h LC_{50} results (mortality as the end point) of 3.7, 6.1 and 7.7 mg/L. While the majority of results indicate benzene is only moderately to slightly toxic to aquatic invertebrates, this species shows benzene may be considered toxic to some aquatic invertebrates.

GDCh (1988) only describes one study where chronic effects were investigated in *Daphnia magna*. In a lifetime and partial lifetime test, no toxic effect of benzene was found at a concentration of 98 mg/L.

Only one chronic test is available in IUCLID where sufficient detail is presented. This test on a crab species (*Cancer magister*) indicates slight toxicity to aquatic invertebrates. Larval stages of the crab were continuously exposed after hatching in a flowing water laboratory culture system at benzene levels of 0.17-0.18, 1.1-1.2 and 6.5-7.0 mg/L. Benzene had little effect on the duration of the larval stages and no effect on the size of surviving larvae. At the lowest concentration, there was no effect on survival. At the other two concentrations, benzene led to an accelerated mortality rate compared to untreated controls. After 10 days of exposure at the

highest concentration, most larvae died. At the middle concentration, most larvae died before day 20 of exposure. Therefore, the 20-day NOEC was 0.17 mg/L.

Algae

Data covered in GDCh (1988) suggest benzene is only slightly to very slightly toxic to algae. A 24-h EC_{50} on the green algae *(Chlorella vulgaris*) based on cell division was >>100 mg/L.

Three 72-h EC_{50} values are reported for sea algae with cell division as the end point. The green algae (*Dunaliella tertiolecta*), siliceous algae (*Skeletonema costratum*) and yellow-green algae *(Cricopshaera carterae*) all had EC_{50} results >100 mg/L. In a 3-day test in the dinoflagellata *Amphidinium carterae*, the EC_{50} with cell division as the end point was reported to be 50 mg/L, indicating slight toxicity (GDCh, 1988).

More recent data from the ECOTOX database (USEPA, 2000) appear more indicative of slight toxicity than the earlier studies reported in GDCh (1988). One 72-h EC_{50} in *Selanastrum capricornutum* of 29 mg/L and a 24-h EC_{50} for the diatom *Thalassiosira pseudonana* of 40 mg/L are reported.

In summary, benzene can be classed as slightly to very slightly toxic to algae under acute exposure.

In 8-day tests, >1400 mg/L benzene had no detectable effect on biomass in the freshwater species *Scenedesmus quadricauda* and the blue alga *Microcystis aeruginosa* (GDCh, 1988). With growth as the end point, the more sensitive species *Selenastrum capricornutum* provided an 8-day EC_{50} of 41 mg/L, although a 14-day EC_{50} of 292 mg/L is also reported for this species (USEPA, 2000).

Predicted No-Effect Concentration (PNEC) in the aquatic environment

As there are results available for both acute and chronic exposure in three trophic levels, the lowest NOEC for chronic exposure, in this case to the aquatic invertebrate crab species *Cancer magister*, will be used with an assessment factor of 10. While this result (NOEC = 0.17 mg/L) is based on unvalidated results from IUCLID, it is considered that there are sufficient data available from published and peer-reviewed sources for this test to be accepted for use in a worst-case PNEC and that there is sufficient detail in the IUCLID report to support the results.

Therefore, the PNEC for the aquatic environment is 0.17/10 = 0.017 mg/L, or 17 µg/L.

8.3.2 Terrestrial organisms

A study in *Eisenia fetida* (earthworm) is reported in the ECOTOX database (USEPA, 2000), in which an LC_{50} of 98 µg/cm^2 was determined in adult worms weighing 300-500 mg placed for 48 h on filter paper impregnated with a solution of benzene in water, acetone and trichloromethane.

According to GDCh (1988), use of benzene as a solvent for plant protection agents in bioassay tests showed that it is slightly toxic to various insect species. The LD_{50} for the house fly (*Musca domestica*) was 0.8 mg per animal. Exposure to benzene in the vapour phase exhibited toxic action in the grain weevil (*Calandra granaria*), although the concentration is not reported. Benzene acted as a repellent to the adults of certain species of flies (*Diptera*).

In plants, air concentrations >50 mg/m^3 (>15.5 ppm) have a lethal effect. However, all plant species investigated recovered from sublethal effects. In water, higher concentrations of 0.9-1.3 g/L have a growth-inhibiting effect (GDCh, 1988).

It is difficult to translate the earthworm measurement to an application rate likely to lead to adverse impacts in soil and a PNEC cannot be determined from these data.

8.4 Summary

Benzene is expected to partition predominantly to the atmosphere, with the primary route of degradation coming from indirect photolysis through reaction with hydroxyl radicals. Direct photolysis or reactions with oxygen or ozone are not expected to be major removal processes from the atmosphere. Based on the accepted global concentration of hydroxyl radicals, the degradation half-life of benzene from the atmosphere is calculated at 8 days.

Benzene is largely abiotically stable in water, with the major removal process expected to be volatilisation. The high water solubility and relatively low log $P_{o/w}$ indicate that benzene will not adsorb significantly to organic matter and sediments.

When released to the terrestrial compartment, benzene may be relatively mobile and may leach to groundwater if released underground, for example, from leaking storage tanks. The chemical is unlikely to adsorb readily to soils and may readily volatilise from soil surfaces.

Benzene may be considered biodegradable under aerobic conditions, although under anaerobic conditions, biodegradation may be expected to be very slow. Based on the chemical's low log Pow and experimental results, bioaccumulation is not expected to any significant degree, and at worst, benzene can be described as moderately concentrating.

Aquatic organisms exhibit only a low level of sensitivity to benzene, with the chemical being slightly toxic to fish following acute exposure under static conditions and moderately toxic under flow through conditions. Chronic exposure of fish to benzene gave results indicative of slight toxicity. Invertebrates appear to be the largest group of aquatic organisms tested. For the majority of species tested, benzene was only slightly to very slightly toxic. However, one crab species was relatively sensitive, with results in the range of a moderately toxic chemical. Chronic results show benzene to be slightly toxic to aquatic invertebrates. Benzene may also be classified as slightly to very slightly toxic to algae. The PNEC for the aquatic environment is 17 μg/L.

Limited data on the toxicity of benzene to terrestrial organisms show the chemical to be slightly toxic to various insect species and the earthworm. In plants, high concentrations in air have a lethal effect, although all plants investigated recovered from sublethal effects.

9. Kinetics and Metabolism

The toxicokinetics and metabolism of benzene have been extensively investigated in several animal species and, to a lesser extent, in humans. Studies relevant to the toxicokinetics of benzene have been reviewed and summarised in this section. The metabolites and their modes of action are further discussed in Section 12. A number of reviews of benzene toxicokinetics and metabolism are available, including IPCS (1993) and ATSDR (1997).

9.1 Absorption

9.1.1 Animal studies

Inhalation

Schrenk et al. (1941) found the absorption of benzene vapour by dogs after inhalation exposure to be rapid. Inhalation of the vapour (800 ppm) over 4-7 h resulted in the concentration of benzene in arterial blood approaching equilibrium conditions by 30 minutes. Although considerable inter-animal variation was noted, a linear relationship was demonstrated between the concentration of benzene in air over the range from 200-1300 ppm and the equilibrium concentration in blood. In another study, the absorbed dose after inhalation (nose-only) of [^{14}C]-benzene (approximately 10-1000 ppm) for 6 h by rats (F344) and mice (B6C3F$_1$) was found to be non-linear. The percentage of benzene absorbed decreased from 33% to 15% in rats and from 50% to 10% in mice as the exposure concentration increased from 10 to 1000 ppm. Due to apparent physiological differences in respiration between the two species, mice inhaled approximately twice the amount of benzene compared to rats (Sabourin et al, 1987). Similarly, Eutermoser et al. (1986) found that the absorption rate of benzene vapour (300 ppm) by male rats (Sprague-Dawley) decreased with increasing duration of exposure. When determined after 1, 3 and 6 h of continuous exposure and compared to baseline values, benzene absorption decreased to 33, 22 and 9% respectively. Male mice (Swiss) when exposed to benzene (310 ppm) for 1, 3 and 6 h of continuous exposure and compared to baseline values gave values of 65, 76 and 81% respectively. Thus after the first hour, the rate of benzene uptake by rats decreased significantly compared to mice.

Dermal

Dermal absorption of liquid benzene was investigated by Maibach & Anjo (1981) using intact and abraded skin of rhesus monkeys. Under conditions where evaporative losses were allowed, the application of a single dose of benzene to intact skin resulted in absorption of 0.17% of the dose while the application of multiple doses (11 exposures with an interval of 15 min) resulted in 0.85% of the dose being absorbed. In contrast, abraded skin resulted in 0.91% of the applied dose being absorbed. Similar results were obtained by Franz (1984) who found that after a single dermal application of benzene, 0.14% and 0.09% was absorbed by rhesus monkeys and miniature pigs respectively. It was concluded from the in vitro studies that the major factor influencing percutaneous absorption of benzene was its contact time with the skin. Susten et al. (1985) reported similar findings with

hairless mice (HRS/J) using a skin chamber where less than 1% of the applied dose was absorbed.

Adsorption of benzene onto soil matrices (sandy or clay soil) was found to modify the dermal absorption of [^{14}C]-benzene when applied topically to male rats (Sprague-Dawley) over a 72-h period using a glass skin chamber. While the peak plasma level of radioactivity after exposure to benzene adsorbed onto sandy soil was comparable to that obtained for pure benzene, a statistically significant lower plasma level was obtained for benzene adsorbed onto clay, however, neither soil type altered the time to reach peak plasma levels which was 12 h (Skowronski et al, 1988).

Dermal absorption of benzene vapour has also been addressed. Dermal absorption (whole-body) of benzene vapour over 2, 4 or 6 h was investigated by the use of male nude mice attached to respirators. The dermal absorption rates for exposures of 200, 1000 and 3000 ppm were 4.11, 24.2 and 75.5 nmol/cm^2/h (0.3, 1.9 and 5.9 μg/cm^2/h) respectively, demonstrating a linear relationship between the two parameters. Dermal absorption was also found to be linear with respect to exposure time. The dermal absorption coefficient for the mouse was determined to be 0.619 cm/h (Tsuruta, 1989). McDougal et al. (1990) exposed male rats (F344; whole-body) to benzene vapour (40,000 ppm) for periods up to 4 h. The rats were shaved of all fur prior to exposure and provided with latex face masks attached to a fresh air supply during exposure. Benzene blood levels at 0.5 h were 8 μg/mL and rose to 11 μg/mL at 4 h indicating that benzene is rapidly absorbed by the dermal route. The dermal absorption rate was determined to be 0.0191 mg/cm^2/h and the dermal absorption coefficient 0.152 cm/h.

Oral

Following the administration by gavage of [^{14}C]-benzene (340-500 mg/kg) to rabbits, approximately 80% of the ingested radiolabel was recovered in exhaled breath and urine indicating substantial gastrointestinal absorption at these dose levels (Parke & Wiliams, 1953). Similar results were obtained by the administration of lower doses of [^{14}C]-benzene (0.5-150 mg/kg) to rats (F344 and Sprague-Dawley) and mice (B6C3F$_1$) where it was determined that >97% of the dose was absorbed (Sabourin et al, 1987).

9.1.2 Human studies

Inhalation

In a study of 23 subjects exposed to benzene vapour (47-110 ppm) over 2-3 h, maximal absorption (70-80% of dose) occurred within 5 min of initial exposure. Subsequent absorption declined rapidly and reached a plateau at 15 min. Absorption remained constant for the remainder of the exposure duration at approximately 50% (range: 20-60%) of the exposure dose (Srbova, et al, 1950). Comparable results have been obtained in a number of other studies. Nomiyama & Nomiyama (1974a) exposed 6 volunteers (3 males and 3 females) to benzene vapour (52 to 62 ppm) for 4 h and showed that after an initially high absorption rate (50-60%), the rate decreased to reach a plateau of approximately 30-40% after 3 h of exposure. The mean retention of benzene, after allowances for respiratory excretion, was determined to be 30.2% for a 3-h exposure. Similarly, Snyder et al. (1981) demonstrated that during continuous exposure to benzene vapour approximately 50% of the dose is absorbed by the lungs. Pekari et al. (1992)

exposed 3 non-smoking volunteers to benzene vapour (1.6-9.4 ppm) for 4 h. The absorbed dose was estimated to be 52% and 48% for the low and high dose exposure respectively based on the average difference in concentration between the inhaled and exhaled air.

Further evidence for the absorption of benzene by inhalation is provided by studies of cigarette smokers. Analysis of cigarette smoke has shown the presence of substantial amounts of benzene, with the yield within the range of 0.4-104 μg/cigarette (see Section 16.1). Analysis of breath samples from 198 smokers and 322 non-smokers showed significantly higher ($p < 0.001$) benzene concentrations in the breath of smokers (16 $\mu g/m^3$) compared to non-smokers (2.5 $\mu g/m^3$). Benzene breath levels were significantly correlated ($p < 0.01$) with the number of cigarettes smoked per day (Wallace & Pelizzari, 1986; Wallace et al, 1987). Pekari et al. (1992) found 6 non-smokers to have venous blood benzene levels of <1-2 nM compared to 3 smokers (1 pack/day) with 4-13 nM in the morning and 5-8 nM in the afternoon. Cessation of smoking for a period (duration not stated) resulted in a reduction of blood benzene levels to <2 nM. In a similar study, it was found that the mean venous blood benzene levels of 14 smokers were significantly higher (7.0 nM; range 3.7-12.1 nM) compared to 13 non-smokers (2.8 nM; range 1.4-5.8 nM); however, the number of cigarettes consumed were not stated (Hajimiragha et al, 1989). With the exception of cigarette smoking, there were no other known activities undertaken by the subjects that may have resulted in benzene exposure prior to or during either study.

Dermal

A number of studies indicate that benzene is absorbed via the dermal route in humans. A study of 2 men exposed to benzene (approximately 0.06 g/cm^2 applied to the forearm, 35-43 cm^2, under occluded conditions for 1.25-2 h) determined the dermal absorption rate to be 0.4 $mg/cm^2/h$ based on urinary excretion of phenol (Hanke et al, 1961). Approximately 0.05% of the applied dose of [^{14}C]-benzene (0.0026 mg/cm^2) was absorbed when applied to the forearm skin of 4 volunteers. Absorption was determined by urinary excretion of radiolabel which indicated that absorption was rapid. Evaporative losses during the absorption period were not accounted for (Franz, 1984).

The absorption of benzene due to dermal exposure to petrol has been studied in car mechanics having direct skin contact with petrol for 30-150 min during work on car fuel systems, with the concentration of benzene in the breathing zone ranging from 0.2 ppm (detection limit) to 3.7 ppm averaged over the duration of the task. Blood benzene levels determined 2-9 h after exposure ranged from 3-16 nM. Based on expected benzene blood levels derived from the airborne concentrations, it was estimated that dermal absorption accounted for up to 80% of the total absorbed dose of benzene. The mechanics did not wear protective gloves (Laitinen et al, 1994). However, the estimation assumed that the mechanics were exposed to non-detectable benzene air concentrations during the remainder of the working day and would therefore have overestimated the extent of skin absorption if this were not the case.

In an in vitro study, benzene (pure benzene, air saturated with benzene vapour or a saturated aqueous solution of benzene) was shown to diffuse across hydrated stratum corneum prepared from human skin. Absorption, initially preceded by a lag phase (range: <1-1.5 h), was linear over the duration of the experiment (4 h). The rates of benzene absorption due to pure benzene and air saturated with benzene

vapour were 2.1 and 1.0 μL/cm^2/h (1.8 and 0.88 mg/cm^2/h) respectively. It was further demonstrated that the barrier characteristics of human skin alter in response to the presence of other solvents (Blank & McAuliffe, 1985). Lodén (1986) determined the amount of benzene absorbed by excised human skin to be 0.17 mg/cm^2 after 0.5 h and 0.93 mg/cm^2 at steady state (13.5 h). The total absorption of benzene over 13.5 h in skin and receptor fluid was 1.92 mg/cm^2 and the resorption rate (that is, the amount of substance migrating to the receptor fluid below the skin) was determined to be 99 μg/cm^2/h.

Oral

No studies were identified addressing the absorption of benzene by the oral route in humans. Cases of accidental or intentional ingestion indicate that benzene is readily absorbed by the gastrointestinal tract, with a dose of 125 mg/kg proving fatal (see Section 11.1).

9.2 Distribution

9.2.1 Animal studies

Inhalation

Schrenk et al. (1941) observed that in dogs continuously exposed to the vapour, benzene preferentially partitions to the organs and tissues with a higher fat content, although considerable inter-animal variation was noted. The establishment of an equilibrium between most tissues (except fat) and blood levels appeared to be rapid (≤15.5 h). When exposed to various concentrations of benzene vapour (850-1320 ppm) for periods ranging from 0.65-5 days, benzene levels were highest in bone marrow (57.6-64.1 mg/100 g tissue) followed by peritoneal fat (40.3-61.4 mg/100 g tissue) and subcutaneous fat (39.9-48.6 mg/100 g tissue). All other tissues or organs had substantially (generally 20-fold) lower levels of benzene. A comparable distribution pattern was observed when dogs were exposed to 800 ppm benzene vapour for 8 h/day for 38-272 days. Rickert et al. (1979) studied the distribution and residence times of benzene and three major metabolites, phenol, hydroquinone and catechol, in male rats (F344) exposed to benzene vapour (500 ppm) for up to 8 h. The steady-state benzene concentrations at 6 h were determined for the following tissues: fat (164.4 μg/g), bone marrow (37.0 μg/g), kidney (25.3 μg/g), lung (15.1 μg/g), liver (9.9 μg/g), brain (6.5 μg/g) and spleen (4.9 μg/g), while blood contained 11.5 μg/mL. The half-times for tissues to reach steady-state levels for benzene were essentially the same for all tissues (0.9-2.0 h) as were the elimination times (0.4-0.8 h), with the exception of fat which was 1.6 h. The concentrations of phenol in blood and bone marrow were maximal within 2 h after cessation of exposure and declined rapidly thereafter. Hydroquinone and catechol concentrations were sustained for 9 h after exposure with higher concentrations found in bone marrow.

Ghantous & Danielsson (1986) demonstrated the transplacental distribution of benzene and its metabolites in mice following inhalation exposure to [^{14}C]-benzene. Benzene was detected in the placenta and the foetus immediately following and for up to 1 h after exposure, as were benzene metabolites. The metabolites did not reach the same tissue concentrations as in maternal tissues and no metabolites were retained in the placenta or the foetus.

Dermal

Susten et al. (1985) examined the distribution of radiolabel after dermal application of undiluted [^{14}C]-benzene and a 0.5% (v/v) solution in rubber solvent using a skin chamber attached to male hairless mice (HRS/J) for 4 h. Approximately 5% and 8% of the benzene in the pure sample and rubber solvent respectively remained associated with the site of application while approximately 23% and 22% respectively was associated with the carcass. Skowronski et al. (1988) examined the tissue distribution of radiolabel in male rats (Sprague-Dawley) 48 h following the topical application of benzene (300 μL) using a glass skin chamber. The highest levels of radiolabel (expressed as % of initial dose per g of tissue) were found in the kidneys (0.026%), liver (0.013%) and treated skin (that is, below the site of application; 0.011%). Untreated skin gave a value of 0.002%. Subcutaneous fat from below the area of application gave 0.008% while subcutaneous fat from a different site gave 0.005% as did bone marrow. All other tissues and organs examined (including the brain) accounted for less than 0.04% of the initial dose.

Oral

Analysis of rabbit tissues and organs (1 animal) 2 days after dosing by gavage with [^{14}C]-benzene (500 mg/kg) showed the highest level of radioactivity to occur in muscle (1.6%), fat (1.5%), liver (0.07%), stomach (0.05%), testes (0.02%) and kidneys (0.015%). No radioactivity was detected in the brain, spinal cord or blood (Parke & Wiliams, 1953). Low et al. (1989) found that the distribution of radiolabel in female rats (Sprague-Dawley) varied with the dose of [^{14}C]-benzene administered. At 1 h after a single dose of 0.15 or 1.5 mg/kg by gavage, radiolabel was highest in the liver and kidneys (0.198-2.043 μg/g tissue), intermediate in blood (0.086-0.769 μg/mL), and lowest in the Zymbal gland, nasal cavity tissue, oral cavity tissue, mammary gland and bone marrow (0.034-0.547 μg/g tissue). In contrast, at 15 mg/kg, the amount of radiolabel found in the mammary gland and bone marrow had substantially increased in comparison to other tissues. At the highest dose, bone marrow and adipose tissue had the highest concentrations of benzene.

9.2.2 Human studies

Studies of the distribution of benzene in humans are generally limited to a number of fatal cases of accidental or deliberate benzene exposure. Autopsy data from such cases indicate that benzene preferentially partitions into lipid-rich tissues.

Analysis of tissue and fluid samples from a youth who died after sniffing benzene (reagent grade) showed the following order for tissue benzene content: brain, 39 mg/kg; abdominal fat, 22.3 mg/kg; blood, 0.02 mg/mL; kidneys, 19 mg/kg; liver, 16 mg/kg; bile, 0.011 mg/mL; stomach, 10 mg/kg and urine, 0.0006 mg/mL (Winek & Collom, 1971). Similar findings were demonstrated at autopsy of 3 cases of acute industrial benzene poisoning indicating that benzene preferentially distributes to lipid-rich tissues such as body fat (range: 68->120 mg/kg) and brain tissue (range: 58-63 mg/kg) with lesser amounts in blood (range: 30-129 mg/mL), liver (range: 15-38 mg/kg), lungs (positive findings) and bile (range: trace to 45 mg/mL) (Avis & Hutton, 1993). In a similar industrial accident involving acute fatal benzene poisoning analysis of tissue and fluid samples revealed the following benzene concentrations: blood, 0.0317 mg/mL; brain, 178.7 mg/kg; lungs, 22.2 mg/kg; heart, 182.6 mg/kg; liver, 378.6 mg/kg; kidneys, 75.2 mg/kg and urine, 0.0023 mg/ml (Barbera et al, 1998). In the above case reports the individuals are

believed to have inhaled benzene vapour for some time before death occurred. In one case in which an individual died suddenly during an industrial accident involving benzene, precluding extensive inhalation of the vapour, autopsy findings revealed the following benzene concentrations: blood, 0.0038 mg/mL; brain, 13.8 mg/kg; liver, 2.6 mg/kg (Tauber, 1970).

Limited data indicate that developing foetuses and infants may be exposed to benzene as a result of maternal exposure. Benzene can cross the placenta and concentrations in umbilical cord blood have been shown to be equal to or greater than in maternal blood (Dowty et al, 1976). Due to the richly perfused nature of breast tissue and the high fat content of human milk (approximately 4%), benzene is expected to partition from blood into human milk from which it can transfer to nursing infants (Fisher et al, 1997). Qualitative analysis of 12 human milk samples revealed the presence of benzene in 8 of them (Pellizzari et al, 1982).

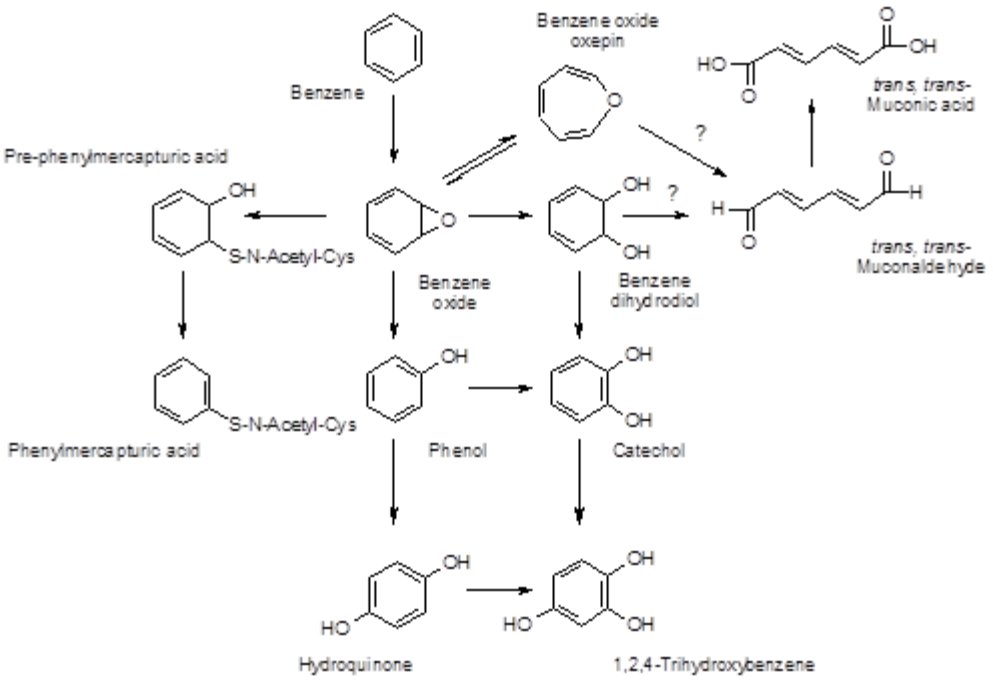
9.3 Metabolism

The metabolism of benzene has been extensively investigated in several species of animals including humans. Benzene toxicity has been attributed to the formation of reactive metabolites that appear to exert their toxic effect in combination, with no one metabolite accounting for all of the observed effects. The metabolism of benzene has been reviewed by Ross (1996) and Snyder & Hedli (1996).

9.3.1 General metabolic pathways

Urinalysis of several species exposed to benzene has demonstrated qualitative similarities in the spectrum of metabolites produced, indicating that the metabolism of benzene follows similar pathways between species. Urinary benzene metabolites identified from rabbits, rats, mice, monkeys and humans include conjugates of phenol, hydroquinone, catechol and 1,2,4-trihydroxybenzene while phenylmercapturic acid and *trans*,*trans*-muconic acid have also been identified. The conjugates are principally glucuronides and sulfates (Parke & Williams, 1953; Rothman et al, 1998; Sabourin et al, 1988, 1992). Analysis of rat and human blood samples has further revealed the presence of benzene oxide and its S-phenylcysteine adducts following benzene exposure (Bechtold et al, 1992a, 1992b; Lovern et al, 1997). The general metabolic pathways for benzene metabolism are provided in Figure 9.1. The initial step in the formation of toxic metabolites is the conversion of benzene to the benzene oxide/oxepin which can be further metabolised to phenolic compounds or cleaved to give *trans*,*trans*-muconaldehyde. Detoxification pathways primarily involve conversion of benzene oxide to pre-phenylmercapturic acid and phenylmercapturic acid while the phenolic compounds form glucuronide and sulfate conjugates.

Figure 9.1. The metabolism of benzene, with question marks indicating suspected pathways for which definitive evidence is lacking (after Sabourin et al. (1988) and Schlosser et al. (1993))



The primary site for benzene metabolism is the liver. It has been observed that animals that have undergone partial hepatectomy metabolise less benzene and exhibit reduced benzene-mediated toxicity compared to animals with intact livers (Sammet et al, 1979). The initial biotransformation of benzene involves oxidation by the action of a cytochrome-P450 (CYP) to produce the benzene oxide/oxepin intermediate (Jerina et al, 1968). Studies of liver microsomal preparations from rats and rabbits, using inhibitor and immunochemical techniques, have identified the cytochrome as CYP2E1 (Johansson & Ingelman-Sundberg, 1988; Koop et al, 1989; Nakajima et al, 1989). Similar studies with human liver microsomal preparations have shown CYP2E1 to be the major cytochrome involved in the metabolism of benzene by humans (Guengerich et al, 1991). Valentine et al. (1996) confirmed the role of CYP2E1 in the in vivo metabolism of benzene using transgenic CYP2E1 knockout mice (*cyp2e1*$^{-/-}$). Analysis of urine samples after exposure to [^{14}C]-benzene by nose-only inhalation showed reduced levels of urinary metabolites compared to wild-type mice (*cyp2e1*$^{+/+}$). The study further demonstrated that, while oxidative metabolism of benzene occurs primarily through CYP2E1, other cytochromes are involved.

Studies of rat liver microsomes have shown there to be high affinity (K_m = 20 μM) and low affinity (K_m = 0.3 mM) binding sites for benzene (Johansson & Ingelman-Sundberg, 1988). Nakajima et al. (1989), using monoclonal antibodies, identified two distinct rat enzymes, a high affinity and a low affinity binding type involved in benzene oxidation. Subsequent studies of rat microsomal P450 isozymes, CYP2E1, CYP2C11/6, CYP1A1/2 and CYP2B1/2, by Nakajima et al. (1992) using monoclonal antibodies showed that all four isozymes are involved in the initial oxidation of benzene. However, while CYP2E1 has been characterised as a high affinity enzyme with respect to benzene metabolism, CYP2B1/2 exhibits low affinity but high capacity (Gut et al, 1996; Nakajima et al, 1989) and CYP2C11/6

and CYP1A1/2 exhibit low affinity and low efficiency towards benzene (Nakajima et al., 1992).

Several studies have demonstrated the inducible nature of CYP2E1 and subsequent enhancement of benzene metabolism by phenobarbital, acetone or ethanol treatment of rats (Johansson & Ingelman-Sundberg, 1988; Koop et al., 1989; Nakajima et al., 1989). In addition, it has been demonstrated that benzene is able to stimulate its own metabolism by inducing CYP2E1 activity (Arinç et al., 1991; Gut et al., 1993). However, it has also been demonstrated in mice that repeated oral exposure to benzene can diminish CYP2E1 activity (Daiker et al., 1996). One postulated mechanism for reduced cytochrome activity, demonstrated in vitro, requires inactivation of the cytochrome by quinones formed by oxidation of hydroquinone, catechol and 1,2,4-trihydroxybenzene (Soucek et al., 1994).

The initial oxidation product of benzene, benzene oxide, has been estimated to have a half-life, in vitro, of approximately 8 min in blood (Lindstrom et al., 1997). Thus the oxide has sufficient stability to allow it to participate in a variety of reactions. Minor reactions of benzene oxide include alkylation with DNA and RNA (Mueller et al, 1987) and proteins (Bechtold et al, 1992a, 1992b) while epoxide hydrolase converts it to benzene dihydrodiol (1,2-dihydroxycyclohexadiene).

The presence of benzene oxide in blood has been detected by the presence of S-phenylcysteine adducts of haemoglobin and albumin (Bechtold et al, 1992a; 1992b). Haemoglobin adducts were detected in the blood of rats (F344) and mice ($B6C3F_1$) after inhalation exposure (600 ppm, 6 h/day, 5 days/week for 2 weeks) or gavage (rats only; 0, 100, 1000 or 10,000 μmol/kg). Albumin adducts were also detected in the plasma of rats exposed to benzene vapour (Bechtold & Henderson, 1993). While the haemoglobin adduct has been found to be relatively stable in the rat (F344) with decay rates consistent with the life-span of erythrocytes (approximately 60 days), albumin adducts were found to have a half-life of 0.4 days compared to unmodified albumin (half-life approximately 3 days) (Troester et al, 2000). Lindstrom et al. (1998) estimated the half-life of benzene oxide in blood, under *in vitro* conditions, to be approximately 6.6 min in mice ($B6C3F_1$), 7.9 min in rats (F344) and 7.2 min in humans. When benzene oxide (0-184 μM) was incubated with mouse, rat or human blood for 3 h it was observed that haemoglobin adduct formation was proportional to the oxide concentration. The order of reactivity for the oxide with haemoglobin was rat >> mouse > human. Negligible haemoglobin adduct formation was observed with human blood. All three species formed albumin adducts with the order being rat ≈ human > mouse.

9.3.2 Formation of phenolic metabolites

Studies with microsomal preparations, which preclude conjugation (detoxification) pathways, indicate that the major pathway for the further metabolism of benzene oxide involves the spontaneous rearrangement to phenol (Jerina & Daly, 1974; Jerina et al, 1968). It has been demonstrated, using liver microsomes and reconstituted enzyme systems, that phenol can also arise by the direct oxidation of benzene by hydroxyl radicals derived from the reduction of molecular oxygen by cytochrome P450 activity (Johannson & Ingelman-Sundberg, 1983). However, Gorsky & Coon (1985) observed that when benzene is present at concentrations approaching the K_m of CYP2E1 for benzene, hydroxyl radicals do not contribute significantly to benzene oxidation. The further oxidation of phenol by cytochrome P450 results in hydroquinone (Koop et al, 1989; Valentine et al, 1996) and catechol while 1,2,4-trihydroxybenzene arises from the P450-mediated oxidation of either

hydroquinone or catechol (Schlosser et al., 1993). In addition, catechol can be produced from benzene dihydrodiol by the action of dihydrodiol dehydrogenase (Bolcsak & Nerland, 1983).

The hydroquinone species derived from benzene, that is, hydroquinone, catechol and 1,2,4-trihydroxybenzene, readily undergo autoxidation to their respective semiquinone and quinone forms and the presence of peroxidases facilitate the oxidation process (Schlosser et al., 1989; Smith et al., 1989). Quinones are chemically reactive and capable of forming adducts with macromolecules. Further discussion of the secondary metabolism of benzene-derived phenol and hydroquinone species, along with their biological effects, is presented in Section 12.

The detoxification of the phenolic benzene metabolites occurs primarily by conjugation to glutathione (GSH), glucuronide or sulfate (Parke & Williams, 1953). Conjugation of benzene oxide with GSH by glutathione-S-transferase (GST) results in the formation of pre-phenylmercapturic acid and, by dehydrogenation, phenylmercapturic acid, both of which have been identified as urinary metabolites. The major metabolites, phenol, hydroquinone, catechol and 1,2,4-trihydroxybenzene, all form glucuronide and sulfate conjugates (Parke & Williams, 1953; Sabourin et al., 1988).

9.3.3 Formation of *trans,trans*-muconaldehyde

Cleavage of the oxidised aromatic ring results in the formation of *trans,trans*-muconaldehyde which is subsequently converted to *trans,trans*-muconic acid prior to excretion. A number of in vivo studies of several animal species, including humans, have shown *trans,trans*-muconic acid to be an end-stage product of benzene metabolism (Parke & Williams, 1953; Rothman et al., 1998; Sabourin et al., 1988). While the opening of the benzene ring and subsequent formation of muconic acid have been shown to occur in isolated perfused rat livers, as has the conversion of *trans,trans*-muconaldehyde to *trans,trans*-muconic acid (Grotz et al., 1994), the precise mechanism of ring opening remains elusive. It has been proposed that benzene oxide, while in the oxepin state, undergoes secondary oxidation by cytochrome P450 to produce *trans,trans*-muconaldehyde (Davies & Whitham, 1977) and small quantities of *trans,trans*-muconaldehyde have been found to be produced by mouse liver microsomal preparations on incubation with benzene (Latriano et al, 1986). However, hydroxyl radicals have also been implicated in the formation of *trans,trans*-muconaldehyde. Incubation of benzene with Fenton's reagent, which produces reactive oxygen species, results in the formation of *cis,trans*-muconaldehyde which, through a series of rearrangements, yields the *trans,trans*-isomer (Zhang et al., 1995). An alternative proposed mechanism for aldehyde formation requires cleavage of benzene dihydrodiol (Latriano et al., 1986), however, the aldehyde was not produced when benzene dihydrodiol was incubated with Fenton's reagent (Zhang et al., 1995). The subsequent conversion of *trans,trans*-muconaldehyde to *trans,trans*-muconic acid involves several steps requiring the action of an aldehyde dehydrogenase (Kirley et al, 1989; Zhang et al, 1993). Conjugation of *trans,trans*-muconaldehyde with GSH via hepatic GST has been demonstrated as a detoxification pathway for this metabolite (Goon et al., 1993a, 1993b).

9.4 Elimination and excretion

9.4.1 Animal data

Inhalation

Benzene was detected in the urine of dogs exposed to benzene vapour (850-1320 ppm) at levels ranging from 29.3-48.3 mg/100 g (Schrenk et al, 1941). Sabourin et al. (1989) identified the urinary metabolites of benzene metabolism in rats and mice following inhalation exposure to benzene vapour (nose-only) for 6 h. The results are presented in Table 9.1.

Table 9.1: Major urinary metabolites after inhalation of benzene, expressed as a percentage of total urinary metabolites from 24-h samples (adapted from Sabourin et al. (1989))

Species	Dose (ppm)	Phenol conjugates	Hydroquinone conjugates	Catechol conjugates	Pre-phenyl-mercapturic acid	Muconic acid
Rat (F344)	5	57	5.7	ND*	9.5	19
	600	74	2.0	ND	17	4.0
Mouse ($B6C3F_1$)	5	37	33	ND	6.0	23
	600	67	11	ND	15	5.0

***** ND = not detected.

Dermal

Franz (1984) observed that peak excretion of radioactivity in the urine of rhesus monkeys after the application of 0.5 mL of [^{14}C]-benzene occurred during the first 2 h and decreased rapidly thereafter but remained detectable for up to 30 h. Skowronski et al. (1988) found that after the topical application of 300 µL of [^{14}C]-benzene to male rats (Sprague-Dawley) by means of a glass skin chamber, the major excretory route for radiolabel was in the urine, with substantially lesser amounts in faeces and expired air. Excretion in the urine was greatest during the 12- to 24-h interval after application, accounting for 58.8% of the initial dose with 68.4% recovered in 24 h and 86.2% after 48 h. In contrast, 0.2% of the initial dose was recovered over 48 h in the faeces. Expired air accounted for 12.0% in the first 24 h with the following 24 h accounting for only a further 0.8%.

Oral

Analysis of urinary benzene metabolites from several species following administration of [^{3}H]-benzene by gavage has shown similar profiles of metabolites. As indicated in Table 9.2, the principal urinary metabolites for the species shown are conjugates (glucuronides and sulfates) of phenol and, to a lesser extent, hydroquinone. The mouse is quantitatively different from the other species with a substantially higher production of hydroquinone conjugates and *trans,trans*-muconic acid. In addition to species differences, the table shows the effect of changes in dose levels on urinary metabolites for rats and mice. Increasing the dose of benzene leads to an increase in the excretion of phenol conjugates and a decrease in hydroquinone conjugates by the mouse but no substantial change in the rat. In contrast, *trans,trans*-muconic acid excretion is diminished in both the rat and the mouse at higher doses.

Table 9.2: Major urinary metabolites after oral administration of benzene, expressed as a percentage of total urinary metabolites from 24-h samples (adapted from Parke & Williams (1953), and Sabourin et al. (1989, 1992))

Species	Dose (mg/kg)	Phenol conjugates	Hydroquinone conjugates	Catechol conjugates	Pre-phenyl-mercapturic acid	Muconic acid
Rat (F344)	1	70	4.0	ND*	11	13
	10	71	2.8	ND	15	10
	200	75	2.0	ND	18	5.0
Mouse ($B6C3F_1$)	1	30	47	ND	2.7	20
	10	38	39	1.0	4.5	16
	200	63	16	ND	11	9.0
Rabbit	340	24	4.8	2.2	No data	1.3

***** ND = not detected.

Within 2 days of administering [^{14}C]-benzene (0.34-0.5 g/kg) to rabbits by gavage, approximately 45% of the dose was detected in expired air (43% as unchanged benzene and 1.5% as carbon dioxide) and approximately 35% appeared in the urine. Urinary radiolabel was predominantly in the form of conjugated phenols, with phenol comprising approximately 23% of the administered dose and with hydroquinone, catechol and 1,2,4-benzenetriol making up 4.8%, 2.2% and 0.3% respectively (as conjugates). Approximately 1.3% of the dose was recovered as *trans,trans*-muconic acid and a further 0.5% as phenylmercapturic acid. No diphenyl or its derivatives were detected in the urine. The residual radioactivity (5% to 10%) was associated with the tissues and faeces (Parke & Williams, 1953).

The elimination of benzene by the metabolic route appears to be saturable. Oral doses of [^{14}C]-benzene ≤15 mg/kg resulted in the excretion in the urine over 48 h of >89% of the administered radioactivity by rats (F344 or Sprague-Dawley). Doses ≥50 mg/kg bw resulted in a dose-dependent reduction in urinary excretion and a corresponding dose-dependent increase in exhaled ^{14}C, predominantly as the parent molecule. At all doses, residual ^{14}C in the carcass amounted to less than 8%. Excretion in the faeces did not exceed 11% of the administered dose up to the maximum dose of 300 mg/kg. Mice (B6C3F1) demonstrated similar elimination characteristics to rats (Sabourin et al, 1987).

Other routes

Analysis of urine from male cynomolgus monkeys administered [^{14}C]-benzene (5, 50 and 500 mg/kg) by intraperitoneal injection revealed that urinary excretion of radiolabel diminished with increasing dose. At 5 mg/kg an average of 56% of the administered dose was recovered in the urine compared to 13% at 500 mg/kg over a 95-h period. In contrast, recovery of radiolabel from the urine of chimpanzees administered a dose of benzene (1 mg/kg) by intravenous injection was complete after 24 h with >90% of the radiolabel collected within the first 8 h. As shown in Table 9.3, phenyl sulfate was found to be the major metabolite (45-74% of total urinary metabolites) for all doses. Lesser amounts of hydroquinone glucuronide, muconic acid, phenyl glucuronide, hydroquinone sulfate and catechol sulfate were also present. No unconjugated metabolites were detected. The amount of excreted hydroquinone sulfate and muconic acid decreased and phenyl glucuronide and catechol glucuronide increased as the benzene dose increased. A similar urinary profile of metabolites was obtained with female chimpanzees administered an intravenous dose of [^{14}C]-benzene (1 mg/kg), although the formation of catechol conjugates was not detected (Sabourin et al, 1992).

Table 9.3: Major urinary metabolites after intraperitoneal administration of benzene, expressed as a percentage of total urinary metabolites from 24-h samples (adapted from Sabourin et al. (1992))

Species	Dose (mg/kg)	Phenol conjugates	Hydroquinone conjugates	Catechol conjugates	Pre-phenyl-mercapturic acid	Muconic acid
Cynomolgus monkey	5	61	27	8.0	No data	4.4
	50	73	15	6.0	No data	3.1
	500	78	8.9	9.9	No data	1.3
Chimpanzee	1	75	8.0	ND*	0.5	5.5

* ND = not detected.

9.4.2 Human data

Inhalation

The elimination of benzene across the lungs of 10 subjects was studied. Subjects inhaled benzene (47-84 ppm) for 2-3 h after which breath samples were taken over a further 5-7 h. The results showed 16.4-41.6% of the absorbed benzene to be exhaled with the greatest rate occurring during the first hour. Excretion in the urine accounted for a maximum of 0.2% of the absorbed dose (Srbova et al, 1950). It appears that urinary benzene metabolites were not measured by the protocol employed. Comparable results were produced after a 4-h exposure to benzene vapour (52-62 ppm) where 6 volunteers (3 males and 3 females) were shown to exhale 16.3% (men) and 17.2% (females) of the inhaled benzene (Nomiyama & Nomiyama, 1974a). The ratio of respiratory elimination of non-metabolised benzene to retained benzene was determined to be 114.8% for males (considered by the authors to be unreliable) and 39.8% for females (Nomiyama & Nomiyama, 1974b). Using 4 volunteers (male non-smokers) exposed to benzene vapour (mean daily exposure 26.2-42.2 ppm) for 5 consecutive daily 6-h periods, Berlin et al. (1980) showed the clearance of benzene across the lungs to be biphasic with a half-time of 2.6 h for the rapid phase and 24 h for the slow phase. At higher benzene concentrations (99 ppm for 1 h), Sherwood (1988) identified one individual with an initial rapid phase and 2-3 slower phases while urinary excretion displayed a biphasic pattern.

Ghittori et al. (1993) found a linear correlation between benzene in the breathing zone and unmetabolised benzene in the urine of workers. Subsequently, Ghittori et al. (1995) identified a linear relationship between benzene in the breathing zone of workers and urinary levels of *trans,trans*-muconic acid and phenylmercapturic acid.

Dermal and oral

Peak excretion of radioactivity in the urine of 4 human volunteers after the application of 0.4 ml of [^{14}C]-benzene to the ventral forearm occurred rapidly within the first 2 h and decreased rapidly thereafter but remained detectable for up to 30 h (Franz, 1984).

No studies were identified that address the elimination of benzene or its metabolites from humans after exposure by the oral route.

9.5 Comparative kinetics and metabolism

As discussed above, CYP2E1 is a high affinity, low capacity enzyme. Consequently, the pathway for the hepatic metabolism of benzene becomes saturated at relatively low doses. Henderson et al. (1989) found a single oral dose of benzene of 50 mg/kg or greater, when administered to rats or mice, resulted in saturation of the metabolic pathway with consequent loss of unmetabolised benzene by exhalation. Rats and mice administered an oral dose of 150 mg/kg exhaled approximately 50% and 85% respectively as unmetabolised benzene. This loss of benzene by exhalation becomes a limiting factor in the maximal tissue concentrations of metabolites that can be achieved following oral dosing. However, higher tissue concentrations of benzene metabolites can be achieved by the inhalation route. It has been observed that mice accumulate substantially more benzene metabolites than rats during inhalation exposure. This appears to be due to physiologic and metabolic differences between the two species. Mice have a higher respiratory minute volume per kg body weight compared to rats allowing for the blood benzene level to achieve equilibrium faster than in the rat (Sabourin et al, 1989, 1990). Mice also have a higher metabolic rate, based on increased oxygen consumption (approximately 1.8 times greater than the rat), resulting in faster removal of benzene from the circulation. This allows for higher levels of metabolites to accumulate within body tissues compared to the rat. Doses of benzene that lead to metabolic saturation also produce changes in the metabolic profile of benzene metabolites (Sabourin et al, 1989; Daiker et al, 1996).

9.5.1 Oral studies

The content of water-soluble benzene metabolites in bone marrow has been examined following oral administration of benzene to male rats and mice. Table 9.4 shows that phenol conjugates accounted for the major proportion of metabolites in the rat and remained relatively constant over the dose range as did the mercapturic acid derivatives. The *trans,trans*-muconic acid content diminished with increasing doses of benzene and hydroquinone conjugates remained at relatively low levels. In contrast, the mouse produced comparable bone marrow levels of phenol and hydroquinone conjugates at the lowest dose with the amount of hydroquinone conjugates decreasing as the benzene dose increased. Both phenyl mercapturic acid and *trans,trans*-muconic acid increased with the dose of benzene (Sabourin et al, 1989).

Table 9.4: Major bone marrow metabolites after oral administration of benzene, expressed as a percentage of total water-soluble metabolites from pooled samples (adapted from Sabourin et al. (1989))

Species	Dose (mg/kg)	Phenol conjugates	Hydroquinone conjugates	Pre-phenyl-mercapturic acid	Phenyl-mercapturic acid	Muconic acid
Rat (F344)	1	75	ND*	15	ND	10
	10	74	3.0	15	4.0	4.0
	200	84	2.3	13	ND	0.2
Mouse ($B6C3F_1$)	1	50	50	ND	ND	ND
	10	52	35	ND	13	ND
	200	56	9.0	ND	27	8.0

* ND = not detected.

9.5.2 Inhalation studies

Animal data

The profile of metabolites produced by male rats (F344) and mice ($B6C3F_1$) exposed (nose-only) to benzene vapour for 6 h at 5 ppm or 600 ppm is presented in Table 9.1. Phenol conjugates account for the major proportion of metabolites produced at either concentration by both species. At 5 ppm, hydroquinone conjugates and *trans,trans*-muconic acid are present in higher amounts than at 600 ppm while pre-phenylmercapturic acid increases with the administered dose (Sabourin et al, 1989).

Tissue and blood levels of non-conjugated benzene metabolites were determined in male rats (F344) and mice ($B6C3F_1$) after inhalation of benzene vapour (50 ppm) for 6 h. While phenol, hydroquinone and catechol could not be detected in the liver, lung or blood of the rat, detectable levels of phenol and hydroquinone were found in the mouse with catechol detected only in the liver. The data for male rats and mice are presented in Table 9.5.

Table 9.5: Major non-conjugated benzene metabolites (nmol/g tissue) in rat and mouse tissues (adapted from Sabourin et al. (1988))

	F344 rats			$B6C3F_1$ mice		
Metabolite	**Liver**	**Lung**	**Blood**	**Liver**	**Lung**	**Blood**
Phenol	ND*	ND	ND	0.3	0.6	1.3
Hydroquinone	ND	ND	ND	2.1	1.2	4.3
Catechol	ND	ND	ND	0.3	ND	ND

* ND = not detected.

In contrast, conjugated derivatives of phenol, hydroquinone and catechol were detected in substantially greater amounts in the tissues and blood of both species (Table 9.6).

Table 9.6: Major conjugated benzene metabolites (nmol/g tissue) in rat and mouse tissues (adapted from Sabourin et al. (1988))

	F344 rats			$B6C3F_1$ mice		
Metabolite	**Liver**	**Lung**	**Blood**	**Liver**	**Lung**	**Blood**
Phenylglucoronide	ND*	ND	ND	6.3	1.2	ND
Cathecholglucoronide	1.0	ND	ND	0.8	0.5	ND
Hydroquinoneglucoronide	0.4	ND	ND	26	15	12
Phenylsulfate	1.5	15	20	28	36	36
Hydroquinone monosulfate	ND	ND	ND	2.8	0.6	ND
Pre-phenylmercapturic acid	6.9	0.9	ND	44	2.1	2.3
Phenylmercapturic acid	ND	ND	ND	ND	ND	ND
Muconic acid	8.4	1.9	0.7	228	18	1.0

* ND = not detected.

As shown in the table, the level of *trans,trans*-muconic acid in the mouse liver was very much greater than observed in lung tissue or blood for either species (Sabourin et al, 1988). Henderson et al. (1989) observed that the mouse metabolised more of an inhaled dose of benzene than the rat under comparable conditions and that a greater proportion was converted to the putative toxic metabolites. It was found that

detoxification (conjugation) pathways were low-affinity, high-capacity whereas toxic metabolite formation appeared to be high-affinity, low capacity.

A short-term benzene inhalation study (exposure for 6 h/day for 6 days) with male Swiss mice showed that at 199 ppm or less, the major metabolite in blood was phenylsulfate while above 199 ppm a dose-dependent increase in phenyl-glucuronide occurred. At all benzene concentrations, the blood phenol level increased in a dose-dependent manner (Wells & Nerland, 1991).

Human data

Studies of humans are generally limited to analysis of urine or blood samples of workers occupationally exposed to benzene.

Bechtold and Henderson (1993) conducted analyses on the urine and blood of non-smoking female workers exposed to benzene vapour. Five women exposed to approximately 4.4 ppm for 8 h showed the presence of elevated urinary levels of *trans,trans*-muconic acid (6.2 μg/mg creatinine) compared to 8 females with no known exposure (0.27 μg/mg creatinine). Blood samples from 10 women exposed to benzene vapour (0-23.1 ppm) showed a linear relationship between benzene exposure levels and albumin-S-phenylcysteine adducts, however, no haemoglobin-S-phenylcysteine adducts were detected.

9.5.3 Dermal studies

Comparative studies of the metabolism of benzene after dermal absorption were not identified.

9.5.4 In vitro studies

The metabolism of low levels of benzene by microsomes prepared from 10 human liver samples was investigated. When [^{14}C]-benzene (3.4 μM) was incubated with microsomal preparations, the major metabolites were phenol and hydroquinone accounting for up to 48% of the recovered radiolabel while minor metabolites were catechol and 1,2,4-trihydroxybenzene which accounted for <2% and 0.2% respectively. A further metabolite, tentatively identified as 2,2'-biphenol, accounted for approximately 4% of radiolabel. The CYP2E1 activities of the individual liver samples were found to vary 13-fold as determined by a standard hydroxylation assay with activities ranging between 0.253 to 3.266 nmol/mg/min. When benzene was used as the substrate, a 6-fold difference between liver samples was noted that ranged from 10% to 59%. Comparison of individual liver samples over a 16-min incubation period showed that phenol was the major metabolite formed with the exception of two samples where hydroquinone predominated. These latter two samples had higher CYP2E1 activities and the sample with the highest activity produced equal quantities of phenol and hydroquinone. The rate of benzene metabolism by each of the 10 liver samples correlated with their CYP2E1 activity (Seaton et al, 1994). In a subsequent report by Seaton et al. (1995) addressing the *in vitro* sulfonation of phenol and glucuronidation of hydroquinone by human liver cytosolic and microsomal preparations from 10 donors, there was a 3-fold difference in the rates of conjugation for each reaction.

9.6 Summary

Benzene is readily absorbed by the inhalation, oral and dermal routes in all animal species tested. In humans, the absorption of benzene by the inhalation route is maximal within minutes of exposure and subsequently declines to a constant level. Dermal absorption is generally low compared to inhalation due to volatilisation, with less than 1% of an applied dose being absorbed unless skin exposure is prolonged. The variation in benzene absorption between individuals following inhalation is high. Partitioning of benzene is expected to occur into lipid-rich tissues due to the lipophilic nature of benzene. Several studies have confirmed that benzene accumulates in the adipose tissue, bone marrow and brain of animals and humans.

The metabolism of benzene is qualitatively similar between various animal species, including humans, and proceeds predominantly by hepatic CYP2E1-mediated oxidation of the aromatic ring to yield benzene oxide/oxepin. Subsequent pathways for metabolism of the oxide/oxepin include spontaneous rearrangement to phenol or ring cleavage to give *trans*,*trans*-muconaldehyde. Phenol can be further oxidized to polyphenols (hydroquinone, catechol and 1,2,4-trihydroxybenzene). Detoxification pathways involve conjugation of benzene oxide or *trans*,*trans*-muconaldehyde with GSH while the phenolic metabolites are conjugated to either glucuronate or sulfate. The metabolism of benzene is rapid with water-soluble metabolites appearing in the urine within 2 h of exposure. The major urinary metabolites from several species are conjugates of phenol followed by lesser and variable amounts of hydroquinone conjugates and of pre-phenylmercapturic acid and *trans*,*trans*-muconic acid. Conjugates of catechol have been detected in small amounts in the urine of mice, rabbits and primates.

Due to the limited capacity of hepatic CYP2E1 to metabolise benzene, a substantial proportion of absorbed benzene is eliminated unchanged in exhaled air, with the remainder being eliminated via the urine, principally as metabolites. Urinary excretion appears to be biphasic with a fast phase followed by a prolonged phase, suggesting the slow removal of benzene from adipose tissue. Due to the readily saturable nature of benzene metabolism, exposure at higher doses results in greater elimination of unmetabolised benzene via exhalation.

While comparative studies of urinary benzene metabolites have shown common pathways for benzene metabolism to exist between various species, physiological as well as metabolic differences contribute to some of the observed differences. The easily saturated nature of benzene metabolic pathways and greater respiratory minute volume of the mouse allow the mouse to expire more of an oral dose of benzene compared to the rat. Similarly, respiratory differences and the greater metabolic rate of the mouse allow tissue levels of benzene metabolites to reach higher levels compared to the rat.

10. Effects on Laboratory Mammals and Other Test Systems

The aim of this section is to describe the toxic effects and corresponding effect levels of benzene in animals. In the case of end points studied extensively in humans (mainly haematological and genetic toxicity), the assessment is based on recent reviews by ATSDR (1997) and USEPA (USEPA 1998a, 1998c). For other adverse effects, individual animal studies have been reviewed for this assessment. These include all carcinogenicity studies as well as investigations of the toxic effects of benzene on the central nervous system (CNS), immune function, reproductive organs and foetus.

Most of the available studies do not comply with Good Laboratory Practices (GLP) or international standards such as the OECD Test Guidelines. In consequence, all available publications with a relevant end point have been included in the review irrespective of their compliance with formal quality criteria. However, studies providing insufficient scientific detail to permit a critical appraisal of their findings are clearly identified as such. Unless otherwise indicated, only effects that were statistically different ($p < 0.05$) from controls have been considered.

10.1 Acute toxicity

The acute toxicity of benzene in experimental animals is summarised in Table 10.1, which includes the highest and the lowest values reported in the published literature. Mortality is due to cardio-respiratory arrest from severe CNS depression and/or cardiac arrhythmia (Nahum & Hoff, 1934).

Table 10.1: Acute toxicity of benzene

Route	Species	Measure*	Results	Sex	Reference
Inhalation	Mouse	$LC_{50(7\ h)}$	9980 ppm	Not specified	Svirbely et al. (1943)
	Rat	$LC_{50(4\ h)}$	13,700 ppm	Females	Drew & Fouts (1974)
		$ALD_{(4\ h)}$	16,000 ppm	Males	Smyth et al. (1962)
	Rabbit	$LC_{100(30\ min)}$	45,000 ppm	Both sexes	Carpenter et al. (1944)
Oral	Mouse	LD_{50}	4700 mg/kg	Not specified	RTECS (2000)
			6500 mg/kg	Males	Spanò et al. (1989)
	Rat	LD_{50}	810 mg/kg	Males	Cornish & Ryan (1965)
			5600 mg/kg	Males	Wolf et al. (1956)
			9900 mg/kg	Males	Smyth et al. (1962)
Dermal	Guinea pig, rabbit	LD_{50}	>8200 mg/kg	Male guinea pigs Male and female rabbits	Roudabush et al. (1965)
SC	Mouse	ALD	3500 mg/kg	Males	Watanabe & Yoshida (1970)

* ALD = approximate lethal dose; LC_{50} = median lethal concentration; LC_{100} = concentration leading to 100% mortality; LD_{50} = median lethal dose; SC = subcutaneous.

10.2 Irritation and corrosivity

Several rabbit tests for skin and eye irritation have been reported. From 10-20 daily applications of undiluted benzene to the skin caused redness, oedema, skin peeling and blistering (Wolf et al, 1956). The chemical was also reported to cause skin irritation in a test according to OECD Test Guideline No. 404, however, further details were not provided (Jacobs, 1992, as cited in OECD, 2000). One or two drops of undiluted benzene applied to the eye produced moderate irritation of the conjunctiva and very slight, transient corneal injury (Wolf et al, 1956). Smyth et al. (1962) reported similar skin and eye lesions rated as grade 3 on a 10-point scale.

Rats exposed to benzene vapours for 6 h/day, 5 days/week for 10 weeks exhibited lacrimation during the first 3 weeks of exposure to levels ≥10 ppm (Shell, 1980, as cited in ATSDR, 1997).

10.3 Sensitisation

There are no studies of skin or respiratory sensitisation to benzene in animals.

10.4 Repeated dose toxicity (other than carcinogenicity)

10.4.1 Short-term exposure

The toxic effects of benzene have been investigated in numerous short-term studies in mice and rats. In these studies, benzene was administered orally in vegetable oil or drinking water for 2 days to 24 weeks, or by whole-body exposure to vapours, usually for 6 h/day, 5 days/week. The dose levels tested ranged from 1-600 mg/kg/day by mouth and from 0.44-6600 ppm by inhalation. Repeated dose dermal studies could not be identified.

Neurotoxicity

Evans et al. (1981) exposed male CD-1 and C57BL mice to inhalation of 0, 300 or 900 ppm benzene for 6 h/day. After the 5th exposure, the mice were observed and scored for 7 behavioural categories at 30 and 75 min post-exposure. In both strains, there were increases in the frequency of eating and grooming, and a decrease in sleeping and resting. These stimulatory effects were more pronounced at 75 than at 30 min post-exposure and in the 300 than in the 900 ppm exposure groups, indicating an association with brain concentrations below a certain level.

Immediately following single and repeated 6-h exposures of male mice to 100, 300, 1000 or 3000 ppm benzene, there were increased milk licking at 100 ppm and a reduction in hind limb grip strength at ≥1000 ppm, but no effects on locomotor activity (Dempster et al, 1984). In the absence of motor disturbances, hind limb grip strength is a test for unconditional reflexes. Milk licking, however, may be influenced by hunger and mucosal membrane irritation.

In groups of 10 adult male mice exposed to 0, 0.78, 3.13 or 12.52 ppm benzene for 2 h/day, 6 days/week for 30 days, tests for behaviour (time taken to run to a safety area in a Y-maze following an electric shock) and forelimb grip strength showed stimulation at 0.78 ppm and depression at 12.52 ppm, but no effect on locomotor activity (Li et al, 1992). Compared to unexposed controls, the average change in the frequency of rapid shock responders was +30% at 0.78 ppm and –24% at 12.5 ppm. For grip strength, it was +77% and –11% respectively. As the concentration

of benzene in the air was not checked after the first three days of the experiment and there were extraordinary changes in bone marrow morphology on day 30, actual benzene exposure may have been higher than reported (USEPA, 1998c). On the other hand, the changes in behaviour were observed already on the first 1-2 days of exposure when air level monitoring did take place.

Tegeris & Balster (1994) evaluated the acute behavioural effects in mice of a 20-min inhalation exposure to 2000, 4000 and 8000 ppm benzene and five derivatives (toluene, ethyl benzene, propyl benzene, *m*-xylene and cumene). All six chemicals produced a nearly identical profile of CNS depressant effects that paralleled those of the anaesthetic drug pentobarbital, except that they were short-lived, with recovery beginning within minutes of cessation of exposure.

In mice, administration for 4 weeks of 8-180 mg/kg/day benzene in drinking water had no behavioural effects, but induced a dose-related increase in the level of noradrenaline, dopamine, serotonin and their metabolites in a number of brain regions (Hsieh et al, 1988b). There was also a dose-dependent stimulation of hypothalamic-pituitary-adrenocortical activity (Hsieh et al, 1991). Changes in brain noradrenaline, dopamine, serotonin and/or their metabolites were also found in rats 2 h after a single oral dose of 950 mg/kg benzene or following inhalation of 1500 ppm benzene, 6 h per day for 3 days (Andersson et al, 1983; Kanada et al, 1994). The most consistent finding in these studies was an increase in noradrenaline and dopamine levels in the hypothalamus and other subcortical brain regions. In a rat inhalation study, benzene also induced noradrenaline release from post-ganglionic sympathetic nerves in the ovaries and uterus (Ungváry & Donáth, 1984).

A 30-day drinking water study found a reduction in brain weight in mice at 350 but not at 195 mg/kg/day (Shell 1992, as cited in ATSDR, 1997). No studies were identified that specifically looked for benzene-induced morphological changes in nervous organs or tissues.

Immunotoxicity

When administered to mice by inhalation or in drinking water, benzene suppressed a number of lymphocyte (LC) functions. These included T- and B-LC response to mitogens; interleukin-2 production in T-helper LC; the activity of cytotoxic, alloreactive and suppressive T-LC; B-LC antibody production; and T-LC and macrophage resistance to intracellular infection with *Listeria monocytogenes* (Fan, 1992, as cited in USEPA, 1998c; Hsieh et al, 1988a; Irons et al, 1983; Rosenthal & Snyder, 1985, 1987; Rozen et al, 1984; Rozen & Snyder, 1985; Stoner et al, 1981, as cited in IPCS, 1993; White et al, 1984, as cited in USEPA, 1998c). Based on the above effects, the lowest observed adverse effect level (LOAEL) was 10 ppm by inhalation (Rozen et al, 1984) and 12 mg/kg/day by the oral route (White et al, 1984, as cited in USEPA, 1998c). A no observed adverse effect level (NOAEL) was not achieved, although Hsieh et al. (1988a) found a bimodal response with a reduction in LC proliferation at 40 mg/kg/day and an increase at 8 mg/kg/day, the lowest dose tested. However, Daiker et al. (2000) recently found no changes in spleen LC cellularity, subtype profile or function in mice exposed to inhalation of 0.44 ppm benzene for 7 h/day, 5 days/week for 6 weeks.

In these studies in mice, immunosuppression generally occurred at exposure levels which were also associated with reduced absolute lymphocyte counts (ALC). However, in one 30-day study, mitogen-stimulated LC proliferation was decreased at 12 mg/kg/day (the lowest dose tested) in the absence of any other blood or bone marrow toxicity (White et al, 1982, as cited in USEPA, 1998c). There is no

evidence of specificity with respect to antigen or immune response type. Overall, these findings indicate that benzene-induced immunosuppression is the outcome of a general impairment of the ability of LC to respond to antigenic stimuli by rapid clonal expansion, with little, if any, interference with antigen recognition.

In wild cotton rats given three consecutive intraperitoneal injections of benzene at a dosage of 0, 100, 300, 600 or 1000 mg/kg/day and a battery of tests for cellular and humoral immune functions on days 1-9 after the last treatment, there was no evidence of immunosuppression in any of the treatment groups (McMurry et al, 1991).

In a subacute inhalation study in male Sprague-Dawley rats exposed to 0, 30, 200 or 400 ppm benzene for 6 h/day, 5 days/week for 2-4 weeks, Robinson et al. (1997) determined a NOAEL/LOAEL of 200/400 ppm based on spleen weight, cellularity, total T-LC, T-helper LC, antigen-stimulated and unstimulated B-LC content, and thymus weight. As such, rats appear to be less sensitive than mice to the immunotoxic effects of benzene.

Effects on blood and blood forming organs

ATSDR (1997) and USEPA (1998c) have reviewed a large number of published and unpublished study reports that address the effects of short-term exposure to benzene on the blood and blood forming organs of mice and rats. Based on these reviews, the overall findings can be summarised as follows:

- In peripheral blood, there was a decrease in the quantity of some or all of the formed elements, including red blood cells (RBC), white blood cells (WBC), LC and blood platelets (Plt). In some studies, there was also a reduction in haemoglobin (Hb) levels and the average RBC size (mean corpuscular volume (MCV)) was either increased or decreased.
- There was bone marrow hypoplasia, with decreased numbers of multipotential stem cells and cells that differentiate into RBC, WBC and macrophages, but an increase in immature RBC such a micronucleated polychromatic and normochromatic RBC.
- In the spleen, there was a decrease in the number of all LC types, but an increase in haematopoiesis in general[3].
- There was a decrease in the weight of the thymus, which is the main site of T-LC proliferation.

The order of susceptibility to these effects was male mice > female mice > rats. In terms of target organ, it was spleen ≥ peripheral blood ≥ bone marrow > thymus. In mice, the most sensitive indicators of benzene toxicity were spleen weight, bone marrow cellularity, and WBC and RBC counts, one or more of which were affected at concentrations around 10 ppm and above for inhalation and at 8 mg/kg/day and above for oral exposure. In rats, the most sensitive end points were ALC and WBC counts, which were affected at 100 ppm by inhalation and 25 mg/kg/day by oral administration.

[3] Haematopoiesis is the sum of processes involved in the production and development of the blood cells. The haematopoietic processes are usually confined to the bone marrow, but may also take place in the spleen and liver, for example, in foetuses and newborn animals, or when there is a substantial increase in the demand for blood cells.

Two 2-16 week studies in the mouse showed that all haematological abnormalities returned to normal or near-normal within 4-25 weeks post-exposure (Cronkite et al, 1985; Snyder et al, 1988).

Other effects

There are no consistent reports of respiratory, cardiovascular, gastro-intestinal, hepatic or renal effects of short-term exposure to benzene by any route (ATSDR, 1997). Effects on reproductive organs are reviewed in Section 10.5. Mortality was generally low and only a few studies reported decreases in body weight (BW) gain.

Other experimental animals

There is limited evidence that airborne exposure to benzene for 3-4 weeks induces leukopoenia in guinea pigs and lymphocytopoenia, leukopoenia and impaired cellular immunity in pigs at levels ≥88-100 ppm (Dow, 1982, as cited in ATSDR, 1997; Wolf et al, 1956).

10.4.2 Long-term exposure

Blood and blood forming organs

ATSDR (1997) and USEPA (1998c) have reviewed more than a dozen published reports which describe the results of nine separate studies of the long-term effects of benzene exposure on blood and blood forming organs. In these studies, mice or rats were exposed to benzene for ≥26 weeks by oral administration in vegetable oil or by whole-body inhalation for 5-6 h/day, 4-5 days/week, at dose levels ranging from 1-500 mg/kg/day by mouth and from 88-300 ppm by inhalation.

The most consistent long-term effect on the blood was a reduction in RBC, WBC and LC counts. In some studies, the number of neutrophilic granulocytes and reticulocytes (young RBC) was increased. The bone marrow and the spleen showed hypoplasia in some studies and an increase in haematopoietic tissue in others.

Haematological effects were recorded at the lowest dose level examined in all long-term tests, except for one poorly reported rat study in which the NOAEL was 1 mg/kg/day by mouth (Wolf et al, 1956). This study also recorded a lower LOAEL than any of the other available studies, namely 88 ppm by inhalation based on WBC count and spleen weight and 10 mg/kg/day by oral administration based on WBC count. In more adequately reported studies, the LOAEL was 100 ppm by inhalation and 25 mg/kg/day by mouth in both mice and rats (ATSDR, 1997; USEPA, 1998c).

Other effects

There are no consistent reports of non-neoplastic cardiovascular, liver or kidney abnormalities from long-term exposure to benzene by any route (ATSDR, 1997). There was chronic irritation of the forestomach epithelium in male rats and mice and hyperplasia of the Harderian gland[4] and pulmonary alveolar epithelium in male and female mice in 2-year, but not in 17-week oral gavage studies (NTP, 1986[5]). Lesions occurred at 200 mg/kg/day in rats and at dose levels ≥25 mg/kg/day in

[4] A tear gland in the median angle of the eye which is rudimentary in humans.

[5] The major findings in the studies conducted by the National Toxicology Program (NTP) have been published by Huff et al. (1989).

mice. Reproductive effects are described below. The median survival time and BW gain were generally reduced in a dose-dependent manner.

Other experimental animals

There is limited evidence that airborne exposure to benzene for 35-38 weeks induces leukopoenia and increased spleen weight in guinea pigs and leukopoenia in rabbits at dose levels ≥80-88 ppm (Wolf et al, 1956).

10.5 Reproductive toxicity

10.5.1 Effects on fertility and lactation

Data on fertility and lactation are available from three repeated-dose toxicity tests, three one-generation fertility studies and a limited number of other studies.

Repeated-dose toxicity and one-generation fertility studies

In a 13-week inhalation study, Ward et al. (1985) exposed groups of 150 mice and 50 rats per sex to inhalation of 0, 1, 10, 30 or 300 ppm benzene for 6 h/day, 5 days/week. There was clear evidence of haematological toxicity at the highest dose level in both species and sexes, but no consistent exposure-related trends in mortality, clinical observations or mean BW data. The testes and ovaries from 20 mice/sex/group and from 10 rats/sex exposed to either 0 or 300 ppm benzene were examined microscopically. In mice from the highest exposure group (300 ppm), there were 4 animals with cystic ovaries, 7 with bilateral testicular atrophy or degeneration, 6 with decreases in the number of spermatozoa in the epididymal ducts and 9 with an increase in abnormal sperm forms. Similar lesions of doubtful biological significance were seen in both sexes at lower dose levels. No abnormalities were found in the gonads of rats exposed to 300 ppm benzene.

A study in mice administered benzene at 25, 50 or 100 mg/kg/day by gavage for 2 years found the following number of animals with epithelial hyperplasia or follicular atrophy of the ovaries (NTP, 1986):

Ovarian lesions:	0 mg/kg/day	25 mg/kg/day	50 mg/kg/day	100 mg/kg/day
No. of mice examined	47	44	49	48
Epithelial hyperplasia	12	39	31	29
Senile atrophy	15	35	32	22

The statistical significance of these findings is not reported. However, when analysed for this assessment, the increase in the incidence of epithelial hyperplasia was significant at all dose levels, whereas the incidence of senile atrophy was significantly elevated at 25 and 50, but not at 100 mg/kg/day ($p < 0.05$; test for exact confidence limits). Testes were not examined microscopically, as they had no grossly visible lesions. A parallel study in rats found no macroscopic abnormalities in the gonads, even at the highest dose level tested (100 mg/kg/day in females, 200 mg/kg/day in males) (NTP, 1986).

In an early inhalation study, Wolf et al. (1956) observed sedation, growth depression, mortality and a moderate increase in testis weight in male rats exposed to 6600 ppm benzene for 13 weeks. The testes were normal in rats exposed to 88 or 2200 ppm for 30 weeks. At these dose levels there were mild lesions of the blood and lymphatic system, but no mortality. In guinea pigs and rabbits exposed to 80-88 ppm benzene for 35-38 weeks, there was no mortality, mild haematological

changes and a slight increase in testis weight and in mild degenerative lesions of the seminiferous tubules. Further details were not reported and it is unclear whether these findings were statistically significant.

In female mice, a single intraperitoneal injection of benzene at the maximum tolerated dose of 1250 mg/kg did not reduce the number of offspring and litters produced in a reproductive capacity test involving the observation of 35 treated and untreated breeding pairs for 347 days (Bishop et al, 1997).

In a one-generation fertility study, groups of 26 female rats were exposed to 0, 1, 10, 30 or 300 ppm for 6 h/day, 5 days/week for 10 weeks prior to mating and then daily on days 0-20 of gestation and days 5-20 of lactation (Kuna et al, 1992). In the dams, there was no exposure-related effect on BW gain, clinical observations or necropsy findings and no fertility-related effects. When the neonates were examined at weaning on day 21 postpartum, there was a dose-related, 6-9% increase in relative kidney weight in female offspring of dams exposed at 10 ppm and above. Female offspring of dams exposed to 300 ppm benzene also had a 10% BW reduction and a 14% reduction in absolute liver weight.

In another fertility study, female rats were kept in inhalation chambers where they were exposed for 24 h/day to 0, 0.3, 1.6, 6.3, 15, 18, 20 or 200 ppm benzene (Gofmekler, 1968). Exposure began 10-15 days prior to mating, when males were introduced into the chambers for 6-10 days, and continued throughout the entire pregnancy period until spontaneous delivery. There were no pregnancies at the highest dose level. In dams exposed to 0.3-20 ppm benzene, the average litter size was 7.5 compared to 8.4 in the controls, but there was no exposure-related effect on the birth weight of the pups.

Other studies

In early experimental studies, benzene caused degenerative changes in the testes and severely hypoplastic ovaries, degenerated ovarian follicles and chromosomal damage and mitotic interruption in the ova when administered by subcutaneous injection or inhalation to male and female mice and female rabbits (Hett & Mark, 1938; Vara & Kinnunen, 1946). The dose levels used in mice were not given, but were high enough to induce marked leukopoenia. Rabbits were administered 1000 mg/kg/day for 10 days.

In a study in adult mice, testicular germ cell suspensions were examined for DNA content by flow cytometry at 1, 2, 3, 4 and 10 weeks after a single sublethal dose of 1-7 mL (880-6160 mg) benzene/kg administered by oral gavage (Spanò et al, 1989). These doses had no effect on body or testis weight, but resulted in a dose-dependent reduction in the relative cell count in the primary spermatocyte and spermatid fractions. The primary spermatocyte fraction was most affected at 2 weeks, the round spermatid fraction at 3 weeks and the elongated spermatid fraction at 4 weeks post-treatment, as one would expect from a cytotoxic insult resulting in a transient reduction in the number of differentiating spermatogonia.

Conclusions

Overall, the above studies indicate that benzene exposure may cause degenerative changes in the gonads of mice, whereas there is insufficient evidence of similar effects in other species. There was also epithelial hyperplasia in the ovaries of mice in the NTP (1986) 2-year oral bioassay. However, this is likely to represent a preneoplastic lesion as ovarian tumours occurred with a significant positive trend in

this study and epithelial hyperplasia was found in other organs with neoplastic lesions, namely the Harderian gland and the lungs.

Compound-related testicular atrophy or degeneration was observed in male mice exposed to 300 ppm benzene by inhalation. Ovarian atrophy was observed in mice at 25 mg/kg/day by mouth and cystic ovaries at 300 ppm by inhalation. In both sexes, these lesions occurred at dose levels that were associated with haematological effects, but not with mortality or other signs of generalised toxicity.

The available data on reproductive capacity are inconclusive.

The changes in body, liver and relative kidney weights observed by Kuna et al. (1992) in 21-day old female neonates of rats exposed to inhalation of benzene during pregnancy and lactation are modest, but nonetheless indicative of developmental toxicity. Because of the study design it cannot be determined whether these effects were lactational or the result of exposure *in utero*.

10.5.2 Developmental toxicity

Standard tests

Developmental toxicity tests have been conducted in mice, rats and rabbits exposed to benzene by inhalation, mouth or subcutaneous injection during the gestation period (Table 10.2). All foetuses were examined for external defects and in all but two studies (Exxon Chemical Company, 1986, as cited in USEPA, 1998c; Watanabe & Yoshida, 1970) for visceral and skeletal abnormalities as well.

Overall, there were no major structural abnormalities in the foetuses, except in one study in the mouse in which a single SC injection of a maternally toxic dose of 2600 mg/kg benzene on GD 13 was associated with cleft palate and jaw malformations (Watanabe & Yoshida, 1970). However, several inhalation and oral studies conducted in mice or rats found evidence of other foetal effects at dose levels where no toxic effects were recorded in the dams. These include a small (4-6%), but statistically significant reduction in foetal BW (Coate et al, 1984; Murray et al, 1979; Seidenberg et al, 1986) and a significant increase in the frequency of minor skeletal abnormalities (Green et al, 1978; Murray et al, 1979). Moreover, in two studies on which little experimental detail is available, there was an increase in resorptions in rats (Litton Bionetics, 1977, as cited in USEPA, 1998c) and a decrease in foetal BW in mice (Nawrot & Staples, 1979), in both cases in the absence of any signs of maternal toxicity.

In rabbits, continuous inhalation of 310 ppm benzene was associated with abortions, an increase in resorptions or foetal deaths, a decrease in foetal BW and an increased incidence of minor abnormalities in the presence of maternal toxicity (reduced BW gain), whereas 155 ppm had neither foetal nor maternal effects (Ungváry & Tátrai, 1985).

Table 10.2: Summary of developmental toxicity tests*

Species	Study design	Daily dose	Foetal effects†	Maternal effects†	Reference
Mouse	SC injection on GD 8-9 or GD 12-13	1760 mg/kg	None	Decreased Hgb	Matsumoto et al. (1975)
	8-11 pregnancies per group	3520 mg/kg	Decreased BW (3%) Decreased placenta weight (5%) in GD 12-13 group Delayed ossification in GD 12-13 group	Decreased Hgb Decreased WBC count	
	Inhalation, 7 h/day, GD 6-15 26-30 pregnancies/group	500 ppm	Decreased BW (6%) Unspecified increase in 'minor skeletal variants'	None	Murray et al. (1979)
	Oral gavage 3 times daily, GD 6-15 No. of pregnancies not given	800 mg/kg	Decreased BW	None	Nawrot & Staples (1979)
		1300 mg/kg	Increase in resorptions Decreased BW	Increase in mortality	
		2600 mg/kg	Increase in resorptions Decreased BW	Increase in mortality	
	Oral gavage 3 times daily,GD 12-15 No. of pregnancies not given	2600 mg/kg	Increase in late resorptions Decreased BW	Increase in mortality	Nawrot & Staples (1979)
	Inhalation, 24 h/day, GD 6-15 15 exposed pregnancies 115 control pregnancies	155 ppm	'Weight retardation' (25 vs. 7% of foetuses) Delayed ossification (10 vs. 5% of foetuses)	No information	Ungváry & Tátrai (1985)
		310 ppm	'Weight retardation' (27 vs. 7% of foetuses) Delayed ossification (11 vs. 5% of foetuses)	No information	
	Oral gavage, GD 8-12 28 pregnancies/group	1300 mg/kg	Decreased BW (4%)	None	Seidenberg et al. (1986)
	Single SC injection on GD 11, 12, 13, 14 or 15 15 pregnancies per group No controls External foetal examination only	2600 mg/kg	Increased incidence of cleft palate and jaw malformations in offspring of dams injected on GD 13 compared to foetuses of dams injected on GD 11-12 or 14-15	Decrease in WBC count in all dams No difference in fall in WBC count or in BW gain between dams with or without malformed foetuses	Watanabe & Yoshida (1970)

Table 10.2: Continued

Species	Study design	Daily dose	Foetal effects†	Maternal effects†	Reference
Rat	Inhalation, 6 h/day, GD 6-15 26-31 pregnancies/group	10 ppm	Increase in resorptions	None	Litton Bionetics (1977), as cited in EPA (1998c)
		40 ppm	Increase in resorptions	None	
	Inhalation, 7 h/day, GD 6-15 14-18 pregnancies/group	100 ppm	Missing sternebrae (9/18 vs. 1/16 litters)	None	Green et al. (1978)
		300 ppm	Delayed ossification of sternebrae (10 vs. 2% of female foetuses)	None	
		2200 ppm	Decreased BW (10%) Decreased crown-rump length (5%) Delayed ossification of sternebrae (11 vs. 1% of female foetuses) Missing sternebrae (11/15 vs. 2/14 litters)	Decreased BW gain Lethargy	
	Inhalation, 24 h/day, GD 9-14 19 exposed pregnancies 28 controls	313 ppm	Decreased BW (12%) Delayed ossification (11 vs. 0% of foetuses) Fused sternebrae and extra ribs (9 vs. 1% of foetuses)	Decreased BW gain (57%)	Hudák & Ungváry (1978)
	Inhalation, 24 h/day, GD 7-14 17-20 pregnancies/ exposure group 46 control pregnancies	50 ppm	Decreased BW (5%)	Decreased BW gain (27%) Decreased placenta weight (9%)	Tátrai et al. (1980)
		150 ppm	Resorbed or dead foetuses (42 vs. 6%) Decreased BW (28%) Skeletal abnormalities (57 vs. 5% of foetuses)	Mortality (3/20 vs. 0/48) Decreased BW gain (45%) Increased relative liver weight (9%) Decreased placenta weight (7%)	
		500 ppm	Resorbed or dead foetuses (32 vs. 6%) Decreased BW (20%) Skeletal abnormalities (66 vs. 5% of foetuses)	Mortality (1/22 vs. 0/48) Decreased BW gain (55%) Increased relative liver weight (14%) Decreased placenta weight (16%)	
		1000 ppm	Resorbed or dead foetuses (29 vs. 6%) Decreased BW (22%) Skeletal abnormalities (55 vs. 5% of foetuses)	Mortality (3/22 vs. 0/48) Decreased BW gain (41%) Increased relative liver weight (10%) Decreased placenta weight (20%)	

Table 10.2: Continued

Species	Study design	Daily dose	Foetal effects†	Maternal effects†	Reference
Rat	Inhalation, 7 h/day, GD 6-15 14-15 pregnancies/ exposure group 11 control pregnancies	10 ppm	None	Increased BW gain (33%) on GD 15-20	Kuna & Kapp (1981)
		50 ppm	Decreased BW (14%) Increase in foetuses with skeletal and/or visceral variations (18 vs. 3%)	Decreased BW gain (34%) on GD 5-15	
		500 ppm	Decreased BW (18%) Decreased crown-rump length (7%) Increase in foetuses with skeletal and/or visceral variations (21 vs. 3%)	Decreased BW gain (37%) on GD 5-15 Increased BW gain (40%) on GD 15-20	
	Inhalation, 7 h/day, GD 6-15 32-38 pregnancies/group 2 control groups	1 ppm	None	None	Coate et al. (1984)
		10 ppm	None	None	
		40 ppm	None	None	
		100 ppm	Decreased BW (6%)	None	
	Oral gavage, GD 6-15 20-22 pregnancies/group External foetal examination only	50 mg/kg	None	None	Exxon Chemical Company (1986), as cited in EPA (1998c)
		250 mg/kg	None	Decreased feed consumption	
		500 mg/kg	Decreased BW	Decreased BW gain Decreased feed consumption	
		1000 mg/kg	Decreased BW	Decreased BW gain Decreased feed consumption Alopecia	
Rabbit	Inhalation, 7 h/day, GD 6-18 18-19 pregnancies/group	500 ppm	None	Increased feed and water consumption	Murray et al. (1979)
	Inhalation, 24 h/day, GD 7-20 11-15 exposed pregnancies/ group 60 control pregnancies	155 ppm	None	None	Ungváry & Tátrai (1985)
		310 ppm	Abortions (6/15 vs. 0/60 dams) Resorbed or dead foetuses (16 vs. 5%) Decreased BW (17%) 'Minor anomalies' (86 vs. 34% of foetuses)	Decreased BW gain (62%; not corrected for the effect of abortions) Increased relative liver weight (17%)	

* BW = body weight; GD = gestation day; Hgb = haemoglobin; SC = subcutaneous; WBC = white blood cell.

† Where available, information on the incidence or magnitude of effects compared to non-exposed controls is shown in brackets.

Other studies

According to Ungváry (1985), continuous inhalation of benzene (125 ppm), benzene plus toluene, or benzene plus xylenes had foetotoxic effects in rats, but only in the presence of maternal toxicity. Exposure to 830 ppm benzene over 48 h on GD 10-13 increased the severity of maternal toxicity and incidence of malformations induced by a single oral dose of 250-500 mg/kg acetyl salicylic acid administered at the end of the exposure period.

Keller & Snyder (1986, 1988) investigated the effects of low level maternal exposure to benzene on the blood and blood forming organs of mouse foetuses, neonates and young adults. Groups of 5-10 dams were exposed to inhalation of 0, 5, 10, or 20 ppm benzene for 6 h/day on GD 6-15. Tests on the progeny comprised RBC, WBC, differential blood cell count, and blood cell morphology; Hb and haematocrit (Hct); quantification of colony forming units of erythrocyte (CFU-E) and granulocyte/macrophage (CFU-GM) progenitor cells; and microscopic examination of blood forming tissue in the liver, bone marrow and spleen. The number of progeny examined included 2/sex/litter/dose on GD 16, 2/sex/litter/dose on day 2 after birth, and 1/sex/ litter/dose at 6 weeks after birth.

In 16-day old foetuses exposed to 20 ppm benzene *in utero*, liver CFU-E was depressed in both sexes. In peripheral blood from the 2-day old neonates, there was a dose-related, marked decrease in the number of nucleated RBC. At 20 ppm, there was also an increase in CFU-E (males only), CFU-GM, non-dividing and dividing granulocytes in hematopoietic liver tissue, and in non-dividing granulocytes in peripheral blood. In 6-week old young adult progeny, bone marrow CFU-E was depressed and spleen CFU-E increased in males exposed to 10 but not to 20 ppm *in utero*. In the 20 ppm group, there was a decrease in early nucleated RBC in the bone marrow and an increase in blast cells in the spleen. There were no effects on BW or BW gain, feed consumption and clinical signs in the dams, or on BW and structural abnormalities in the foetuses at any dose level.

In a subsequent study on the interaction between alcohol and inhaled benzene in mice, CFU-E was significantly depressed in the liver of 16-day old male (but not female) foetuses exposed *in utero* to 10 ppm benzene for 6 h/day on GD 6-15 (Corti & Snyder, 1996). This study comprised a total of 9 exposed and 12 control litters.

The embryotoxicity of benzene and its major metabolites has also been investigated *in vitro* in GD 10-12 rat conceptuses. There were no toxic effects at concentrations of 0.4-0.8 mM (32-64 mg/L) benzene (Brown-Woodman et al, 1994; Chapman et al, 1994). Phenol was not toxic at 1.6 mM, but caused 100% lethality at 0.2 mM in the presence of several CP450-dependent bioactivating systems. In the absence of metabolic activation, catechol, hydroquinone, and quionone each produced 100% lethality at 0.1 mM and the combination of phenol and hydroquinone showed a greater than additive effect (Chapman et al, 1994).

Conclusions

In several studies in pregnant animals exposed to benzene by inhalation or ingestion, there was a small, but statistically significant decrease in foetal BW and an increase in the incidence of minor skeletal abnormalities at dose levels at which there was no evidence of maternal toxicity. Major structural abnormalities and abortions only occurred at dose levels that also caused marked toxicity in the dams. As such, benzene can be characterised as foetotoxic, but not teratogenic. Based on

adequately reported rat studies that found foetal effects in the absence of any signs of maternal toxicity, the inhalation NOAEL for foetal growth disturbances is 40 ppm (Coate et al, 1984), with a LOAEL of 100 ppm (Coate et al, 1984; Green et al, 1978). Reliable oral effect levels cannot be determined from the available data.

In a small number of pregnant mice, inhalation of 10-20 ppm benzene resulted in specific adverse effects on multipotential haematopoietic stem cells (colony forming units) and other blood cells in the liver, bone marrow or spleen of the offspring (Corti & Snyder, 1996; Keller & Snyder, 1986, 1988). These effects occurred in the absence of any other signs of developmental toxicity and at levels similar to those that are known to be toxic to the blood and blood forming organs of adult mice (Section 10.4).

In vitro studies indicate that some benzene metabolites, including catechol, hydroquinone and quinone (but not phenol) are substantially more toxic to rat embryos than benzene itself.

10.6 Genotoxicity

The toxic effects of benzene on human genetic material have been investigated in numerous in vivo studies which are addressed in Section 11.6 below. As such, the assessment of studies conducted in animals and various in vitro systems is limited to an overview of the most significant findings. Unless otherwise indicated, the information presented is summarised from ATSDR (1997), IARC (1987), IPCS (1993) and USEPA (1998a).

In vitro tests

Tests with benzene itself have predominantly produced negative results in conventional in vitro gene mutation assays in bacteria and mammalian cell systems, with and without metabolic activation. In vitro assays for chromosome aberrations have also generally been negative, unless special precautions were taken to prevent the evaporation of benzene from the test system (Randall et al, 1993). Likewise, conventional in vitro tests for DNA breaks, unscheduled DNA synthesis and DNA synthesis inhibition have produced inconsistent results. However, sister chromatid exchanges (SCE), micronuclei (MN) and unscheduled DNA synthesis have been induced in vitro by metabolites such as catechol, hydroquinone and/or quinone, and DNA adducts with phenol, hydroquinone and quinone have been detected in a number of in vitro systems. Benzene itself has recently been shown to induce morphological transformation, gene mutations through base substitutions, and aneuploidy in Syrian hamster embryo cells, but is less potent than its metabolites (Tsutsui et al, 1997). In the alkaline single cell gel electrophoresis (Comet) assay, pronounced, contact time-dependent DNA damage has been detected in non-cycling (G_0) human LC after treatment not only with catechol, hydroquinone, quinone, 1,2,4-trihydroxybenzene or muconic acid, but also with benzene itself (Anderson et al, 1995).

Tests in *Drosophila*

Benzene was consistently negative in the sex-linked recessive lethal test in *Drosophila melanogaster*, which is a specific, but insensitive test for the potential of chemicals to cause heritable gene mutations and chromosome aberrations. However, benzene has been shown to induce a statistically significant number of

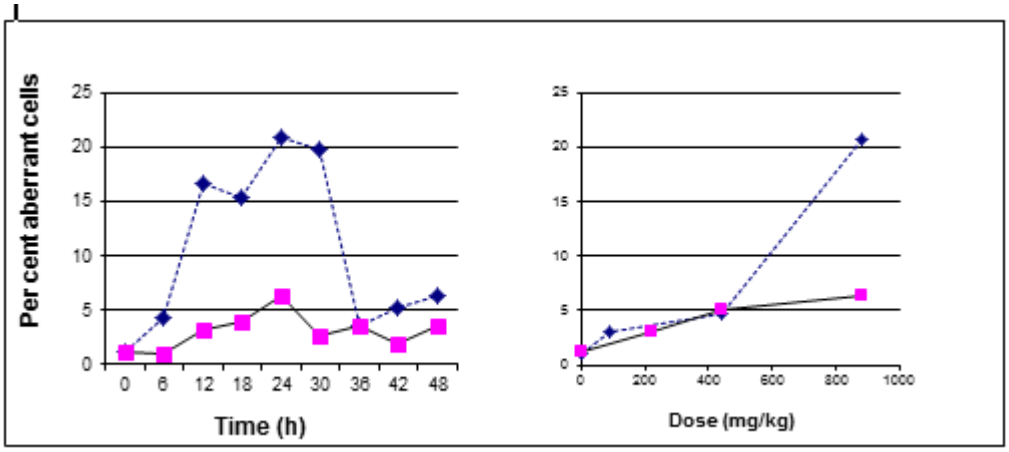
so-called delayed lethal mutations, which may be the result of heritable mutations in one rather than in both DNA strands of the X chromosome (Kale & Kale, 1995).

In vivo tests in rodents

There is ample evidence that benzene is genotoxic in a broad spectrum of *in vivo* tests in rodents, in which the chemical was administered by inhalation, oral gavage or parenteral injection. These include tests for SCE and MN induction in peripheral blood cells, bone marrow cells, foetal liver cells, lung fibroblasts (Ranaldi et al, 1998), and Zymbal gland cells (Angelsanto et al, 1996); gene mutations in LC, lung and spleen cells; chromosome aberrations in LC, bone marrow cells, spleen cells, and spermatogonia; and DNA adducts in nucleated blood and bone marrow cells. Furthermore, many of these effects have been shown to be mitigated by inhibitors of benzene metabolism and reproduced by benzene metabolites such as hydroquinone and 1,2,4-trihydroxybenzene.

In an in vivo chromosome aberration study in male mice, the sensitivity and dose response to a single oral dose of benzene was found to differ markedly between bone marrow cells and differentiating spermatogonia, as illustrated in Figure 10.1 (Ciranni et al, 1991).

Figure 10.1: Chromatid aberrations excluding gaps in mouse bone marrow cells (broken lines) and spermatogonia (solid lines) at 6-48 h after oral treatment with 880 mg/kg benzene (left) and at 24 h after oral treatment with 88, 220, 440 or 880 mg/kg benzene (right) (Ciranni et al, 1991)



10.7 Carcinogenicity

Table 10.3 highlights the principal findings in the 23 carcinogenicity tests that have been reported in the open literature. They include oral gavage studies in B6C3F1, RF/J and Swiss mice and F344, Sprague-Dawley and Wistar rats and inhalation studies in AKR, C57BL, CBA, CD-1 and HRS mice and Sprague-Dawley rats.

Table 10.3: Principal findings in inhalation (I) and oral gavage (O) carcinogenicity studies in mice and rats

Strain	I/O	Protocol	Principal findings*	Reference
Mice				
AKR†	I	0, 100 ppm for 6 h/day, 5	No increase in tumour incidence	Snyder et al.

		days/week for life (72 weeks)		(1980)
	I	0, 300 ppm for 6 h/day, 5 days/week for life (28 weeks)	No increase in tumour incidence	Snyder et al. (1978)
$B6C3F_1$	O	0, 25, 50, 100 mg/kg/day for 5 days/week, 103 weeks	Harderian gland tumours, lung tumours, lymphoma, mammary gland carcinoma, ovarian granulosa cell and mixed benign tumours, preputial gland carcinoma, Zymbal gland carcinoma	NTP (1986)
C57BL‡	I	0, 300 ppm 6 h/day, 5 days/week for 16 weeks, with life-long observation (about 110 weeks)	Lymphoma, ovarian tumours, Zymbal gland carcinoma (no statistical analysis)	Cronkite et al. (1985)
	I	0, 300 ppm for 6 h/day, 5 days/week for life (70 weeks)	Lymphoma	Snyder et al. (1980)
	I	0, 300 ppm 6 h/day, 5 days/week, 1 out of every 3 weeks for life (118 weeks)	Zymbal gland carcinoma	Snyder et al. (1988)
	I	0, 1200 ppm 6 h/day, 5 days/week for 10 weeks, with life-long observation (about 146 weeks)	No increase in tumour incidence	Snyder et al. (1988)
CBA§	I	0, 100 ppm for 6 h/day, 5 days/week for 16 weeks, with life-long observation (about 135 weeks)	Unspecified, non-hepatic, non-haematopoietic tumours	Cronkite et al. (1989)
	I	0, 300 ppm for 6 h/day, 5 days/week for 16 weeks, with life-long observation (about 115 weeks)	Non-hepatic, non- haematopoietic tumours (including Harderian gland carcinoma, lung adenocarcinoma, mammary gland carcinoma, neoplasms resembling acute myeloblastic and chronic granulocytic leukaemia, Zymbal gland carcinoma)	Cronkite et al. (1989)
	I	0, 300 ppm for 6 h/day, 5 days/week for 16 weeks, with life-long observation (78 weeks)	Lung adenoma, lymphoma, preputial gland carcinoma	Farris et al. (1993)
CD-1	I	0, 300 ppm for 6 h/day, 5 days/week for life (not further specified)	Sporadic cases of suspected myeloid leukaemia ($p = 0.147$)	Goldstein et al. (1982)
	I	0, 300 ppm for 6 h/day, 5 days/week 1 out of every 3 weeks for life (about 60 weeks)	Lung adenoma	Snyder et al. (1988)
	I	0, 1200 ppm for 6 h/day, 5 days/week for 10 weeks, with life-long observation (about 130 weeks)	Lung adenoma, Zymbal gland carcinoma	Snyder et al. (1988)
HRS	I	0, 400 ppm for 6 h/day, 5 days/week for 26 weeks	No leukaemia or lymphoma in either hr/hr (leukaemia-prone) or hr/– (leukaemia-resistant) strains	Stoner et al. (1980), as cited in Cronkite et al. (1985)
RF/J	O	0, 500 mg/kg/day for 5 days/week, 52 weeks	Lymphatic neoplasms, lung tumours, mammary gland carcinoma (no statistical analysis)	Maltoni et al. (1989)
Swiss	O	0, 500 mg/kg/day for 5 days/week, 78 weeks	Lung adenomas, mammary gland carcinoma, Zymbal gland carcinoma (no statistical analysis)	Maltoni et al. (1989)

Table 10.3: Continued

Strain	I/O	Protocol	Principal findings	Reference
Rat				

F344	O	0, 50, 100, 200 mg/kg/day in males and 0, 25, 50, 100 mg/kg/day in females for 5 days/week, 103 weeks	Oral cavity tumours, skin tumours, Zymbal gland carcinoma	NTP (1986)
Sprague-Dawley	I	0, 100 ppm for 6 h/day, 5 days/week for life (123 weeks)	No increase in tumour incidence	Snyder et al. (1984)
	I	0, 300 ppm for 6 h/day, 5 days/week for life (99 weeks)	No increase in tumour incidence	Snyder et al. (1978)
	I	0, 200-300 ppm for 4-7 h/day, 5 days/week, 104 week	Oral cavity carcinoma, Zymbal gland carcinoma (no statistical analysis)	Maltoni et al. (1989)
	O	0, 50, 250 mg/kg/day, 5 days/week, 52 weeks	Mammary gland tumours (lowest dose level only), Zymbal gland carcinoma in females (no statistical analysis)	Maltoni et al. (1989)
	O	0, 500 mg/kg/day, 5 days/ week, 104 weeks	Forestomach carcinomas, liver angiosarcomas, nasal and oral cavity carcinomas, skin carcinomas, Zymbal gland carcinoma (no statistical analysis)	Maltoni et al. (1989)
Wistar	O	0, 500 mg/kg/day, 5 days/week, 104 weeks	Nasal and oral cavity carcinoma, Zymbal gland carcinoma (no statistical analysis)	Maltoni et al. (1989)

* Positive findings were statistically significant ($p < 0.05$) unless otherwise indicated.
† Carries a virus causing spontaneous lymphoma in 90% of animals by 52 weeks of age.
‡ Carries a virus yielding a high incidence of lymphoma from exposure to radiation, immunosuppression and certain carcinogens.
§ Highly susceptible to radiation-induced thymic lymphoma.

There was a frequent association between benzene exposure and the occurrence of solid tumours in epithelia of the mouth, nasal cavities, lung alveoli, Harderian, Zymbal, preputial and mammary glands, and the ovary.

With regard to the blood and lymphatic system, the incidence of lymphoma was elevated in several studies conducted in B6C3F1, C57BL, CBA and RF/J mice. There was also a statistically significant increase in the incidence of lesions resembling acute myeloblastic and chronic granulocytic leukaemia in a study in CBA mice exposed to 300 ppm benzene for 16 weeks (Cronkite et al, 1989). In addition, 3/40 CD-1 mice exposed to 300 ppm and 1/40 Sprague-Dawley rats exposed to 100 ppm benzene developed suspected myeloid leukaemia after 27-38 weeks of exposure (Goldstein et al, 1982; Snyder et al, 1984). However, the increase in lymphoma incidence was limited to strains where this is a common spontaneous tumour type and the lesions resembling leukaemia may not have been malignant but rather an intense proliferation of myeloid cells caused by infections or necrotic processes in benzene-induced tumours in other organs (Farris et al, 1993). Furthermore, early findings of lymphoma or leukaemia-like lesions in a given strain have not been consistently reproduced in later studies (Farris et al, 1993; Snyder et al, 1988).

Some of the target organs in rodents such as the forestomach, Harderian, Zymbal and preputial glands have no anatomical equivalent in humans. Moreover, human exposure to benzene is not associated with tumours of the mouth, nasal cavities or lung alveoli (see Section 11). However, as there is limited evidence of an elevated risk of malignant melanoma and breast cancer in humans exposed to benzene-containing products, skin and mammary tumours are further analysed below.

Skin tumours

The incidence of skin tumours was increased in F344 and Sprague-Dawley rats in 2-year oral gavage studies (NTP, 1986; Maltoni et al, 1989). By contrast, no skin tumours developed in groups of 10 mice after oral, subcutaneous or topical application of 800 mg/kg benzene followed 4 weeks later by topical application of the tumour promoter 12-*o*-tetradecanoylphorbol-13-acetate 3 times a week for 20 weeks (Bull et al, 1986). Furthermore, although benzene was once widely used as a solvent in tests for skin cancer induction in mice resulting in large numbers of controls being topically exposed to benzene alone, there has been no indication that it induced skin tumours in these models (IARC, 1982a).

In F344 rats, skin tumours were found on the face, back, flank, and other locations. Microscopically, they represented a spectrum from pure squamous cell papillomas or carcinomas to mixed tumours containing basal cell, sebaceous gland or hair follicle elements. By incidental tumour tests, the incidence was elevated in male rats at 200 mg/kg/day (12/50 vs. 1/50 in controls; $p < 0.01$), but not at 50 mg/kg/day (7/50) or 100 mg/kg/day (5/50), or in female rats treated with 25, 50 or 100 mg/kg/day. Based on mortality and BW data, high dose male rats were probably exposed to benzene levels that exceeded the maximal tolerated dose (NTP, 1986).

In Sprague-Dawley rats, skin carcinomas (not further specified) occurred in 9/40 male animals administered 500 mg/kg/day by oral gavage for 2 years. The incidence was zero in male controls and treated females (Maltoni et al, 1989). The authors did not comment on the statistical significance of these results, however, when analysed for this assessment, the difference in incidence between exposed and control males was statistically significant ($p < 0.05$; test for exact confidence limits). Compared to their controls, male rats had an increased survival rate but a reduction in BW that ranged from 6-18% during the course of the study (Maltoni et al, 1983).

Mammary gland tumours

Mammary tumours have been found in $B6C3F_1$, CBA, RFJ and Swiss mice and Sprague-Dawley rats (Cronkite, 1986; NTP, 1986; Maltoni et al, 1989).

In a 2-year oral bioassay in $B6C3F_1$ mice, benzene induced a significantly elevated incidence of carcinomas and carcinosarcomas in mid- and high-dose females, with a trend for dose-dependence (Table 10.4). The carcinomas often showed extensive squamous cell metaplasia, whereas the carcinosarcomas contained a prominent spindle-cell component resembling malignant fibroblasts. The historical incidence of mammary gland carcinoma in this strain is approximately 1% (NTP, 1986).

Table 10.4: Mammary gland lesions in female $B6C3F_1$ mice in a 2-year oral carcinogenicity study (NTP, 1986)

Lesions	Controls	25 mg/kg/day	50 mg/kg/day	100 mg/kg/day
Hyperplasia	2/49 (4%)	4/45 (9%)	2/50 (4%)	1/49 (2%)
Carcinoma	0/49 (0%)	2/45 (4%)	5/50 (10%)*	10/49 (20%)†
Carcinosarcoma	0/49 (0%)	0/45 (0%)	1/50 (2%)	4/49 (8%)*

* $p < 0.05$ (incidental tumour tests).
† $p < 0.01$ (incidental tumour tests).

Among male and female CBA mice exposed to 100 ppm benzene for 6 h/day, 5 days/week for 16 weeks, 20% had developed mammary gland tumours at follow-up

102 weeks after the last exposure (Cronkite, 1986). Details on tumour incidence in concurrent or historical controls were not given and the histopathology of the tumours was not described, although a later publication refers to them as adenocarcinomas (Cronkite et al, 1989).

In female RF/J mice administered 500 mg/kg/day by oral gavage for 52 weeks, the incidence of mammary carcinomas was 22.5%, compared to 2.5% in controls. In female Swiss mice receiving the same treatment for 78 weeks, the incidence was 47.5% compared to 5.0% in controls (Maltoni et al, 1989). The statistical significance of these findings is not discussed in the paper. When analysed for this assessment, the incidence in exposed females was significantly different from controls ($p < 0.05$; test for exact confidence limits) in Swiss but not in RF/J mice.

In female Sprague-Dawley rats given benzene by oral gavage for 1 year, the incidence of total/malignant mammary tumours was 53.3/13.3% in controls, 73.3/13.3% in animals treated with 50 mg/kg/day, and 45.7/20.0% in animals treated with 250 mg/kg/day. In female rats given 500 mg/kg/day for 2 years, the incidence was 32.5/17.5% compared to 42.0/14.0% in controls (Maltoni et al, 1989). The tumours comprised fibroadenomas, adenocarcinomas and carcino-sarcomas similar to the spontaneous mammary gland tumours commonly found in ageing female Sprague-Dawley rats (Maltoni et al, 1983). The investigators did not report on the statistical significance of their findings. When analysed for this assessment, there was no difference between any of the groups in the incidence of either total or malignant mammary tumours ($p > 0.05$; test for exact confidence limits).

Conclusions

The available carcinogenicity studies provide clear evidence of a causal relationship between benzene exposure and malignant neoplasms in mice and rats. The tissues most commonly involved are various glandular or non-glandular epithelia of the oral cavity, nasal cavity, lungs and skin (Table 10.3). The incidence of lymphoma was increased in several studies, but only in mice where this is a common spontaneously occurring tumour type. In one study in mice, there was a significant increase in bone marrow lesions described as resembling myeloblastic or granulocytic leukaemia (Cronkite et al, 1989), but this may have been the result of an intense inflammatory response (Farris et al, 1993). As such, a proven reproducible animal model for benzene-induced leukaemia is not available.

The lowest exposure levels associated with an increase in tumour incidence in rodents was 100 ppm by inhalation for 16 weeks in CBA mice and 25 mg/kg/day in a 2-year oral gavage test in $B6C3F_1$ mice and F344 rats (Cronkite, 1989; NTP, 1986). However, there was no increase in tumour incidence in two out of three inhalation tests in rats exposed to 100-300 ppm benzene for 99-123 weeks (Maltoni et al, 1989; Snyder et al, 1978, 1984).

There was an increased incidence of epithelial skin tumours in male rats in two 2-year oral bioassays. In both studies, however, the increase only occurred at the highest dose level tested (200 and 500 mg/kg/day respectively), which may have exceeded the maximum tolerated dose. Mammary gland carcinomas were increased in female mice at 50 and 100 mg/kg/day in a 2-year and at 500 mg/kg/day in a 78-week test.

10.8 Summary and conclusions

Taken together, the tests summarised above clearly demonstrate that benzene is not highly acutely toxic to experimental animals, whereas it is a potent, multi-organ toxicant by repeated administration. The target organs include the CNS, skin, eyes, immune system, blood and blood forming organs, gonads and developing foetus. Benzene is also toxic to genetic material and induces a variety of solid tumours, including mammary cancer in female mice.

The only consistently reported acute systemic effects are CNS depression and cardio-respiratory arrest. In rats, the median lethal dose is 810-9900 mg/kg by mouth and 13,700 ppm by 4-h inhalation.

Topically, benzene appears to be irritating to the skin and eyes.

Of the available repeated dose oral studies, only the US National Toxicology Program's 2-year bioassays in mice and rats have been conducted and reported in full compliance with GLP and other internationally recognised quality standards (NTP, 1986). In these studies, benzene administered by oral gavage induced leukopoenia and lymphocytopoenia and an increase in the incidence of malignant tumours at the lowest dose level tested, namely 25 mg/kg/day in male and female mice and female rats and 50 mg/kg/day in male rats. In other oral studies of a lesser quality, benzene produced leukopoenia in mice and rats and signs of immunosuppression in mice at dose levels from 8-12 mg/kg/day.

With regard to repeated exposure by inhalation, which is the predominant route in humans, the studies available for assessment were either poorly reported or inadequate for the determination of dose-response relationships for other reasons, such as an insufficient number of animals or range of exposure levels. Nonetheless, the weight of evidence indicates that the following approximate effect levels are likely to apply:

- In mice but not in rats, subtle signs of neurobehavioural stimulation may be detectable at vapour concentrations around 1 ppm, whereas gross CNS impairment only occurs at and above 1000 ppm. ;
- There are functional disturbances of the immune system at and above 10 ppm in mice, but no such effects in rats below 400 ppm. The NOAELs were determined to be 0.44 and 200 ppm for mice and rats respectively;
- Abnormal blood counts and morphological abnormalities in blood forming organs are found at and above 10 ppm in mice (including mouse foetuses exposed *in utero*) and at and above 100 ppm in rats. As effects were observed at all concentrations tested, a NOAEL could not be determined;
- There are degenerative changes in the gonads at 300 ppm in mice, but not in rats. The NOAEL was determined to be 30 ppm for mice ;
- Benzene is foetotoxic, but not teratogenic in rats and mice exposed during pregnancy at levels in the 100-500 ppm range, with an inhalation NOAEL for foetotoxicity of 40 ppm in rats; and
- The incidence of solid tumours is increased in mice exposed to 100-300 ppm benzene for 16 weeks, but not consistently in mice exposed to 1200 ppm for 10 weeks or in rats exposed to 100-300 ppm for 99-123 weeks.

The relevance of these findings for human risk characterisation will be examined in Section 13, in the context of the interspecies variations in benzene metabolism

addressed in Section 9, the human health effects reviewed in Section 11, and the molecular mechanisms of action discussed in Section 12.

11. Human Health Effects

The literature on human health effects of benzene is extensive and contains data on hundreds of thousands of people. This section summarises and reviews studies that are relevant to the characterisation of the toxic effects of benzene and the corresponding effect levels. Because of the nature of the available studies, the review is predominantly based on findings in people who were exposed to benzene at work or held jobs with the potential for exposure to the chemical.

The findings reported below must be interpreted with caution, as they rely on inherently uncertain information about the exposure of individuals or populations to benzene, which was either inferred or, at best, estimated from limited monitoring data. Furthermore, in the vast majority of cases there was co-exposure to other chemicals. These may be hazardous in their own right or inhibit the metabolism of benzene to toxic metabolites, thus resulting in either an over- or underestimation of the toxic potential of benzene. For example, the aromatic organic solvent toluene may interfere with the metabolism of benzene as well as cause brain atrophy and developmental toxicity (IPCS, 1985; Wilkins-Haug, 1997); some of the polycyclic aromatic hydrocarbons (PAHs) that occur in petroleum, coal gas, coal tar and vehicle exhaust are genotoxic and cause anaemia, immunosuppression and non-melanoma skin cancer (IPCS, 1998); and 1,3-butadiene found in vehicle exhaust is genotoxic and may increase the risk of blood and lymphatic cancers (IARC, 1999). Moreover, many studies are not controlled for confounding by smoking, although tobacco smoke contains benzene (see Section 16.1) and several studies have found an association between active smoking and leukaemia and reproductive effects such as semen quality and pregnancy outcome (Brownson et al, 1993; Vine, 1996; Werler, 1997).

Unless otherwise mentioned, all results were statistically significant in comparison with unexposed controls ($p < 0.05$). In occupational studies, chronic inhalation exposures refer to 8-h TWA (TWA_8) concentrations. Technical terms used to describe epidemiological study designs and statistics have the meaning given in Last (1995).

11.1 Acute toxicity

Cases of acute intoxication have occurred because of workplace accidents and in persons sniffing benzene-containing products for recreational purposes (Avis & Huton, 1993; Barbera et al, 1998; Tauber, 1970; Winek & Collum, 1971). The approximate lethal dose is 20,000 ppm by inhalation for 5-10 min, or 125 mg/kg by ingestion, whereas exposure to 25 ppm for 8 h is reported to be without clinical effects (Gerarde, 1960; Thienes & Haley, 1972, as cited in IPCS, 1993). No adverse effects were reported in three kinetic studies in healthy volunteers exposed to benzene levels of 26-42 ppm for 6 h, 52-62 ppm for 4 h or 47-110 ppm for 2-3 h (Berlin et al, 1980; Nomiyama & Nomiyama, 1974a; Srbova et al, 1950). Clinical signs at higher exposure levels include generalised symptoms such as dizziness, headache and vertigo at levels of 250-3000 ppm, leading to drowsiness, tremor, delirium and loss of consciousness at 700-3000 ppm (ATSDR, 1997; USEPA, 1998c). Unless fatal, the CNS symptoms are reversible following cessation of exposure. Autopsy findings are typical of cardio-respiratory arrest.

11.2 Irritation

Aspiration of liquid benzene has been observed to cause immediate pulmonary oedema and bleeding at the site of contact (Gerarde, 1960). Benzene vapours have been reported to cause eye and mucous membrane irritation in workers exposed at 33-59 ppm and irritation of the skin, nose, mouth and throat at levels ≥60 ppm (Midzenski et al, 1992; Yin et al, 1987a). Acute tracheitis, laryngitis, bronchitis and massive haemorrhage of the lungs were observed in a youth who died from an overdose of intentionally inhaled benzene (Winek & Collum, 1971). Second degree burns to the face, trunk and limbs were reported in chemical cargo ship crew accidentally exposed to fumes at a concentration resulting in death within minutes (Avis & Hutton, 1993).

11.3 Sensitisation

There are no reports of skin or respiratory sensitisation to benzene in humans.

11.4 Repeated dose toxicity (other than carcinogenicity)

11.4.1 Neurological effects

Yin et al. (1987a) found a dose-dependent increase in the prevalence of dizziness and headache in a survey of female Chinese workers in the footwear and printing industries. This study included 87 unexposed controls and two groups exposed to benzene at levels ranging from 1-40 ppm (40 cases) or 41-210 ppm (47 cases). In the two groups combined, benzene levels averaged 59 ppm. Both groups were co-exposed to low levels of toluene (≤16 ppm).

Peripheral neuropathy was reported in a small number of Turkish workers with benzene-induced aplastic anaemia or preleukaemia (Baslo & Aksoy, 1982). At a benzene-manufacturing petrochemical plant in Estonia, frequent headaches at the end of the shift, tiredness, sleep disturbances and memory loss occurred in 61% of workers exposed to levels in the 2-16 ppm range for several years (Kahn & Muzyka, 1973). In a survey of deck crew on nine Norwegian petroleum product tankers, headache, dizziness or nausea were reported by 5/11 workers exposed to >0.3 ppm benzene whereas there were no CNS complaints in 10 workers exposed to ≤0.3 ppm (Moen et al, 1995). Psychological examinations in 28 men exposed to a mixture of benzene (0.56-1.8 ppm), toluene (2.1-9.8 ppm) and xylenes (0.43-12 ppm) indicated diminished function of some cortical centres and impaired motor reaction time (Sikora & Langauer-Lewowicka, 1998). Varelas et al. (1999) used computed tomography imaging to visualise abnormal calcifications and cortical atrophy in the brains of 122 petrol station workers, taxi and bus drivers in central Athens. The subjects had been in their present employment for a minimum of 3 and an average of 16-17 years. Whereas blood lead levels were unremarkable in all three groups, there was mild to moderate cortical atrophy in 19/37 petrol station workers, 14/44 taxi drivers and 14/41 bus drivers. The prevalence in petrol station workers was higher than in taxi and bus drivers and unrelated to smoking or alcohol habits. None of these studies included an unexposed control group.

11.4.2 Effects on the immune system

There was a decrease in circulating IgA and IgG immunoglobulins, accompanied by an increase in IgM and an elevated occurrence of leukocyte auto-antibodies, in

painters co-exposed to benzene, toluene and xylenes at air levels ranging from 3-57, 21-71 and 27-680 ppm respectively (Lange et al, 1973a, 1973b). In workers co-exposed to benzene, toluene and xylenes at air levels that averaged from 1-35, 2-32 and 4-28 ppm respectively over an 11-year period, total LC and T-LC counts were slightly lower in workers exposed for 55-122 months than in an unexposed control group, whereas there were no differences in LC function as determined by LC transformation and tuberculin tests (Moszczynsky & Lisiewicz, 1984).

11.4.3 Cardiovascular effects

Kotseva & Popov (1998) conducted a routine cardiological examination of a sample of male and female petrochemical workers aged 20-60 years. It included 118 workers concomitantly exposed to ≤20 ppm benzene and low levels of toluene and petrol as well as 154 workers concomitantly exposed to <3 ppm benzene, ≤32 ppm xylenes and low levels of toluene and petrol. Compared to unexposed controls matched for age, sex, salt intake, smoking and body mass index, the prevalence of arterial hypertension and minor electrocardiographic abnormalities was approximately twice as high in the exposed groups.

11.4.4 Haematological effects

Benzene has been known to be toxic to the blood for more than a hundred years and in the past was sometimes given orally to leukaemia patients to reduce WBC count (ATSDR, 1997; Landrigan, 1996).

Occupational exposure

Table 11.1 summarises a number of surveys of non-cancerous blood disorders in workers exposed to airborne benzene. Overall, these studies point to a strong association between recent or current exposure to airborne benzene and the occurrence of decreased ALC, WBC, RBC and Plt counts, Hb and haematocrit (Hct), and an increase in MCV. Such cases are sometimes described as ‘benzene poisoning’ (BP). Depending on the pattern and magnitude of these changes and the histological findings in a bone marrow biopsy, they may be clinically diagnosed as lymphocytopoenia, leukopoenia, anaemia, thrombocytopoenia, pancytopoenia, agranulocytosis, myelofibrosis, or aplastic anaemia. They may be accompanied by clinical signs such as paleness, increased susceptibility to infections, and a tendency to bruising and bleeding. BP is generally reversible upon cessation of exposure, except aplastic anaemia which may be fatal or progress to acute myeloid leukaemia (AML) (Aksoy, 1989).

Among the studies summarised in Table 11.1, three surveys comprising a total of 795 workers found no adverse haematological effects from long-term benzene exposure at levels averaging 0.55, 0.81 and 0.53 ppm respectively (Collins et al, 1997; Khuder et al, 1999; Tsai et al, 1983). These studies have limitations with respect to blood analysis methodology, exposure assessment and/or control for confounders such as smoking and co-exposure to other chemicals. Nevertheless, taken together they indicate that the NOAEL for bone marrow toxicity is likely to be >0.5 ppm.

Table 11.1: Summary of haematological effects in workers exposed to airborne benzene

Industry	Country	Benzene exposure (TWA_8)*	Condition(s) observed†	Comments	Reference
Chemical	USA	Range = 0.01-1.40 ppm for an average of 7.3 years	In 200 exposed compared to 268 non-exposed workers there was no consistent benzene-related effect on haematology surveillance indicators		Collins et al. (1991)
	USA	Mean (range) = 0.55 (0.01-88) ppm, with <5% of workers exposed to levels >2 ppm	In 387 exposed compared to 553 non-exposed workers there was no difference in the prevalence of decreased ALC, RBC, WBC or Plt counts, decreased Hb levels, or increased MCV values		Collins et al. (1997)
	USA	Mean >24 ppm for an average of 9.6 years	10/10 workers had increased MCV values and 9/10 also had decreased Hb levels		Fishbeck et al. (1978)
	USA	From <2 to about 30 ppm for 1-20 years	Marginally lower RBC count and total bilirubin in 282 exposed workers compared to an equal number of matched controls	2/282 exposed workers died from leukaemia during the study period (1967-74)	Townsend et al. (1978)
Coke oven by-products	USA	0.1-31.4 ppm	No differences in WBC, RBC or Hb values between groups of 17-37 workers with no, low (<2 ppm-years), intermediate (2-20 ppm-years) or high (>20 ppm-years) exposure		Hancock et al. (1984)
Footwear manufacturing	Turkey	15-210 ppm for 3 months to 17 years	Increased incidence of reduced WBC and/or Plt or CBC counts in 217 workers compared to 100 controls matched for sex, age and general living conditions	Exposed to adhesives. No correlation with duration of exposure	Aksoy et al. (1971)
	Croatia	Median (range) = 5.9 (1.9-14.8) ppm (area monitoring)	Decreased mean Hb concentration and percentage of B-LC and increased MCV and band neutrophils in 49 exposed females compared to 27 unexposed controls	Benzene contaminated glues, cleaners and paints; co-exposed to 11-50 ppm toluene	Bogadi-Šare et al. (1997, 2000)
Miscellaneous uses of benzene-based solvents	Italy	>20 ppm	Of 301 workers referred to an occupational health clinic with suspected benzene intoxication, 153 had transient and 39 progressive bone marrow abnormalities; 11 died from aplastic anaemia and 21 developed cancers of the blood and lymphatic system	There was a highly significant correlation between severity of bone marrow disease and current or recent exposure	Vai et al. (1989)
	China	Median (range) current personal exposure = 31 (1.6-328.5) ppm, with an average duration of exposure of 6.3 years	In 44 exposed workers compared to an equal number of controls matched for sex, age, cigarette and alcohol consumption, WBC, ALC, Plt, RBC and Htc levels were reduced and MCV values increased. In 11 workers exposed to a median (range) level of 7.6 (1-20) ppm, only ALC was decreased	No correlation between any haematological parameter and cumulative exposure	Rothman et al. (1996a, 1996b)
	China	Mean (range) = 5.8 (0.7-139) ppm (assessment method not specified)	26% of 326 exposed workers had leukopoenia (WBC count <4.5 x 10^9/L) compared to 8.9% of 236 non-exposed workers		Xia et al. (1995)
	China	Mean (maximum) = 59.2 (210) in women and 47.9 (210) ppm in men, for an average of 5 years	Decrease in ALC in 83 exposed women compared to 85 unexposed controls, but no differences between 61 exposed men and 44 unexposed controls	Co-exposed to 6-7 ppm toluene	Yin et al. (1987a)

Table 11.1: Continued

Industry	Country	Benzene exposure (TWA_8)	Condition(s) observed	Comments	Reference
Petroleum refining	Canada	Mean (range) = 0.81 (0.14-2.08) ppm for an average of 10 years	In 105 exposed workers, levels of WBC, RBC, Hb, MCV and Plt were generally in the low normal range. MCV and Plt values were negatively correlated with duration of employment, but not with individual benzene exposure		Khuder et al. (1999)
	USA	Median = 0.53 ppm	All haematological parameters generally within normal limits in 303 workers followed from 1959-1980		Tsai et al. (1983)
	UK	≤10 ppm	In 66 exposed compared to 33 non-exposed workers, there was no difference in various unspecified haematology and serum biochemistry values, except for a small increase in MCV values in exposed workers	All absolute MCV values were within the normal clinical range	Yardley-Jones et al. (1988)
Printing	USA	11-1060 ppm for 3-5 years	130/332 exposed workers showed signs of intoxication, including anaemia, increased MCV, reduced Plt counts and/or reduced WBC counts	No cases of relapse after benzene use was discontinued	Greenburg et al. (1939)
Rubber manufacturing	USA	Median exposure estimated at 30-54 ppm	In 161 workers hired between 1946-49, there was a 10% decline in WBC counts over the first 4 months of employment, but no consistent changes in RBC levels	Pliofilm cohort (Section 11.6.1)	Cody et al. (1993)
	USA	Mean estimated at 75 ppm during 1940-48 and at 15-20 ppm during 1949-78	In a longitudinal study of 459 workers, WBC, RBC and Hb levels decreased with total exposure between 1940-48, but showed no persistent trends over the ensuing 25 years	Pliofilm cohort (Section 11.6.1)	Kipen et al. (1988, 1989)
	USA	Range estimated at <5-34 ppm	Haematological screening data for 657 workers exposed between 1939 to 1975 showed a relationship between benzene exposure and the risk of a low WBC or RBC count which was stronger for WBC, with no evidence for a threshold exposure level	Pliofilm cohort (Section 11.6.1)	Ward et al. (1996)
	USA	Mean and range estimated at 100 and 50-500 ppm respectively	Following complaints of malaise, nausea, vomiting, and bleeding, blood counts were done on 1104 workers. ALC was abnormally low in 83 of them and 25 had severely reduced WBC, RBC and Plt counts. Of these, 9 were hospitalised, where aplastic anaemia was diagnosed by bone marrow biopsy; 3 died	Outbreak coincided with large war orders for synthetic rubber	Wilson (1942)
Ship repair	USA	60-600 ppm	9/15 workers exposed over several days from the degassing of shipboard tanks developed abnormal WBC, ALC, Hb, Plt and/or MCV values within 4 months. At 12 months, 7/15 still had one or more abnormal values	No relationship between blood changes and duration of exposure	Midzenski et al. (1992)
Tyre cord manufacturing	Turkey	0-110 ppm (area monitoring)	Decreased WBC count in 9, decreased Plt count in 4 and decreased WBC, RBC and Plt count in 1 of 231 exposed workers	Used thinners and solvents containing up to 6-8% benzene	Aksoy et al. (1987)

* TWA_8 = 8-h time-weighted average.
† CBC = complete blood cell count; for other abbreviations, see text.

In 44 Chinese workers exposed to a median benzene concentration of 31 ppm, with a range from 1.6-328.5 ppm, Rothman et al. (1996a, 1996b) found a decrease in WBC, RBC and Htc, an increase in MCV and an inverse correlation between ALC and benzene exposure. In a subgroup of these workers with a median exposure level of 7.6 ppm (range: 1-20 ppm), the lowest exposure group examined, the only haematological finding was a 16% decrease in ALC (1.6 x 10^9/L compared to 1.9 x 10^9/L in controls; p = 0.03). This study is small, but had a well-matched control group, minimal exposure to other chemicals (toluene and xylenes) and a dose-response relationship was established between ALC and benzene exposure as measured by repeated personal monitoring as well as with benzene metabolites in the urine.

Three other studies reported haematological effects in workers whose exposure was stated to range from 1.9-14.8 (median: 5.9), <5-34 and 0.7-139 (mean: 5.8) ppm respectively (Bogardi-Ŝare et al, 1997; Ward et al, 1996; Xia et al, 1995). However, these studies assessed exposure by means of area monitoring, a job-exposure matrix or unspecified methods and are therefore less suitable for dose-response characterisation.

Repeated exposure at higher levels was usually associated with clear signs of BP in some workers, with little or no relationship with cumulative exposure (Aksoy et al, 1971; Midzenski et al, 1992; Rothman et al, 1996a, 1996b; Vai et al, 1989).

Dosemeci et al. (1997) evaluated the statistical relationship between a clinical diagnosis of BP and benzene exposure in a subgroup of 412 cases drawn from a large Chinese cohort study (Hayes et al, 1997), which is described in detail in Section 11.6.1. The cumulative incidence of BP (defined as (1) a WBC count <4 x 10^9/L or a WBC count <4.5 x 10^9/L and a Plt count <80 x 10^9/L over several months, (2) occupational benzene exposure for ≥6 months and (3) exclusion of other causes of abnormal blood counts) rose sharply with increasing estimated intensity of benzene exposure over a period of 18 months prior to diagnosis, as shown by the following relative risks (RRs):

Exposure	<5 ppm	5-19 ppm	20-39 ppm	≥40 ppm
RR (95% CI)[6]	1.0 (reference level)	2.2 (1.7-2.9)	4.7 (3.4-6.5)	7.2 (5.3-9.8)

The clear trend with the level of exposure is noteworthy, even if the absolute exposure levels may have been underestimated, as discussed in Section 11.6.1 below.

The risk of BP developing into cancer was assessed in a subgroup of 11,177 benzene-exposed workers from the same Chinese cohort, 103 of whom had BP as defined above (Rothman et al, 1997). At follow-up 4-14 years after diagnosis, three of the cases had developed acute non-lymphocytic leukaemia (ANLL), non-Hodgkin's lymphoma (NHL) and myelodysplastic syndrome (MDS) respectively, compared to 6 cases of cancer of the blood and lymphatic system (including 2 with ANLL) and 1 case of MDS among the 11,074 workers without a diagnosis of BP (Table 11.2)[7]. The corresponding RRs indicate that a diagnosis of BP is associated with a 42-fold increase in the risk of pre-cancer or cancer of the blood and lymphatic system and with a 71-fold increase in the risk for ANLL/MDS. The RRs

[6] Throughout this section, ranges in brackets immediately following a relative risk (RR), odds ratio (OR), standardised mortality rate (SMR) or standardised incidence rate (SIR) represent the 95% confidence interval (CI) of the statistic.

[7] ANLL comprises all acute leukaemias other than acute lymphocytic leukaemia and can usually be equated to AML. MDS is a term that encompasses a variety of preleukaemic disorders.

changed little upon adjustment for cumulative exposure, indicating that the elevated cancer risk was not due to a higher cumulative exposure in the 103 BP cases.

Table 11.2: Benzene poisoning and subsequent risk of blood and lymphatic system cancer and related disorders (Rothman et al, 1997)

Parameter*	Without benzene poisoning	With benzene poisoning
Person-years of follow-up	122,620	848
RR (95% CI) of all pre-cancer or cancer of the blood and lymphatic system	1.0	42.3 (10.7-167.0)
RR (95% CI) of ANLL/MDS	1.0	70.6 (11.4-439.3)
RR (95% CI) of all pre-cancer or cancer of the blood and lymphatic system, adjusted for cumulative benzene exposure	1.0	47.4 (11.7-191.9)
RR (95% CI) of ANLL/MDS, adjusted for cumulative benzene exposure	1.0	61.3 (9.8-384.3)

* ANLL = acute non-lymphocytic leukaemia; CI = confidence interval; MDS = myelodysplastic syndrome; RR = relative risk.

Similarly, Vai et al. (1989) reported 28 cases of fatal blood cancer among 304 workers in Northern Italy who were hospitalised 15-35 years earlier with suspected BP, representing a 13.3-fold increase over the incidence in the general population in the region.

Public exposure

In the 1980s, the US Federal Department of Health and Human Services created a National Exposure Registry to assess the health consequences to the general population from long-term, low-level exposure to specific substances in the environment. A Benzene Subregistry was established in 1991 based on a population health survey in a community in Texas, USA, where tap water from the public water system was known to have contained ≤66 μg/L benzene since 1 January 1979 (Burg & Gist, 1998). The survey included 1,143 persons who had used contaminated water as the sole source of drinking, bathing and cooking for at least 30 consecutive days. These persons were administered a questionnaire and follow-up telephone interviews were conducted one and two years later. The questions asked were similar to those used in the National Health Interview Survey (NHIS) conducted every year in USA, except that the benzene questionnaire contained a qualifier relating to professional rather than self diagnosis of ailments, so as to minimise reporting bias. Findings were compared with concurrent NHIS data subsets matched for demographic variables and current and ever smoking rates. The initial response rate was 97%. There was a loss of 9% for each follow-up from the previous data collection.

The outcome of anaemia and related blood disorders within the last 12 months was reported in excess at all three data collections, with 40 observed vs. 14.1 expected cases at baseline, 32 observed vs. 11.6 expected cases at one year ($p < 0.01$), and 28 observed vs. 11.9 expected cases at two years. There was no difference in the reporting of cancer.

Conclusions

Several occupational surveys show that chronic exposure to benzene may lead to bone marrow depression, with manifestations that range from small reductions in blood count parameters to aplastic anaemia. The available data indicate that both the incidence and severity of this effect is dose-related. In a small, but reliable study, the only haematological effect in workers with a median (range) exposure of 7.6 (1-20) ppm (TWA_8) was a modest reduction in ALC. As this was the lowest exposure group examined, 7.6 ppm (TWA_8) is currently considered the best estimate for a LOAEL which may be close to the point of departure for the onset of haematological effects (USEPA, 1998c). An appropriate NOAEL has not been determined, but studies with various limitations indicate that it is likely to be >0.5 ppm (TWA_8).

The only available epidemiological study in the general population found an excess occurrence of anaemia and related disorders in a community whose tap water contained ≤66 μg/L benzene.

There is some evidence that bone marrow depression is associated with a substantially increased risk for ANLL/MDS.

11.4.5 Reproductive effects

Effects on fertility

Vara & Kinnunen (1946) reported a variety of gynaecological disorders in 12 female rubber workers who were exposed to unspecified levels of benzene on a daily basis. All 12 women had menstruation disorders, with sparse bleeding being the most common complaint. Although most of the women practised regular unprotected intercourse, only two of them had conceived since they started working and both pregnancies ended in spontaneous abortions (SAb) by the first trimester. Five had ovarian hypoplasia. Other common findings included excessive bruising, tiredness, dizziness, headaches and abnormal haematological findings, particularly low WBC and Plt counts.

Menstruation abnormalities have also been reported in surveys of female workers exposed to mixed aromatic hydrocarbons including benzene or to benzene, petroleum and chlorinated hydrocarbons in Poland and Russia in the 1960s (Michon, 1965; Mukhametova & Vozovaya, 1972; both as cited in ATSDR, 1997) and in female workers at a large petrochemical company in China (Thurston et al, 2000). Huang (1991) reported menstruation disorders in 49% of 223 Chinese leather footwear workers co-exposed to an average of 29 (range: 1-132) ppm benzene and 19 (range: 1-136) ppm toluene compared to a prevalence of 16% in unexposed controls ($p < 0.01$). There is no information on the smoking habits of the study population.

Benzene exposure as a risk factor for fecundability (time to pregnancy) was assessed in a Norwegian case-control study in 558 female dental surgeons and 450 high school teachers with at least one child (Dahl et al, 1999). Forty percent of the dentists reported daily exposure to a now discontinued disinfectant containing 0.25% v/v benzene. There was no difference in fecundability between dental

surgeons exposed to benzene and the controls. Potential confounders were considered, but the level of benzene exposure resulting from the disinfectant was not assessed.

In males, De Celis et al. (2000) studied the sexual functioning and semen profile of 48 Mexican rubbers workers exposed to a mixture of benzene (10-15 ppm), ethyl benzene (~50 ppm), toluene (~50 ppm) and xylenes (~12 ppm) for ≥2 years. Mean sperm count and the mean percentage of motile and normal sperm forms were reduced by 78, 62 and 24% respectively, compared to a group of 42 age-matched controls. There was no correlation between smoking or alcohol intake and alterations in the semen profile. Longer abstinence intervals may have contributed to the reduced sperm concentration and motility in exposed workers as they also had an increased prevalence of reduced libido.

Effects on pregnancy outcome

Huang (1991) investigated pregnancy outcome in 106 Chinese leather footwear workers co-exposed to an average of 29 ppm (range: 1-132) ppm benzene and 19 (range: 1-136) ppm toluene and 209 unexposed controls. Exposure to benzene and toluene was associated with an elevated incidence of SAb (5.8 vs. 2.4%; RR = 2.4; $p < 0.01$), whereas there was no difference in the incidence of preterm delivery or stillbirth. There is no information on the smoking habits of the study population.

Lindbohm et al. (1991) used Finnish census data, hospital records and industry-wide air monitoring results collected in 1975-82 to study the outcome of 11,570 pregnancies with potential paternal exposure to hazardous chemicals compared with a control group of 87,616 unexposed pregnancies. The RR for SAb was elevated for paternal exposure to solvents used in petroleum refineries, but did not differ significantly from unity when analysed separately for exposure to benzene. Although not quantified, benzene exposure levels were estimated to be low.

In a case-control study of female workers in the Finnish pharmaceutical industry which included 44 cases of SAb and 130 matched controls, Taskinen et al. (1986) found a non-significant association between abortion risk and benzene exposure (OR = 2.4 (0.5-12.0)).

The effects of parental occupational exposures on foetal development were investigated in an exploratory case-control study based on probability samples of live births and foetal deaths obtained by the US National Natality and Fetal Mortality survey conducted in 1980 among married women (Savitz et al, 1989). The samples included case groups of stillbirths (2096 mothers, 3170 fathers), preterm deliveries at <37 weeks of pregnancy (363 mothers, 552 fathers) and small-for-gestational age (SGA) infants (218 mothers, 371 fathers). Control pregnancies were drawn from the same survey. Occupational exposures within the last 12 months were defined by industry of employment and relative levels of exposure to individual agents estimated on the basis of a job-exposure linkage system. In computing the OR, adjustments were made for known confounding factors for each pregnancy outcome, such as child's race, receipt of prenatal care, mother's age, number of previous miscarriages, previous induced abortions and maternal smoking and alcohol consumption.

Overall, this study found a significantly elevated SGA risk in the offspring of fathers exposed to benzene at work (OR = 1.5 (1.1-2.3)), with a strong dose-response gradient. Benzene-exposed fathers of SGA infants included a large percentage of engine mechanics and repairers, welders and flame cutters. Maternal

benzene exposure showed a marginally significant association with stillbirths (OR = 1.3 (1.0-1.8)), which was supported by the demonstration of a dose-response gradient. In these mothers, benzene exposure was attributed mainly to work in the textile industry, barbering and cosmetology, with smaller contributions from the chemical, pharmaceutical and paint industries.

Stücker et al. (1994) evaluated the risk of SAb before 28 weeks among the spouses of 1077 male workers at two organic chemical factories in France, on the basis of exposures estimated by plant occupational physicians and questionnaires administered to the men and their wives. Medical records of the women were not examined. There was a total of 1739 pregnancies, of which 171 (9.8%) ended in SAb. The abortion rate was 8.8% in the wives of unexposed workers. Workers were divided into low (<5 ppm) and high (≥5 ppm) exposure categories depending on their estimated past exposure to benzene. After adjustment for maternal tobacco consumption, age and pregnancy order, the risk of SAb did not differ from unity in either of the two exposure groups. Similar results were obtained in analyses of first pregnancies only, and when pregnancy outcome was examined against a more detailed exposure graduation.

A Finnish case-control study of 206 cases of SAb in laboratory workers and 329 individually matched controls identified 11 cases of benzene exposure in the SAb group compared to 25 among the controls and concluded that benzene exposure was not a significant risk factor (Taskinen et al, 1994).

In a Chinese study, the overall risk of SAb in 3070 non-smoking, primiparous women employed at a large petrochemical complex and married to male workers at the same facility was 8.8% in chemical compared to 2.2% in non-chemical workers (Xu et al, 1998a). Benzene, toluene, xylenes and styrene exposure levels in 38 breathing zone samples collected throughout the complex averaged 0.86, 0.40, 0.50 and 0.03 ppm respectively. In analyses for exposure to specific chemicals during the first trimester of pregnancy, the estimated ORs of SAb were significantly elevated for benzene (2.5 (1.7-3.7)) and petrol (1.8 (1.1-2.9)).

Chen et al. (2000) conducted a prospective study of pregnant workers at a Chinese petrochemical plant producing benzene, toluene, xylenes, styrene and phenol. Compared with 459 mothers not exposed to organic solvents, there was a small reduction in birth weight (–58 g; 95% CI = –115 to –2 g) among 366 mothers exposed to 0.02-0.2 ppm benzene with or without other exposures.

Conclusions

There are several reports of menstruation disturbances in female workers and one of reduced semen quality in male workers exposed to benzene.

The available studies of pregnancy outcome have produced mixed results with regard to the risk for SAb. One study found an elevated SGA risk for fathers with occupational exposure to benzene. In another study, there was a marginally significant reduction in birth weight in infants whose mothers had been exposed to low levels of benzene at work.

However, all of the available studies have one or more limitations, such as multiple exposures, inadequate adjustment for other confounders and/or inadequately quantified exposure to benzene as well as other chemicals. Therefore, there is at present no convincing evidence from human studies that benzene may have adverse effects on reproduction.

11.4.6 Other health effects

Chronic tiredness and headache and large, spreading bruises on the arms and legs have been described in a number of workers exposed to benzene air levels in the order of 100-200 ppm (Helmer, 1944).

Yin et al. (1987a) conducted a survey of the prevalence of symptoms of intoxication in Chinese factory workers exposed to high levels of benzene or benzene and toluene for up to 40 years. There was a slight decrease in ALC in both groups. Sore throat and episodes of nose bleeding were common in all exposed workers and their frequency was related to benzene exposure levels.

In an uncontrolled case report, Davidoff et al. (1998) described a group of workers who began complaining about petrol odour and symptoms of nausea, headache, throat and eye irritation, and cough while tunnelling underneath a former service station site. An air sample from the tunnel contained 60 ppm benzene. Eight out of 30 randomly selected workers subsequently investigated in detail reported the post-incident onset of chemical hypersensitivities and other characteristics which, according to the authors, fitted conservative criteria for the diagnosis of multiple chemical sensitivities syndrome.

11.5 Genotoxic effects

Several occupational studies conducted over the past 30 years point to a link between a number of unstable or stable, numerical or structural chromosome aberrations and benzene exposure (ATSDR, 1997; IPCS, 1993). In most cases, these studies were conducted in workers exposed to benzene levels >10 ppm. However, Tompa et al. (1994) analysed whole blood metaphase spreads from workers employed in an environment where improved working conditions over a 3-year period reduced average peak exposures from 21 ppm in 1990 to 8.4 ppm in 1991 and 5.7 ppm in 1992. As shown in Figure 11.1, the reduction in benzene levels was paralleled by a decrease in the frequency of chromosome aberrations, but not in SCEs. These findings provide evidence of a direct relationship between benzene exposure and the extent of chromosome damage, but do not establish a threshold level for the effect.

Figure 11.1: Changes in the frequency of SCEs and chromosome aberrations (excluding gaps) in workers exposed to progressively reduced benzene levels (Tompa et al, 1994)

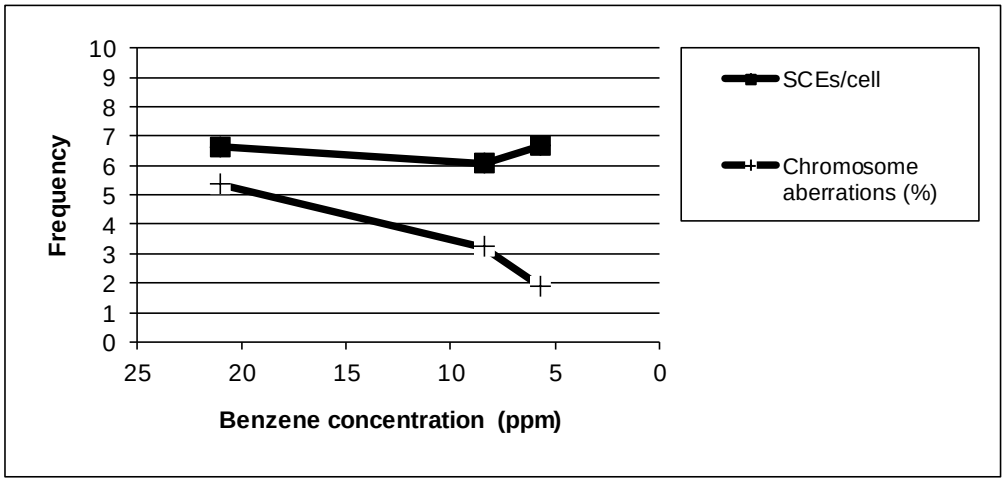


Table 11.3 summarises a number of recent occupational studies which used personal air monitoring to measure benzene exposure and modern cytogenetic techniques such as polymerase chain reaction methods, ^{32}P-postlabelling, fluorescence *in situ* hybridization and alkaline single cell gel electrophoresis to determine the genotoxic effects in various cell samples.

Table 11.3: Genotoxic effects in workers exposed to airborne benzene

Study population (number)			
Exposed	**Controls**	**Effects and effect levels (TWA_8)***	**Reference**
Petrol station attendants (12)	Matched for sex, age and smoking habits (12)	Excess of overall DNA damage and highly damaged cells in freshly isolated non-cycling peripheral blood LC in subjects exposed to a mean air level of 0.11 ppm (range: 0.03-3.0 ppm) (Lagorio et al, 1997)	Andreoli et al. (1997)
Petrol station attendants (12)	Matched for sex, age and smoking habits (12)	No evidence of numerical aberrations involving chromosomes 7, 11, 18 or X in peripheral blood LC of subjects exposed to an average air level of 0.1 ppm	Carere et al. (1998)
Styrene plant workers (25)	Matched for sex and age (25)	Increase in kinetochore-positive MN in T-LC, but no changes in DNA adducts in MC or in DNA single strand breaks, SCE or total MN in LC at average exposure levels corresponding to 0.24 ppm benzene and 0.31 ppm styrene (as well as toluene, xylenes and ethylbenzene)	Holz et al. (1995)
Coke gas plant workers (56)	Matched for age (28)	No increases in the frequency of MN, MN harbouring whole chromosomes or acentric chromosomal fragments or chromosome 9 numerical abnormalities in LC and buccal cells at exposure levels from 0.5-1.2 ppm	Surrallés et al. (1997)
Coke gas plant workers (12) and oven operators (5)	Unmatched inhabitants of neighbouring rural village (8)	Small but statistically significant increase in centromeric breakage of chromosomes 1 and 9 in interphase LC in benzene workers exposed to a geometric average of 1.3 ppm benzene, but not in coking oven workers exposed to a geometric average of 1.0 ppm	Marcon et al. (1999)
Workers using benzene-based solvents (24)	Matched for sex, age, smoking, drinking and obesity (23)	In heterozygous individuals, the frequency of NN but not Nø GPA mutants was doubled in peripheral RBC and strongly correlated with lifetime cumulative benzene exposure, at a mean exposure level of 72 ppm (range: 2-301 ppm)	Rothman et al. (1995, 1996b)
Workers using benzene-based solvents (43)	Matched for sex and age (44)	There was a dose-related increase in hyperdiploidy at chromosomes 8 and 21 and in hypodiploidy at chromosome 8 in LC of workers with a median exposure level of 31 ppm (range not specified). There was also a 15-fold increase in t(8;21) (27 versus 2% LC) and a doubling of t(8;?) and t(21;?) in LC at exposures >31 ppm. All increases were related to current but not to cumulative exposure	Smith et al. (1998)
		Increased frequency of hyperdiploidy at chromosome 9, mainly trisomy, in LC at exposure levels >31 ppm, which correlated with ALC decreases	Zhang et al. (1996)
		Increased frequency of monosomy at chromosomes 5 and 7, in trisomy and tetrasomy at chromosomes 1, 5 and 7, and a dose-dependent, up to 3.5-fold increase in long arm deletions of chromosomes 5 and 7 in whole blood metaphase spreads, at a median exposure level of 31 ppm (range: 2-329 ppm)	Zhang et al. (1998)

* ALC = absolute lymphocyte count
GPA = glycophorin A
LC = lymphocytes
MC = monocytes
MN = micronuclei
RBC = red blood cells
SCE = sister chromatid exchange
t(a;b) = translocations between chromosomes a and b
TWA_8 = 8-h time-weighted average
? = unidentified chromosome.

The studies of Andreoli et al. (1997) and Carere et al. (1998) of petrol station attendants exposed to benzene concentrations that averaged around 0.1 ppm are

difficult to interpret as there is no information on the nature and extent of co-exposure to other chemicals in petrol or vehicle exhaust fumes, which would include 1,3-butadiene and a number of genotoxic PAHs (IARC, 1999; IPCS, 1998). Furthermore, Carere et al. (1998) investigated only one of the six chromosomes in which aberrations have been found at high levels of benzene exposure.

Holz et al. (1995) reported kinetochore-positive (that is, whole chromosome) MN in workers with an average exposure of 0.24 ppm benzene and 0.31 styrene. However, styrene alone is known to cause chromosome damage in human lymphocytes at low concentrations (IARC, 1994).

In coal gas by-product workers, Surrallés et al. (1997) found no chromosome aberrations at benzene levels ≤1.2 ppm, whereas Marcon et al. (1999) found a small increase in centromeric breakages in chromosomes 1 and 9 at 1.3 ppm, but not in coke oven workers exposed to a slighter lower level averaging 1.0 ppm. However, coke oven and coal gas by-product workers are co-exposed to numerous PAHs, many of which have a variety of genotoxic effects at low concentrations (IPCS, 1998).

The main findings at exposure levels ≥31 ppm benzene were aneuploidy, long-arm deletions and translocations involving chromosomes 1, 5, 7, 8, 9 and 21 and gene duplication in nucleated RBC stem cells at the glycophorin A locus on chromosome 4 (Rothman et al, 1995, 1996b; Smith et al, 1998; Zhang et al, 1996, 1998). The subjects of these studies were co-exposed to toluene and xylenes, which may inhibit the metabolism of benzene, but have not been shown to cause chromosome lesions that resemble the above (IPCS, 1997; McGregor, 1994).

As such, whereas studies using modern cytogenetic techniques have shown a clear association between extensive chromosome damage and exposure to high benzene levels, they have not contributed to the definition of a threshold level for genotoxic effects in humans.

11.6 Carcinogenicity

11.6.1 Cohort studies

Cohort studies with poorly characterised benzene exposure levels

Table 11.4 summarises a number of occupational cohort studies with a combined study population approaching 450,000 workers holding jobs with the potential for exposure to benzene, mainly in the petroleum industry. They include the ongoing, prospective Health Watch (1998) cohort study, which covers about 95% of the Australian petroleum industry's 18,000 employees in refineries, natural gas plants, distribution terminals and production sites. They also include two meta-analyses based on a large number of petroleum industry cohorts (Raabe & Wong, 1995; Wong & Raabe, 1996, 2000). The most important limitation of these studies and meta-analyses is their lack of adequate data on benzene exposure levels.

Table 11.4: Summary of cohort studies in workers exposed to poorly characterised benzene levels

Exposed population	Controls	Health outcome*	Ratio (95% CI) †	Comments	Reference
Chemical industry					
259 workers ever employed at a US benzene alkylation plant from 1947-60 and followed up for 17-30 years	National population	Any death rate	No difference	In 194 workers employed for ≥12 months, SMR for CBLS = 3.77 (1.09-10.24)	Decouflé et al. (1983)
822 chemists graduated from university in Stockholm, Sweden, between 1930-50 and followed up till the end of 1974	Architects from same school	All-cause mortality All cancer mortality All CBLS	RR = 1.14 (0.91-1.37) RR = 2.54 (p <0.05) RR = ∞ (p = 0.02)	There were 10 cases of CBLS among the chemists compared to 0 among the architects; nine were organic chemists	Olin & Ahlbom (1980)
Coke oven and coal gas by-product workers					
2708 men employed by British Steel Corporation at 14 coke works in the UK in 1967 and followed up for 20 years	Regional population	*Leukaemia:* All workers By-product workers Coke oven workers	 SMR = 0.41 (0.05-1.47) SMR = 0.98 (0.02-5.57) SMR = 0.35 (0.01-1.92)	Benzene breathing zone levels were reported to average 1.3 ppm in by-product and 0.3 ppm in coke oven workers in the 1980s	Hurley et al. (1991)
3812 men employed by National Smokeless Fuels Ltd at 13 coke works in the UK in 1967 and followed up for 20 years	Regional population	*Leukaemia:* All workers By-product workers Coke oven workers Maintenance workers	 SMR = 0.42 (0.09-1.23) SMR = 0.76 (0.02-4.29) SMR = 0.34 (0.00-1.86) SMR = 0.58 (0.01-3.28)		
5659 coke oven workers employed for ≥6 months from 1945-69 at a Dutch coke plant and followed up for 15-40 years	National population	All-cause mortality, all cancer, liver cancer, and respiratory disease	SMR >1.00 (p< 0.05)	Among 222 benzene plant workers, death rates were similar to the expected figures	Swaen et al. (1991)
Footwear manufacturing					
2013 men and women ever employed at an Italian shoe manufacturing plant from 1939-64 and followed up for 20-45 years	National population	*Male workers (n = 1008):* GI disease and accidents Blood disease All cancer Stomach cancer Leukaemia *Female workers (n = 1005):* Any cause of death	 SMR <1.00 (p <0.05) SMR = 15.66 (5.47-32.64) SMR = 1.40 (1.09-1.81) SMR = 2.40 (1.37-3.78) SMR = 4.00 (1.46-8.70) No difference	Workers in some departments were exposed to glues containing >70% benzene All non-cancer blood disease cases were aplastic anaemia No relationship between leukaemia risk and duration of exposure No information on job categories, which likely may have explained negative findings in female workers	Paci et al. (1989)

Table 11.4: Continued

Exposed population	Controls	Health outcome*	Ratio (95% CI) †	Comments	Reference
Highway maintenance workers					
4849 men employed for at least 1 year between 1945-84 as highway maintenance workers by the Department of Transportation in Minnesota, USA	Regional white population	All-cause mortality and all cancer	SMR <1.00 (p <0.05)	In workers with 30-39 years of employment, the SMR for leukaemia was 4.25 (1.71-8.76)	Bender et al. (1989)
		All CBLS	SMR = 0.95 (0.66-1.33)		
		Leukaemia	SMR = 1.07 (0.62-1.71)	No observed deaths from melanoma compared to 2.9 expected	
Petrol and petroleum distribution					
18,969 men and women employed as petrol station attendants on the day of the 1970 censuses in Denmark, Norway, Sweden and Finland and followed up for deaths and incident cancer cases for 15-20 years	National population of gainfully employed	*Male workers (n = 16,524):*		No information on employment status before or after the census date and hence no adjustment for person-years at risk	Lynge et al. (1997)
		All malignant neoplasms	SIR = 1.1 (1.0-1.1)		
		Cancer of the nose	SIR = 3.1 (1.5-5.7)		
		Lung cancer	SIR = 1.3 (1.1-1.4)		
		Non-Hodgkin's lymphoma	SIR = 1.1 (0.8-1.5)		
		Hodgkin's disease	SIR = 1.0 (0.5-1.8)		
		Multiple myeloma	SIR = 0.6 (0.3-1.1)		
		Leukaemia	SIR = 0.9 (0.6-1.3)		
		Female workers (n = 2445):			
		All malignant neoplasms	SIR = 1.0 (0.8-1.1)		
		Cancer of the nose	SIR = 8.0 (1.0-28.9)		
		Non-Hodgkin's lymphoma	SIR = 0.6 (0.0-2.0)		
		Hodgkin's disease	SIR = IC		
		Multiple myeloma	SIR = IC		
		Leukaemia	SIR = 0.7 (0.1-2.4)		
2665 petrol station workers in the Latium (greater Rome) region in Italy in 1980 and followed up for 10 years	Regional population	All-cause mortality, all cancer, and CV disease	SMR <1.00 (p <0.05)	Benzene exposure levels were reported to be in the order of 0.2 ppm	Lagorio et al. (1994a)
		All CBLS	SMR = 0.40 (0.07-1.26)		
23,306 workers employed for ≥1 continuous year between 1950-75 at UK oil distribution centres and followed up for 15-40 years	Regional populations	All-cause mortality, respiratory, liver and kidney disease, all cancer and cancer of the oesophagus, lung and pleura	SMR <1.00 (p <0.05)		Rushton (1993b)
		Leukaemia	SMR = 1.08 (0.83-1.40)		

Table 11.4: Continued

Exposed population	Controls	Health outcome*	Ratio (95% CI)†	Comments	Reference
Petrol and petroleum distribution: Continued					
18,135 US workers employed for ≥1 year at land-based petrol terminals or on marine petrol tankers from 1946-1985 and followed up for 5-55 years	National population	All-cause mortality, all cancer and circulatory, respiratory and liver disease	SMR <1.00 (p <0.01)		Wong et al. (1993)
		Leukaemia	SMR = 0.89 (0.59-1.29) SMR = 0.70 (0.42-1.09)	Land-based workers Marine workers	
		Lymphoma	SMR = 0.75 (0.58-0.97) SMR = 0.61 (0.43-0.83)	Land-based workers Marine workers	
Petroleum production, refining and distribution					
1583 workers ever employed at an Italian refinery from 1949-82 and followed up for 10-42 years	National population	All-cause mortality, all CV disease, stroke, respiratory disease, liver, and GI disease	SMR <1.00 (p <0.05)	Limited monitoring data indicate that a substantial fraction of the workforce had been exposed to benzene levels >1 ppm	Consonni et al. (1999)
		CBLS (all workers)	SMR = 1.79 (1.00-2.95)		
		CBLS (employment >15 years) Leukaemia (employment >15 years)	SMR = 2.71 (1.09-5.59) SMR = 3.77 (1.01-9.65)		
		CBLS (employment pre-1961)	SMR = 2.82 (1.13-5.81)		
		Lymphoma (employment pre-1961)	SMR = 4.02 (1.08-10.28)		
15,732 male workers employed for ≥5 years in the Australian petroleum industry from 1981-96 and followed up for 5-15 years	National population	All-cause mortality, ischaemic heart disease, stroke, and respiratory, liver and GI disease	SMR <1.0 (p <0.05)	Elevated incidence of leukaemia mainly accounted for by refinery and terminal workers; no definite relationship with length of employment	Health Watch (1998)
		Bladder cancer Multiple myeloma Leukaemia Lymphocytic leukaemia Myeloid leukaemia	SIR = 1.4 (1.0-1.9) SIR = 1.9 (1.0-3.3) SIR = 2.0 (1.3-2.9) SIR = 2.0 (1.0-3.5) SIR = 2.2 (1.2-3.6)	Estimated long-term benzene exposure levels were ≤5 ppm in all cases; estimated cumulative exposures ranged from 0.005-50.9 ppm-years (Glass et al, 1998)	
		Melanoma	SIR = 1.6 (1.3-1.9)	No excess mortality from melanoma (SMR = 0.7 (0.4-1.4)	

Table 11.4: Continued

Exposed population	Controls	Health outcome*	Ratio (95% CI)†	Comments	Reference
Petroleum production, refining and distribution: Continued					
4319 Swedish refinery operators and distribution workers employed for ≥1 year between 1958-91 and followed up for 5-35 years	National population	*All male workers (n = 4128):* All-cause mortality, CV disease, and lung cancer	SMR <1.00 (p <0.05)		Järvholm et al. (1997)
		Refinery operators (n = 1339): Leukaemia	SIR = 3.6 (1.5-7.0)		
		Distribution workers (n = 1391): All cancer and lung cancer Leukaemia	SIR <1.00 (p <0.05) SIR = IC (0-2.0)		
34,560 workers employed ≥1 year in refinery, petrochemical, distribution, marketing, production, drilling and pipeline locations throughout Canada from 1964-83 and followed up for 11-31 years	National population	*Male workers (n = 26,322):* All-cause mortality, endocrine, circulatory, respiratory and GI disease, all cancer	SMR <1.00 (p <0.05)	There was an increase in multiple myeloma (SMR = 1.94 (1.11-3.15)) in marketing and distribution workers	Lewis et al. (2000)
		Leukaemia	SMR = 0.89 (0.67-1.16)		
		Aortic aneurysm	SMR = 1.27 (1.04-1.53)		
		Female workers (n = 8238): All-cause mortality, endocrine, circulatory, respiratory and GI disease	SMR <1.00 (p <0.05)		
		Leukaemia	SMR = 0.86 (0.32-1.88)		
9187 male workers employed for ≥6 months at 10 US refineries from 1970-80 and followed up for 2-12 years	National population	All-cause mortality, all cancer and CV, respiratory and GI disease	SMR <1.00 (p <0.05)		Nelson et al. (1987)
		All CBLS	SMR = 0.60 (0.34-0.97)		
		Skin cancer	SMR = 2.01(1.00-3.60)	10/11 deaths from skin cancer were due to melanoma	
9454 workers employed for ≥3 months in 3 refineries, 1 petrochemical plant and the head office of an oil company in Finland from 1967-82 and followed up for 13-28 years	National population	*All workers:* Kidney cancer	SIR = 1.97 (1.29-2.88)	The breast cancer cases were concentrated among clerical workers (SIR = 1.70 (1.08-2.56)), particularly in the head office (SIR = 2.29 (1.25-3.84)), and the SIRs did not differ from those found in other studies of Finnish women in office jobs	Pukkala (1998)
		Male workers (n = 7512): Non-Hodgkin's lymphoma	SIR = 2.01 (1.00-3.59)		
		Female workers (n = 1942): Breast cancer	SIR = 1.50 (1.05-2.08)		

Table 11.4: Continued

Exposed population	Controls	Health outcome*	Ratio (95% CI)†	Comments	Reference
Petroleum production, refining and distribution: Continued					
34,569 men employed at 8 UK refineries for ≥1 continuous year between 1950-75 and followed up for 15-40 years	Regional populations	All-cause mortality, stroke all heart, respiratory and liver disease, all cancer and cancer of the mouth, pharynx, lung and pleura	SMR <1.00 (p <0.05)	The SMR for melanoma was not elevated in workers first employed before 1955, but reached 2.30 (1.05-4.37) and 4.67 (2.02-9.20) in workers first employed between 1955-64 and after 1965 respectively. It varied markedly between refinery locations and was higher among office staff than in workers employed outdoors.	Rushton (1993a)
		Diseases of the arteries	SMR = 1.20 (1.07-1.35)		
		Leukaemia	SMR = 0.97 (0.76-1.24)		
		Melanoma	SMR = 1.78 (1.20-2.54)		
Workers representing 383,276 man-years of employment in 1962-71 at 8 European affiliates of a US oil company	UK national population	All leukaemias	SMR = 0.77 (0.41-1.13)	In a subgroup of workers exposed for ≥5 years to streams containing ≥1% benzene, the SMR for leukaemia was 1.21 (0.37-	Thorpe (1974)
Meta-analysis of 19 cohorts comprising 208,741 refinery, production, pipeline and distribution workers ever employed in USA and UK from 1937-1989 and followed up for 13-50 years	Various national and regional populations	All leukaemias	MSMR = 1.02 (0.93-1.11)	Meta-analysis of leukaemia mortality by cell type; no data on other death rates	Wong & Raabe (1995); Raabe & Wong (1996)
		Acute lymphocytic leukaemia	MSMR = 1.16 (0.81-1.61)		
		Acute myeloid leukaemia	MSMR = 0.96 (0.81-1.13)		
		Chronic lymphocytic leukaemia	MSMR = 0.84 (0.67-1.04)		
		Chronic myeloid leukaemia	MSMR = 0.89 (0.68-1.15)		
Meta-analysis of 26 cohorts comprising more than 308,000 refinery, production and distribution workers ever employed in Australia, Canada, Finland, Italy, USA and UK from 1937-1996	Various national and regional populations	Non-Hodgkin's lymphoma	MSMR = 0.90 (0.82-0.98)		Wong & Raabe (2000)
Printing					
1361 men ever employed as rotary press workers in Los Angeles from 1949-65 and followed up till 1980	National population	Kidney cancer	SMR = 3.03	Exposed to printing inks and solvents containing benzene No analysis for statistical significance	Paganini-Hill et al. (1980)
		Liver cirrhosis	SMR = 2.05		
		Leukaemia	SMR = 2.47		
Tyre manufacturing					
18,903 male workers employed for ≥10 years at 4 tyre manufacturing plants in Ohio and Wisconsin, USA, from 1945-1964 and followed up for 10 years	National population	All-cause mortality	SMR <1.00	No exposure assessment, but 'benzene was once the most widely used organic solvent in the industry' No analysis for statistical significance	McMichael et al. (1976)
		Stomach/colon/prostate cancer	SMR = 1.48/1.16/1.19		
		CBLS	SMR = 1.31		
		Leukaemia	SMR = 1.30		
		Lymphocytic leukaemia	SMR = 1.58		
		Lymphoma	SMR = 1.29		

Table 11.4: Continued

Exposed population	Controls	Health outcome*	Ratio (95% CI)†	Comments	Reference
Vehicle mechanics					
335 predominantly black men employed for ≥1 year as vehicle maintenance workers in Washington, DC, from 1977-89 and followed up for 3-15 years	Regional population	All-cause mortality and liver and GI disease CBLS (all workers) CBLS (regular contact workers)	SMR <1.00 (p <0.05) SMR = 3.63 (0.75-10.63) SMR = 9.26 (1.12-33.43)	Regular contact workers used petrol to clean engine parts and wash hands or siphoned petrol by mouth	Hunting et al. (1995)
Miscellaneous industries					
74,828 male and female workers employed from 1972-87 in the painting, printing, footwear and chemical industries in China and followed up for 1-15 years	35,805 unexposed workers	All-cause mortality and all cancer deaths Fatal CBLS Fatal leukaemia Fatal lymphoma	No difference RR = ∞ (2.5-∞) RR = 2.3 (1.1-5.0) RR = 4.5 (1.3-28.4)		Yin et al. (1996)

* CBLS = cancer of the blood and lymphatic system; CV = cardiovascular; GI = gastrointestinal; GU = genitourinary.
† IC = incalculable (no observed cases); MSRM = meta-SMR; SIR = standardised incidence ratio; SMR = standardised mortality ratio; RR = relative risk; ∞ = indefinite (no cases in the unexposed group).

Cohort studies with detailed benzene exposure assessments

There are four occupational cohort studies in which the exposure to benzene has been assessed in detail.

The Chinese cohort

The US National Cancer Institute and the Chinese Academy of Preventive Medicine have collaborated to follow up on a large cohort study commenced in 1982 to assess the risks of specific bone marrow disorders in relationship to occupational benzene exposure (Hayes et al, 1997). The final cohort comprises 74,828 male and female benzene-exposed workers employed from 1972 to 1987 in 672 factories in 12 cities in China and 35,805 unexposed workers. The subjects were followed until the end of 1987, for an average of approximately 11 years. RRs were determined for incident cancer of the blood and lymphatic system, NHL, leukaemia, ANLL, a diagnosis of either ANLL or MDS, and leukaemia other than ANLL, with stratification by age and sex. Smoking or other potential confounders were not considered. The exposed workers held permanent jobs in the painting, printing, footwear, rubber and chemical industries. Exposure levels were estimated from available area monitoring data, detailed production and process information, and employee records.

There were 58 specified cancers of the blood and lymphatic system and 18 other bone marrow disorders (2 cases of agranulocytosis, 9 of aplastic anaemia and 7 of MDS) in the cohort, compared to 13 and 0 respectively in the control group.

When the cohort was divided into three categories according to the estimated average benzene exposure level, the RRs for all cancer of the blood and lymphatic system and ANLL/MDS were elevated in all categories, with a positive trend for increasing average exposure, as shown below:

	Estimated average exposure:			
Cancer type/R:	<10 ppm	10-24 ppm	>25 ppm	Trend
Blood and lymphatic system	2.2 (1.1-4.2)	3.1 (1.5-6.5)	2.8 (1.4-5.7)	p = 0.003
ANLL/MDS	3.2 (1.0-10.1)	5.8 (1.8-18.8)	4.1 (1.2-13.2)	p = 0.01

The RR for NHL was 4.7 (1.2-18.1) in workers exposed to ≥25 ppm, but was not elevated in the lower average exposure categories.

When the cohort was divided into three categories according to the estimated cumulative benzene exposure level, the RR for all cancer of the blood and lymphatic system was elevated in all categories, whereas the RRs for leukaemia and ANLL/MDS were elevated at cumulative exposures ≥40 ppm-years:

	Estimated cumulative exposure			
Cancer type/RR	<40 ppm-years	40-99 ppm-years	≥100 ppm-years	Trend
Blood and lymphatic system	2.2 (1.1-4.5)	2.9 (1.3-6.5)	2.7 (1.4-5.2)	p = 0.004
Leukaemia	1.9 (0.8-4.7)	3.1 (1.2-8.0)	2.7 (1.2-6.0)	p = 0.04
ANLL/MDS	2.7 (0.8-9.5)	6.0 (1.8-20.6)	4.4 (1.4-13.5)	p = 0.01

The RR for NHL was not elevated in any of the three cumulative exposure categories.

Only NHL was linked to duration of exposure. None of the RRs were related to the year of initial employment in the study factories. ANLL/MDS was linked to recent exposure (<10 years prior to diagnosis), whereas NHL was linked to distant exposure (≥10 years prior to diagnosis).

The authors concluded that the results suggest an association between benzene exposure and a spectrum of blood cancers and related disorders, with an increase in cancer risk at cumulative exposures <40 ppm-years and a tendency, although not strong, for the risk to rise with increasing levels of exposure.

It should be noted that personal monitoring in a subset of the Chinese cohort measured current exposure levels which were reported to be 'much higher than expected' compared to the estimates that were made in the course of the main study (Rothman et al, 1995, 1996b). As such, the historical exposure levels used to determine the dose-response relationship may have been grossly underestimated (Budinsky et al, 1999; EPA, 1998a; Wong, 1999).

Overall mortality rates in the Chinese cohort have been reported by Yin et al. (1996) and are summarised in Table 11.4. The average latency period of fatal leukaemia in benzene-exposed workers was estimated at 11-12 years, with a range from 10 months to 50 years (Yin et al, 1987b).

The CMA cohort

The Chemical Manufacturers Association (CMA) sponsored a study of 4602 male chemical workers who were employed for ≥6 months from 1946-75 at 7 US plants (Wong, 1987a, 1987b). Two comparison groups were used: the general US population and 3074 unexposed male workers employed at the same plants at the same time as the cohort. Smoking or other potential confounders were not considered. The vital status of all subjects was followed up until the end of 1987 and the findings compared to average and peak exposures as determined from available air monitoring data and employment records obtained from the participating companies.

There were 19 deaths from cancer of the blood and lymphatic system in the exposed workers compared to 3 in the unexposed group. In the exposed group, 7 of the observed cases were diagnosed with leukaemia and the remaining 12 with lymphoma. The subjects with leukaemia comprised 1 case with acute lymphatic leukaemia (ALL), 2 with chronic lymphatic leukaemia (CLL), 1 with unspecified lymphatic leukaemia, 2 with chronic myeloid leukaemia (CML) and 1 with unspecified acute leukaemia. In the unexposed workers, all 3 cases were diagnosed with lymphoma. The SMRs for all cancers of the blood and lymphatic system/leukaemia reached 0.91/0.97, 1.47/0.78 and 1.75/2.76 for cumulative exposures of <180, 180-719 or ≥720 ppm-months respectively, but none of the ratios was significantly different from unity. The RRs for all cancers of the blood and lymphatic system were 2.10, 2.95 and 3.93 respectively for the same cumulative exposure groups, with $p = 0.02$ for trend. The RRs for leukaemia were indefinite as there were no cases in the unexposed workers, with $p = 0.01$ for trend with cumulative exposure. There was no correlation with peak levels or duration of exposure.

Based on the RRs and their trend with cumulative exposure, the author concluded that workers exposed to benzene exhibited a significant excess of deaths from leukaemia as well as from the broader category of all cancers of the blood and

lymphatic system when compared with workers who were not exposed to the chemical.

Ireland et al. (1997) conducted an extended mortality study in production personnel from one of the plants included in the CMA-sponsored study. The workers were stratified into three categories based on cumulative exposure: <12 ppm-months (n = 666), 12-72 ppm-months (n = 378) and ≥72 ppm-months (n = 164). Compared to the regional population, the SMR for leukaemia was 2.5 (0.3-8.9) in the lowest, incalculable (0.0-5.9) in the middle, and 4.6 (0.9-13.4) in the highest exposure category, with no clear dose-response relationship.

The Dow Chemical cohort

This cohort comprised 956 male chemical workers employed at a single site in Michigan, USA, between 1940 and 1982. The workers were exposed to benzene in chlorobenzene or alkylation plants which used benzene as a raw material, or in an ethyl cellulose plant where benzene was used as a solvent (Bond et al, 1986; Ott et al, 1978). They were followed up until the end of 1982. The average exposure duration and length of follow-up were 7 and 26 years respectively. Each job entry was assigned an exposure intensity level on the basis of job classification and representative personal air monitoring data.

The analysis accounted for co-exposure to arsenic, asbestos or high levels of vinyl chloride. Smoking or other potential confounders were not considered. There were 6 deaths from cancer of the blood and lymphatic system against 4.8 expected, including 4 cases of myelogenous leukaemia against 0.9 expected, and 4 from skin cancer (3 melanomas and 1 squamous cell carcinoma) against 0.9 expected, using concurrent US white male mortality rates as reference values. The excess of myelogenous leukaemia was statistically significant ($p = 0.011$; SMR and 95% CI not stated) and the risk for skin cancer was significantly elevated (SMR = 4.41 (1.21-11.38)). There were no significant trends with either work area, cumulative exposure or duration of exposure. Of the 6 cases of blood and lymphatic system cancer, 4 had been exposed to <500 ppm-months and 2 to ≥1000 ppm-months. In the case of myelogenous leukaemia, cumulative exposures varied from 18-4211 ppm-months. The 4 cases of skin cancer all occurred in workers with exposures <500 ppm-months, but otherwise had no unusual or common characteristics.

The authors concluded that their study provided support for an association between exposure to benzene and myelogenous leukaemia.

The Pliofilm cohort

An excess incidence of leukaemia in rubber workers at two Goodyear facilities in Ohio, USA was reported in a preliminary paper by Infante et al. (1977) and in more detail by Rinsky et al. (1981). Depending on its definition, this cohort comprises 1165-1212 male workers employed from 1936-75 in the manufacture of Pliofilm, which is a material made from rubber hydrochloride (Paxton et al, 1994a; Rinsky et al, 1987). The manufacturing process used large volumes of benzene as a solvent and there was no exposure to other known carcinogenic substances. The last worker joined the cohort in 1965 and the most recent follow-up was in 1987.

Excluding deaths before 1950, Rinsky et al. (1987) identified 15 deaths from lymphatic and haematopoietic cancers versus 6.6 expected (SMR = 2.27 (1.27-3.76)) and 9 deaths from leukaemia versus 2.7 expected (SMR = 3.37 (1.54-6.41)). In a later analysis that included deaths between 1940-50, Paxton et al. (1994a)

identified 21 deaths from lymphatic and haematopoietic cancers versus 9.51 expected (SMR = 2.21 (1.37-3.38)) and 14 deaths from leukaemia versus 3.89 expected (SMR = 3.60 (1.97-6.04)). Neither of these analyses considered smoking or other potential confounders.

The individual exposure histories of the cohort members were reconstructed after the plants closed in 1975, from fairly detailed monitoring and health surveillance data and other information on record.

Based on unpublished exposure estimates, Rinsky et al. (1987) found SMRs for leukaemia of 1.09 (0.12-3.94) at a cumulative exposure <40 ppm-years, 3.22 (0.36-11.65) at 40-200 ppm-years, 11.86 (1.33-42.85) at 200-400 ppm-years and 66.37 (13.34-193.93) at >400 ppm-years.

Paxton et al. (1994a) recalculated the SMRs for a different set of cumulative exposure categories and compared them with similar statistics derived from independent, more detailed exposure estimates produced by Crump & Allen (unpublished report prepared for the Occupational Safety and Health Administration in 1984) and Paustenbach et al. (1992), as shown in Table 11.5[8]. The results reproduced in the table suggest a strong dose-response relationship of risk increasing with cumulative exposure, no matter which estimate is used, and indicate that there is a significantly elevated risk for leukaemia (according to 2 of the 3 available exposure estimates) at a cumulative dose >50 ppm-years, corresponding to a long-term average exposure of 1.25 ppm over 40 years.

Table 11.5: SMRs (95% CI) for leukaemia in the Pliofilm cohort, analysed by cumulative exposure as estimated by Crump & Allen (1984, unpublished), Paustenbach et al. (1992) and Rinsky et al. (1987)(from Paxton et al, 1994a)

Cumulative exposure (ppm-years)	Exposure estimate		
	Crump & Allen	Paustenbach et al.	Rinsky et al.
0-5	0.88 (0.02-4.89)	1.33 (0.03-7.43)	1.97 (0.41-5.76)
>5-50	3.25 (0.88-8.33)	1.79 (0.22-6.45)	2.29 (0.47-6.69)
>50-500	4.87 (1.79-10.63)*	2.80 (0.76-7.16)	6.93 (2.78-14.28) †
>500	10.34 (2.13-30.21) †	11.86 (4.76-24.44) †	20.00 (0.51-111.4)

* $p < 0.05$
† $p < 0.01$

As the SMR was not significantly different from unity at cumulative exposures ≤50 ppm-years for any of the three exposure estimates, the authors concluded that the results of the analysis were consistent with a threshold model for benzene-induced leukaemia. However, the power of the analysis was insufficient to support this conclusion. The upper 95% confidence limits given in Table 11.5 range from 6.45-8.33 in the >5-50 ppm-year exposure category and from 4.89-7.43 the 0-5 ppm-year category. In either case, the upper limits are well above unity irrespective of the exposure estimate used. Therefore, it cannot be excluded that a cumulative exposure level ≤50 ppm-years is also associated with an excess mortality from leukaemia.

[8] The major distinction between the three exposure estimates is the disregard by Rinsky et al. (1987) for the likely increase in exposure levels during and in the aftermath of World War II because of wartime conditions and longer working hours. In addition, only Paustenbach et al. (1992) have given consideration to the potential for dermal exposure.

Wong (1995) reanalysed the findings of Paxton et al. (1994a) by cell type (AML and multiple myeloma (MM)), using the Rinsky et al. (1987) exposure estimate which in general is the lowest of the three. He found no relationship between cumulative exposure and the risk of MM, whereas the SMR for AML showed a clear dose response, as follows:

Cumulative exposure	SMR (95% CI)	Statistical significance
<200 ppm-years	0.91 (0.02-5.11)	Not significant
200-400 ppm-years	27.21 (3.29-98.24)	p <0.01
>400 ppm-years	98.37 (20.28-287.65)	p <0.01
Total cohort	5.03 (1.84-10.97)	p <0.01

The author concluded that there was no significant increase in the risk of AML for cumulative exposure to benzene <200 ppm-years, above which the risk rose sharply to a very substantial SMR of 98.37 for >400 ppm-years. However, as the 95% upper confidence limit in the lowest exposure group was 5.11, an increase in mortality from AML at a cumulative exposure <200 ppm-years cannot be ruled out.

In another re-analysis based on the three sets of exposure estimates referred to above, Schnatter et al. (1996b) used the work history of each Pliofilm worker to define each worker's maximally exposed job/department combination over time and the long-term average benzene exposure level associated with the maximally exposed job. They then determined the number of observed and expected cases of leukaemia (all cell types) in subcategories of workers and person-years who were always exposed at levels that did not exceed specific concentrations of benzene. As shown in Table 11.6, this analysis showed that there were fewer observed than expected deaths in all subcategories that were always exposed to benzene concentrations ≤15 ppm, irrespective of the exposure estimate used. However, because of the low number of expected cases, this finding could also be due to chance.

Table 11.6: Observed and expected cases of leukaemia (all cell types) for selected cut-off points for the average long-term exposure level in the maximally exposed job (Schnatter et al, 1996b)

Long-term benzene exposure (ppm)	Exposure estimate					
	Crump & Allen		Paustenbach et al.		Rinsky et al.	
	Observed	Expected	Observed	Expected	Observed	Expected
≤1	0	0.53	0	0.07	1	1.53
≤5	0	1.01	0	0.10	1	1.72
≤10	0	1.04	0	0.11	1	2.00
≤15	0	1.28	0	0.15	1	2.00
≤20	2	1.92	0	0.21	3	2.30
≤25	2	2.13	1	0.80	7	2.92
≤30	3	2.35	1	0.90	7	3.24
≤40	5	2.73	1	1.33	10	4.04
≤50	5	2.98	3	1.96	14	4.79
≤100	8	3.98	5	3.55	14	4.87
≤200	9	4.20	14	4.70	14	4.87
≤260	14	4.87	14	4.87	14	4.87

Conclusions

Cohort studies with poorly characterised benzene exposure levels

Several of the studies summarised in Table 11.4 have associated cancer of the blood and lymphatic system (including but not limited to leukaemia) with the obsolete practice of using benzene-containing adhesives, cleaners and solvents. Some studies indicate a positive association with long-term employment at petroleum refineries, in the chemical industry or in highway maintenance. There was no excess mortality from leukaemia in three cohorts of coke plant workers.

The risk for malignant melanoma or skin cancer (mainly melanoma) was elevated in three petroleum industry cohorts (Health Watch, 1998; Nelson et al, 1987; Rushton, 1993a). The SIR for breast cancer was elevated in female workers in a Finnish oil company cohort (Pukkala, 1998). However, the elevation was mainly due to cases among clerical workers and similar in magnitude to that found in other studies of Finnish women in office jobs.

Cohort studies with detailed benzene exposure assessments

There was an excess mortality from cancer of the blood and lymphatic system in all four cohorts for which detailed benzene exposure assessments are available and a significant trend with cumulative exposure in all but the smallest cohort (the Dow Chemical cohort). As such, it is widely accepted that these studies provide sufficient evidence of a clear dose-response relationship between benzene exposure and the broad category of all cancers of the blood and lymphatic system (ATSDR, 1997; OECD, 2000; IARC, 1982a; IPCS, 1993; USEPA, 1998a). In terms of specific cancer categories, the relationship is primarily due to the risk for AML (ANLL).

In the CMA cohort, the SMR for leukaemia was elevated (2.6) in workers with a cumulative exposure of ≥720 ppm-months (that is, ≥60 ppm-years), but it was not significantly different from unity and therefore could have been due to chance. In a subset of the CMA cohort, the SMR for leukaemia was 4.6 in workers with a cumulative exposure of ≥72 ppm-months (6 ppm-years), but again did not differ significantly from unity. There was no clear dose-response relationship in the Dow Chemical cohort and there is doubt about the true exposures in the Chinese cohort. As such, the Pliofilm cohort is the most suitable for the determination of the carcinogenic potency of benzene. In addition, the Pliofilm cohort has the advantage of limited if any co-exposure to other potentially carcinogenic compounds and a very long follow-up period. However, it suffers from uncertainty about actual exposure levels, particularly prior to 1950, which is important as there are no cases of leukaemia in workers first employed after that year (USEPA, 1998a).

Based on an unpublished assessment of individual exposures in the Pliofilm cohort, Rinsky et al. (1987) determined SMRs for leukaemia that increased exponentially with cumulative exposure, starting from near unity at a cumulative exposure <40 ppm-years. More recent dose-response analyses that include other, more comprehensive exposure assessments indicate that the risk for leukaemia is significantly elevated at a cumulative exposure level above, but not below 50 ppm-years, corresponding to an average exposure level of 1.25 ppm over 40 years (Paxton, 1994b). Moreover, whatever exposure estimate was used, the number of observed cases of leukaemia was consistently below the expected number in all workers whose long-term exposure never exceeded 15 ppm (Schnatter et al, 1996b). However, because of the limited statistical power resulting from the size of

the Pliofilm cohort, these results do not rule out the possibility of an increased risk of leukaemia at exposure levels lower than those cited above.

In the Dow Chemical cohort, there was an association between benzene exposure and skin cancer. However, all cases occurred in the lowest cumulative dose group (<500 ppm-months) and there was no trend with either level or duration of exposure.

11.6.2 Case-control studies

The case-control studies reviewed below have been divided by organ system. They comprise studies based in a specific industry, such as petroleum refining, and studies conducted in a community population. Limitations in statistical power and study quality, particularly in relation to exposure assessment and/or control for potential confounders, pervade all of the studies reviewed.

Cancer of the blood and lymphatic system

Industry-based studies

A study nested within a cohort of male workers at a large tyre manufacturing plant in Ohio, USA included 11 cases of lymphocytic leukaemia and 1350 controls (Checkoway et al, 1984). The OR for direct exposure through routine use or handling of benzene or benzene-containing solutions was 4.50 (95% CI not stated), but did not reach statistical significance (p = 0.22). The ORs for exposure to acetone, carbon disulfide, carbon tetrachloride, ethyl acetate, hexane or methanol ranged from 4.3-18 (95% CIs not stated) and were all statistically significant.

Austin et al. (1986) compared 14 cases of leukaemia in white male workers at a US refinery, including 8 cases of AML, with 50 controls. Neither job category, department nor length of employment was a significant risk factor.

In an exploratory study of cancer mortality at a transformer assembly facility in Massachusetts, USA, where benzene was used for general cleaning purposes until 1950, benzene exposure was not a significant risk factor for leukaemia (OR = 1.4 (0.64-3.2)) (Greenland et al, 1994).

Sathiakumar et al. (1995) studied 69 workers with leukaemia, predominantly AML or CLL (numbers not specified), and 284 controls who had worked for the same US-based petroleum company for ≥1 year from 1976-90. Forty-four risk factors tested for included site of work, involvement in production, job category, duration and year of employment. The only risk factors identified were for AML and included length of employment, with an OR = 8.7 (2.0-37.2) in workers employed for >30 years (trend: p = 0.01), and upstream employment in crude oil production or maintenance (OR = 3.2 (1.1-9.2)).

Schnatter et al. (1996a) compared 7 cases of NHL, 7 cases of MM and 55 controls drawn from the cohort of Canadian petroleum distribution workers described by Lewis et al. (2000). Tests included several measures for benzene exposure. The only risk factors identified were a family history of cancer and cigarette smoking, with cumulative benzene exposure showing no additional risk.

A study nested in the cohort of British petroleum distribution and marketing workers described by Rushton (1993b) compared 91 cases of leukaemia, predominantly ANLL (31) and CLL (31), with 364 controls (Rushton & Romaniuk, 1997). Risk factors tested for included cumulative, mean and maximum airborne

and potential skin exposure to benzene, duration of employment, date of hire, employment as driver, socio-economic status, and age at and years from start of work. For ANLL, none of the ORs differed from unity. For CLL, the risk factors identified included duration of employment, white-collar status and years of work, but not exposure to benzene.

The case-control study nested within the cohort of Australian petroleum industry workers currently comprises 63 cases with lympho-haematopoietic cancers, mainly NHL, MM, AML and CLL, and 315 controls (Health Watch, 1998). In the analysis, the OR was used to compare groups with different levels of exposure to various potential causative agents, relative to the least exposed or baseline group. Compared to the baseline of the rate in refineries, the OR was marginally elevated for work in terminals (1.8 (1.0-3.5)). Length of employment and period of first employment were not significant risk factors. Past exposure to benzene was ranked on a scale from 1-5, depending on AIP jobcode, the company site where the job was carried out and length of service in any job. When cases and controls were compared to the highest benzene rank of any job ever held (ranks 4-5), the OR was 7.9 (1.6-39) times higher than for rank 1 (the baseline). When compared to the benzene rank of the job held longest, the OR was 3.2 (1.1-9.4) times higher than baseline for rank 3 and 6.6 (1.4-30) times higher for rank 4 (the highest rank in this test). The authors concluded that a relatively higher exposure to benzene might be the significant factor leading to an increased risk of leukaemia and MM in the cohort study.

Nilsson et al. (1998) conducted a nested case-control study of Swedish seamen with two study bases. These comprised a total of 92 men who were registered as seamen at the national censuses in Sweden in 1960 and 1970 respectively and recorded in the Swedish National Cancer Register with cancer of the blood and lymphatic system from 1971-88. The controls were 291 age-matched men registered as seamen at the same censuses. NHL (37) and leukaemia (30) accounted for most of the cases. There were no increased risks for the 1960 cohort, in which few cases were exposed to benzene or petrol. In the 1970 cohort, the OR was increased for cancer of the blood and lymphatic system (OR = 2.6 (1.1-5.9)) and for NHL (OR = 3.3 (1.1-10.6)) in seamen who had worked on deck on chemical or petroleum product tankers, but not on crude oil tankers.

Wong et al. (1999) studied 59 cases of leukaemia, including unspecified leukaemia (35), AML (13) and MM (11), and 220 controls drawn from a US-based cohort study of 18,135 petrol distribution workers (Wong et al, 1993). Test variables included duration of employment, duration of exposure, job category, cumulative exposure to hydrocarbons, cumulative frequency of peak exposure to hydrocarbons, and year of first exposure. None of these was identified as a risk factor for any of the study diagnoses.

In a study nested within the Pliofilm cohort described above, Finkelstein (2000) examined the temporal variation of leukaemia risk following exposure to benzene. Each leukaemia case was matched with 6-333 control subjects and the exposure of cases and controls were then assessed according to Rinsky et al. (1987) and compared at various times before the death of the case subject. As expected, leukaemia risk was significantly associated with cumulative exposure ($p = 0.024$). However, exposures incurred in the previous 10 years were found to account for most of the risk and there was no significant difference in the benzene exposure of cases and controls 15 or more years prior to the death of the case subject.

Community-based studies

Exposure to benzene and/or toluene was investigated in 401 cases of various serious blood disorders and 124 controls sampled from the same general hospital in Lyon, France (Girard & Revol, 1970). The prevalence of exposure was significantly higher among patients with acute leukaemia, CLL and aplastic anaemia than in the comparison group. The majority of the exposed patients had worked in small workshops where the main sources of exposure were reported to be cleaning fluids and paint and glue thinners.

Ishimaru et al. (1971) interviewed 303 matched pairs of controls and cases of leukaemia (not further specified) with onset from 1945-67 in Hiroshima or Nagasaki in Japan. The OR was 2.5 ($p < 0.01$) among those with a history of any of 11 occupations with the potential for frequent exposure to benzene or x-rays and showed a positive trend with the length of time in those occupations.

Eighteen (36%) out of 50 working men with ANLL seen at a hospital in Lund, Sweden, were occupationally exposed to petroleum products or vehicle exhaust fumes through occupation as petrol stations attendants, drivers or operators of excavators or power saws (Brandt et al, 1978). By comparison, similar exposure patterns occurred in only 10% of three outpatient control groups ($p = 0.0002$), including a group of male patients with CML or CLL ($p = 0.006$), or 10-11% of the general male population in the region.

Linos et al. (1980) compared 138 cases of acute or chronic leukaemia (not further specified) that occurred in residents in a county in Minnesota, USA between 1955-74 with 276 controls, with regard to past occupational and chemical exposure. The OR for exposure to benzene was not significantly elevated (3.34 (0.60-27.60)).

In a study of 131 cases of MM, 111 cases of CLL and 431 controls resident in a rural woodland district in central Sweden, Flodin et al. (1987, 1988) observed an association with occupational exposure to exhaust fumes from diesel and petrol engines, including tractors and chainsaws. The OR was 2.1 (1.2-3.9) for MM and 2.2 (1.2-4.2) for CLL.

Another Swedish study of 125 cases of acute leukaemia (including 97 AML and 24 ALL cases) and an equal number of controls found a large excess risk for professional painters exposed to solvents that would have contained benzene as an impurity (OR = 13 (2-554) (Lindquist et al, 1987). There was also an excess risk among professional drivers, with an OR = 3.0 (1.1-9.2). The OR reached 5.0 (95% CI not stated; $p < 0.05$) for those who had been drivers for >5 years in their lifetime or >1 year during the 5-20-year period prior to diagnosis and remained after adjustments for exposure to organic solvents, smoking and therapeutic x-ray treatment (Lindquist et al, 1991).

A study of 475 cases of lymphoma, leukaemia and MM in white male residents in Missouri, USA, and 1425 controls found an elevated risk of leukaemia in mechanics (OR = 4.79 (1.42-16.18)) (Brownson & Reif, 1988).

Richardson et al. (1992) conducted an interview study of occupational risk factors of acute leukaemia in French adults, based on 31 cases of ALL, 154 cases of AML and 513 controls. A significant relationship was observed between AML and high or medium exposure to benzene (OR = 3.6 (1.7-7.7)). For ALL and AML combined, the OR for any exposure to benzene was 1.3 (0.8-2.3), whereas it was 2.8 (1.3-5.9) for high or medium exposure.

In an interview study of 622 white males with NHL and 1245 controls drawn from the general population in Iowa and Minnesota, USA during 1980-83, there were no indications that industrial exposures were a major determinant for NHL (Blair et al, 1993). The OR for benzene exposure was close to unity, but did increase slightly with intensity of exposure (lower intensity: OR = 1.1 (0.8-1.4); higher intensity: OR = 1.5 (0.7-3.1)).

In a study of 86 cases of AML, CML or MDS in residents in Turin, Italy, there was a marginally elevated risk of leukaemia/MDS in vehicle mechanics (OR = 2.7 (0.97-7.6)) and truck and other drivers (OR = 2.7 (0.8-9.6)), but no association with exposure to benzene (Ciccone et al, 1993).

A French, hospital-based case-control study of 226 male cases of hairy cell leukaemia and 425 matched controls found no association between occupational exposure to benzene and this rare B-lymphoid chronic leukaemia (Clavel et al, 1996).

A recent review by Savitz & Andrews (1997) identified 12 additional community-based case-control studies of benzene and cancer of the blood and lymphatic system, none of which reported any association between the two.

Childhood leukaemia

Leukaemia is the most common cancer in children under the age of 15 (Shu, 1997). A number of case-control studies have explored the potential relationship between childhood leukaemia and parental exposure to agents that might be toxic to the unborn or breast-fed baby and/or the germ cells of the parents.

Some of these studies have suggested a link between childhood leukaemia and pre-conceptional occupational exposure of the father to solvents, petroleum products, motor vehicle exhaust fumes, benzene, or plastic monomers or polymers (Buckley et al, 1989; Fabia & Thuy, 1974; McKinney et al, 1991; Shu et al, 1999; Vianna et al, 1984). Others have found a weak association with maternal employment in jobs with the potential for exposure to various chemicals including benzene, petrol, solvents and thinners, paints and/or plastic monomers or polymers (Shu et al, 1988, 1999; van Steensel-Moll et al, 1985).

A study of 123 cases of childhood leukaemia and an equal number of matched controls found a significant, dose-related elevation in the risk of leukaemia for children whose parents burned incense in the house during pregnancy or lactation (Lowengart et al, 1987). Incense stick has been reported to emit the same quantity of benzene in smoke as tobacco and herbal cigarettes (Löfroth et al, 1991).

In a study of 97 cases of childhood leukaemia (78 of whom had ALL) and 259 matched controls from Denver, USA, Pearson et al. (2000) found an association between childhood leukaemia and proximal high traffic streets with traffic counts ≥20,000 vehicles per day (OR = 8.28 (2.09-32.80)).

Skin cancer

In a study of 307 cases of non-melanoma skin cancer (basal and/or squamous cell carcinoma) and 229 controls resident in Texas, USA, the most important risk factors were red hair, fair skin, outdoor sun exposure, and a family history of skin cancer (Gamble et al, 1996). Employment at any time in the petroleum industry was associated with a slightly elevated risk of developing concurrent basal and squamous cell carcinomas (OR = 2.10 (1.08-4.09)).

In a Dutch study of 140 cases with non-metastasised melanoma and 181 controls with other types of malignancy, increased risks were found for subjects ever employed in the electronics, metal and transport and communication industries (Nelemans et al, 1993). However, they were not statistically significant and there were no trends for duration of employment or latency. Also, there was no increase in risk for workers in the chemical industry.

The American Cancer Society enrolled 1.2 million randomly selected people in a study of life style and environmental factors in relation to cancer mortality, 2780 of whom had a history of or developed melanoma during the 6-year study follow-up period (Pion et al, 1995). These cases were compared with controls selected from the remaining people enrolled on a 1:3 basis and matched for age, sex, race, and geographic location. In men, the risk of melanoma was elevated in high-paying versus low-paying jobs (OR = 1.58; $p < 0.001$) and in white-collar versus blue-collar jobs (OR = 1.33; $p < 0.001$), but unrelated to outdoor versus indoor occupations. In women, the findings were inconclusive. The only specific work-related risk factor was exposure to x-rays. Other large community-based studies in Australia, Britain and Sweden came to similar results (Burnley, 1997; Vågerö et al, 1990).

Other cancers

Gérin et al. (1998) conducted a community-based case-control study of 19 specific cancers excluding leukaemia in 3730 men and 533 controls aged 35-70 years and resident in Montreal, Canada. Their exposure to various workplace chemicals including benzene, toluene, xylenes and styrene was estimated through interviews and from workplace records. There were 737 subjects, mainly mechanics, service station attendants and shoe workers, who had been exposed to benzene, usually with concomitant exposure to toluene and xylenes. However, there was no evidence that the risks of common cancers such as those of the gastrointestinal tract, lungs, prostate, bladder or kidney were related to exposure to any of the chemicals under investigation. For NHL (215 cases) and melanoma (103 cases), the ORs for benzene exposure were <1.00.

The industry-based study by Wong et al. (1999) mentioned above under cancer of the blood and lymphatic system also included 12 cases of kidney cancer. There was no difference between cases and controls with regard to duration of exposure or to cumulative or peak exposures to hydrocarbons.

Petralia et al. (1999) studied the relationship between the risk of pre-menopausal breast cancer and exposure to benzene or polycyclic aromatic hydrocarbons in 301 cases and 316 controls sampled from two counties in New York State between 1986-91. There were 55 breast cancer cases and 35 controls who had been exposed to benzene, mainly through employment as laboratory technicians, painters, sculptors, craft-artists, or assemblers in the motor vehicle industry. Following adjustment for age, years of education, age at first birth, age at menarche, history of benign breast disease, history of breast cancer in a first-degree relative, body mass index, and months of lactation, four variables relating to benzene had ORs that reached or approached statistical significance. These were duration of exposure ≥4 years (2.57 (1.23-4.73)); medium-to-high probability of exposure (1.95 (1.14-3.33)); low average exposure intensity (2.36 (1.30-4.30)); and medium-to-high cumulative exposure (1.93 (1.00-3.72)).

In Denmark, Hansen (2000) conducted a nationwide register-based case-control study on primary breast cancer in men, which included 230 cases and 12,880

controls. Allowing for a lag time ≥10 years and after adjustment for socio-economic status, the OR was 2.5 (1.3-4.5) in all men with >3 months of employment as car mechanic or petrol station worker and 5.4 (2.4-11.9) in men who were <40 years old when first employed in those occupations. Exposure to benzene was not assessed.

Conclusions

While the case-control studies reviewed above have limitations in statistical power and study quality, there are several which indicate that occupation and/or benzene exposure is associated with an increased risk of cancer of the blood and lymphatic system, including, but not limited to AML and other leukaemias. Positively identified risk factors include employment in upstream petroleum production, at petroleum terminals, on deck on chemical or petroleum product tankers, and as a mechanic, machinist, chemical worker, chemist, painter, driver or logger. The studies by Health Watch (1998) and Richardson (1992) found that the risk was significantly elevated at relatively high, but not at lower levels of exposure to benzene.

There are some indications that parental exposure to benzene and in particular maternal exposure during pregnancy may be linked to childhood leukaemia, but the overall evidence for this association is limited at present. Other tentative findings suggest a relationship between the risk of breast cancer and exposure of female workers to benzene on the one hand and between male breast cancer and exposure to petrol and vehicle exhaust on the other.

11.6.3 Ecological studies

Leukaemia and car traffic variables

Robinson (1982, 1991) found a strong relationship between leukaemia mortality and vehicle usage (as monitored by the annual rate of vehicle fatalities) in Australia, France, Germany, Italy, Japan, The Netherlands, UK and USA. In a study of all incident childhood cancer in Denver, Colerado, USA, between 1976-83, Savitz & Feingold (1989) found a statistically significant association between traffic density at the place of residence at the time of diagnosis and the risk for all leukaemia combined. In a sample of 22 British counties, Wolff (1992) found a significant correlation coefficient between the incidence of AML, lymphoma, ALL, CLL and low-grade NHL for the years 1984-88 and the number of cars per household reported in the 1981 Great Britain Population Census.

Swaen & Slangen (1995) found a non-significant, inverse relationship between leukaemia mortality and petrol consumption in 19 European countries, but a weak positive association between the incidence of myeloid leukaemia and the consumption of petrol per km^2. However, both findings could be due to unrelated factors such as changes in prognosis or country differences in leukaemia case ascertainment. As such, the authors concluded that their study did not support an association between petrol consumption and leukaemia incidence or mortality.

Nordlinder & Järvholm (1997) compared the 1975 car density in Swedish local government areas with the 1975-1985 cumulative incidence of ALL, AML, CML and NHL in persons under 25. None of these showed a significant correlation with car density, although the combined group of areas with >5 cars/km^2 had a higher rate of AML than those with <5 cars/km^2 (95% CI for the difference: 0.1-4.0 cases/10^6 person-years).

Leukaemia and industry emission variables

There was an excess mortality rate between 1950-69 from childhood leukaemia and young adult Hodgkin's disease and lymphoma among residents in the heavily industrialised New Jersey-New York-Philadelphia Metropolitan Region compared to USA as a whole (Greenberg et al, 1980). However, other early studies of populations residing in the vicinity of petroleum refineries and chemical plants have not suggested links with cancers of the blood and lymphatic system (Blot et al, 1977; Hearey et al, 1980; Hoover et al, 1975; Kaldor et al, 1984).

A more recent study of an area within a radius of 3.0 km of a large petrochemical plant in South Wales, UK, compared the 1974-91 incidence of leukaemia and lymphoma with onset before age 25 among study area residents with those in the regional population (Lyons et al, 1995). There were no statistically significant differences, although the number of observed cases was higher than expected for all disease types except myeloid leukaemia. Data from ambient monitoring for benzene around the site showed monthly peak values varying from 4-16 ppb.

11.7 The Illawarra leukaemia cluster

The Illawarra leukaemia cluster refers to a group of 12 cases of leukaemia that occurred in 1989-96 in three contiguous suburbs bordering the Port Kembla steelworks near Wollongong, New South Wales (Westley-Wise et al, 1999). There were 3 cases of AML, 3 of CML and 6 of ALL. All cases were under 44 years of age at the time of diagnosis and nine were ≤20 years of age. Four attended the same local high school in the late 1980s, three of them in the same school year. Using the rest of the region as reference population, only 3.49 cases were expected, corresponding to a SIR of 3.44 (1.42-6.92).

The regional health authority launched an investigation which examined a wide range of possible explanations for the cluster, including benzene emissions from the coking ovens and coal gas by-product plant at the steelworks. It was estimated that ambient air levels of benzene had averaged up to 3 ppb since 1970, although the mean levels measured in 1996 did not exceed 1 ppb within 1.6 km from the plant. As this is less than one-thousandth of the level at which leukaemia risk has been identified in occupational epidemiological studies, the authors concluded that the cause of the cluster was uncertain, although an association with chemical exposures could not be totally excluded. The odds that it was due to chance were calculated at 1 in 4-8000 (Westley-Wise & Hogan, 1997).

11.8 Summary and conclusions

There is anecdotal evidence that acute exposure to benzene vapours causes dizziness and other CNS effects at concentrations above 25 ppm and eye, mucous membrane and skin irritation at levels above 30-60 ppm. Furthermore, aspiration of liquid benzene has been observed to cause lung oedema and bleeding. Deaths from cardio-respiratory arrest have occurred following short-term inhalation of 20,000 ppm benzene, or from ingestion of a single dose of 125 mg benzene per kg BW.

Several studies demonstrate that repeated exposure to benzene may induce bone marrow depression, cause damage to genetic material and induce leukaemia, specifically AML. Some studies also point to an association between benzene exposure and the risk for lymphoma, specifically NHL and MM. For bone marrow depression, the best estimate for a LOAEL is 7.6 ppm (TWA_8), based on current

data. An appropriate NOAEL has not been determined, although studies with various limitations indicate that it is likely to be >0.5 ppm (TWA_8). Dose-related structural or numerical chromosome aberrations have been detected in peripheral LC of workers exposed to benzene levels above 10 ppm (TWA_8), but a threshold level has not been identified. The risk of developing leukaemia increases with exposure and has been shown to be significantly elevated above, but not below, a cumulative exposure of 50 ppm-years, corresponding to an average occupational exposure of 1.25 ppm (TWA_8) over 40 years. However, this finding derives from a single cohort study with insufficient statistical power to rule out the possibility of some increase in leukaemia risk at lower exposures.

In addition, some studies suggest an association between repeated exposure to benzene or benzene-containing products and several other adverse health effects, including menstruation disorders, spontaneous abortions, melanoma and breast cancer in adults and reduced birth weight and leukaemia in the children of exposed parents. However, considering the multiple exposure circumstances in most studies and the limited consistency of the findings reviewed above, the human database does not in itself suffice to establish a causal relationship between these effects and benzene exposure.

12. Modes of Action

While a general overview of benzene metabolism has been presented in Section 9, this section presents a review of the evidence for the molecular basis of the action of benzene metabolites. Several reviews of benzene metabolism and the proposed mechanisms of toxicity have been published (Ross, 1996; Snyder, 2000; Snyder et al, 1993; Snyder & Hedli, 1996; Yardley-Jones et al, 1991).

Exposure to benzene can result in haematotoxicity, immunotoxicity and carcinogenicity in humans and animals. Haematotoxicity resulting from chronic benzene exposure can present as anaemia, aplastic anaemia, leukopenia, lymphocytopenia, thrombocytopenia, or pancytopenia (Aksoy, 1989). The principal carcinogenic response in humans to chronic benzene exposure is leukaemia while other animals tend to produce solid tumours in specific organs. While the liver is the initial site for the biotransformation of benzene, hepatotoxicity is not a consequence of benzene exposure. However, a number of studies have shown that for benzene to produce haematotoxicity in animals it must first be metabolised by the liver (Andrews et al, 1977; Sammett et al, 1979). Subsequent accumulation of the major hepatic metabolites, phenol, hydroquinone and catechol, occurs in the bone marrow where they are known to persist for varying durations after exposure to benzene ceases (Rickert et al, 1979). Longacre et al. (1981) observed that strains of mice that exhibit greater sensitivity towards benzene accumulate more benzene metabolites (water-soluble and covalently bound) in bone marrow compared to less sensitive strains. However, administration of specific benzene metabolites to test animals has failed to reproduce the characteristic toxicity of benzene although co-administration of phenol and hydroquinone has been shown to mimic its haematotoxic effects (Eastmond et al, 1987). These data suggest that phenolic metabolites of benzene in combination and not the parent molecule are responsible for the haematotoxicity of benzene. The data further suggest that subsequent biotransformation of the hepatic metabolites to reactive intermediates is required and that this occurs within the bone marrow and those animal organs exhibiting solid tumours.

12.1 Activation of benzene metabolites

In order for the phenolic metabolites of benzene to exert their toxic effect on bone marrow, they must undergo activation to their oxidised forms. Once activated, they can participate in covalent binding reactions with macromolecules. Several studies have identified the presence of peroxidase enzymes in bone marrow and other tissues as the primary mechanism by which activation of benzene phenolic metabolites is achieved (Eastmond et al, 1986; Lévay et al, 1993). The peroxidases are a diverse class of enzymes that catalyse the general reaction:

$$\text{Donor} + H_2O_2 \rightarrow \text{oxidised donor} + 2H_2O.$$

While peroxidases generally act to detoxify peroxides, including hydrogen peroxide, that form within cells as a result of several metabolic reactions, a number of specialised peroxidases with other functions have evolved. In particular, the leukocytes of several species, including humans, have been shown to possess large amounts of a specific form, myeloperoxidase (Bainton et al, 1971; Himmelhoch et al, 1969). In concert with the leukocyte nicotinamide adenine dinucleotide

phosphate (NADPH) oxidase system that causes hydrogen peroxide to be produced (Patriarca et al, 1971), myeloperoxidase plays a crucial role in the host defence system by producing a potent microbicidal oxidant that protects the host from microorganisms. Immature leukocytes in the bone marrow generally have higher levels of myeloperoxidase than circulating mature cells (Bainton et al, 1971). Consequently, bone marrow has considerable capacity to metabolise suitable electron donors including the benzene metabolites, phenol, hydroquinone, catechol and 1,2,4-trihydroxybenzene, to reactive species.

12.1.1 Activation of phenol

Incubation of phenol with human leukocyte lysates, which contain myeloperoxidase, have demonstrated the formation of reactive intermediates that covalently bind to macromolecules in the presence of hydrogen peroxide as a co-oxidant (Eastmond et al, 1986; Smith et al, 1989). Eastmond et al. (1986) concluded that although 4,4'-biphenol and diphenoquinone were identifiable reaction products derived from the oxidation of phenol, only 6% of the covalent binding could be attributed to diphenoquinone with most of the covalent binding observed due to other reactive species, possibly the phenoxy radical or oxidation products of 2,2'-biphenol or 4,4'-biphenol. However, in the presence of hydroquinone, phenol appears to undergo a recycling process such that the initial phenoxy radical is reduced to phenol by transferring an electron to hydroquinone (Smith et al, 1989), thus limiting the formation of biphenol derivatives.

12.1.2 Activation of hydroquinone and catechol

Under physiological conditions, hydroquinone, catechol and 1,2,4-trihydroxybenzene can undergo autoxidation to their respective semiquinone and quinone forms (Brunmark & Cadenas, 1989) or their oxidation can be facilitated by the presence of a peroxidase and hydrogen peroxide (Sadler et al, 1988; Schlosser et al, 1989; Smith et al, 1989). Quinones are chemically reactive species capable of depleting intracellular glutathione, promoting lipid peroxidation and forming covalent adducts with macromolecules (Bolton et al, 2000; Irons, 1985; Monks et al, 1992). Several studies have shown that hydroquinone and catechol are readily oxidised by human myeloperoxidase (Eastmond et al, 1986; Sadler, et al, 1988) and it has been observed that the oxidation of hydroquinone to benzoquinone by peroxidase enzymes is enhanced by the presence of excess phenol which acts as a co-oxidant obviating the need for hydrogen peroxide to drive the reaction (Smith et al, 1989; Subrahmanyam, et al, 1990). Hydroquinone was found to be metabolised by activated human neutrophils to covalent-binding species and the amount of binding could be increased by approximately 70% by the addition of phenol (Eastmond et al, 1987). Subrahmanyam et al. (1990) reported that the presence of phenol enhanced the covalent binding of [^{3}H]-hydroquinone metabolites to macromolecules of mouse blood and bone marrow, but not to the kidneys or liver. It was further noted that hydroquinone enhanced binding of [^{3}H]-phenol metabolites in blood, bone marrow and the kidneys but inhibited binding in the liver. In contrast, catechol did not enhance [^{3}H]-hydroquinone metabolite binding.

Sadler et al. (1988) observed that the oxidation of catechol by human neutrophil peroxidases (myeloperoxidase) resulted in the formation of 1,2-benzosemiquinone and 1,2-benzoquinone. Bhat et al. (1988) found that the addition of [^{14}C]-catechol to rat or human bone marrow cells resulted in the formation of a glutathione-conjugate and covalent binding of radiolabel to protein. Both conjugate formation and the binding of radiolabel were substantially increased by the presence of

hydrogen peroxide or phenol, however, protein binding could be markedly decreased by the presence of exogenous glutathione (GSH) or hydroquinone.

12.1.3 Role of cyclooxygenase

In addition to activation by peroxidases, phenol and hydroquinones can be activated by prostaglandin H synthase (cyclooxygenase), an enzyme with oxygenase and endoperoxidase activity (Markey et al, 1987; Schlosser et al, 1989). Acting as an endoperoxidase, the enzyme requires an oxidant as a co-substrate which phenol or hydroquinones can replace (Markey et al, 1987). Prostaglandin H synthase is present in a number of bone marrow-derived cells including monocyte/macrophage populations and platelets and converts arachidonic acid to several prostaglandins including prostaglandin E_2 (PGE_2). PGE_2 plays a major role in the inhibition of progenitor cell proliferation and differentiation (Gentile and Pelus, 1987). In vitro, both phenol and hydroquinone are activated by cell lysates containing prostaglandin H synthase or by the purified enzyme and in the presence of arachidonic acid or hydrogen peroxide (Schlosser et al, 1989).

The role of prostaglandin H synthase activity has been demonstrated in a number of mouse strains ($B6C3F_1$, DBA/2 and C57BL/6) where it was shown that bone marrow toxicity could be reduced by prior treatment of the animals with non-steroidal anti-inflammatory drugs (aspirin, indomethacin or meclofenamate) that inhibit prostaglandin H synthase activity (Gaido and Wierda, 1987; Kalf et al, 1989). Pirozzi et al. (1989) further demonstrated that benzene-induced bone marrow depression and micronucleus formation in erythrocytes of C57B1/6 mice could be prevented by the co-administration of indomethacin and that protection was achieved at doses that did not inhibit cytochrome P450 or myeloperoxidase activity.

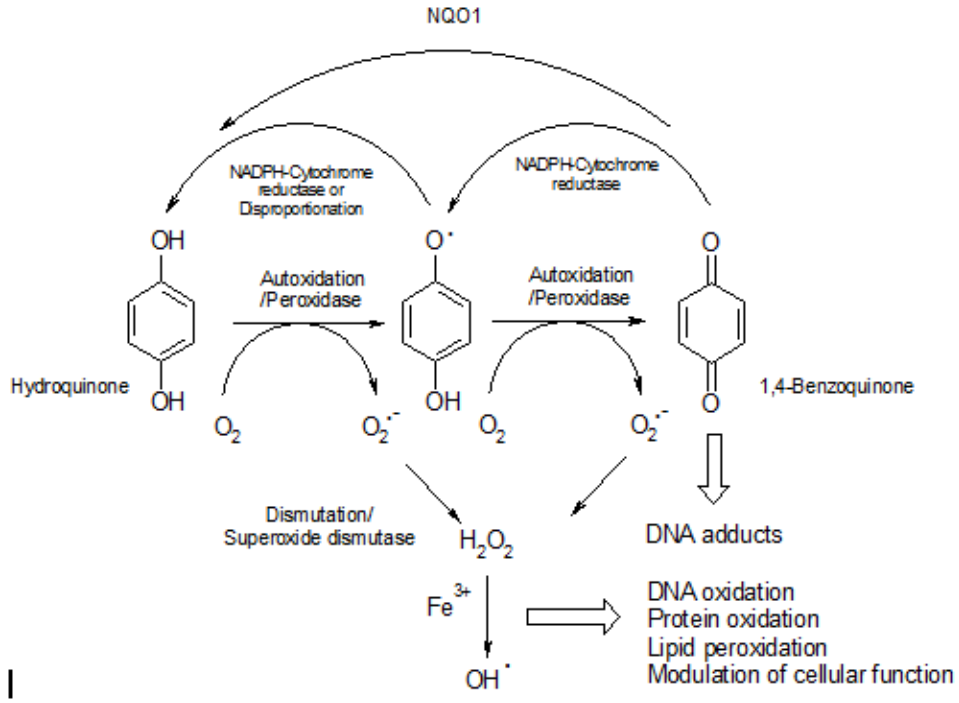
The bio-activation of catechol by prostaglandin H synthase activity in rat bone marrow appears to be limited as the addition of arachidonic acid provided only a small but significant ($p<0.05$) increase in covalent binding which was of limited duration (Bhat et al, 1988).

12.1.4 Formation of reactive oxygen species

In addition to the formation of semiquinone and quinone species, the oxidation of hydroquinones results in the formation of reactive oxygen species. Initially, molecular oxygen is reduced to superoxide anion which, by dismutation, is converted to hydrogen peroxide (Figure 12.1). In the presence of transition metal ions (for example, iron) the very reactive hydroxyl radical can form. These reactive species can promote the oxidation of protein and DNA bases, induction of chromosomal aberrations, lipid peroxidation and the modulation of cellular functions.

While hydroquinone and its semiquinone radical can both reduce molecular oxygen to superoxide, Sadler et al. (1988) found superoxide production by catechol to be limited to the first one electron reduction step to 1,2-benzosemiquinone with molecular oxygen being unable to effect the subsequent oxidation of the semiquinone to the quinone form. In contrast, 1,2,4-benzenetriol undergoes rapid autoxidation to yield hydrogen peroxide (Brunmark & Cadenas, 1988).

Figure 12.1. Redox cycle of hydroquinone with formation of reactive oxygen species and biological effects



The detoxification of quinones can be achieved by a two-electron reduction to their fully reduced forms. Two enzymes involved in the reduction of quinones are NADPH-cytochrome reductase and NAD(P)H:quinone oxidoreductase (NQO1; DT-diaphorase; Lind et al, 1982). In the case of NADPH-cytochrome reductase, reduction of the quinone to a semiquinone is achieved by a one-electron transfer to give a semiquinone and a second electron is transferred to molecular oxygen to yield the superoxide anion. The resulting semiquinone is then free to autoxidise to the quinone producing more superoxide. However, it has been proposed that redox cycling of the semiquinone could not be maintained by NADPH-cytochrome reductase at physiological pH due to protonation of the semiquinone thus minimising superoxide production (Boersma et al, 1994). In the case of NQO1, reduction to the hydroquinone is achieved by a simultaneous two-electron transfer to the quinone with no reduction of molecular oxygen. The redox cycle for hydroquinone, the role of NADPH-cytochrome reductase and NQO1 and the biological effects of these processes are illustrated in Figure 12.1.

In cells that possess both peroxidase and NQO1 activities, the ratio of the two enzymes may determine the extent to which reactive metabolites form. Thus a high intracellular myeloperoxidase/NQO1 ratio, such as occurs in human stroma and $CD34^+$ bone marrow progenitor cells, may result in a greater risk of benzene-induced cellular toxicity (Ross et al, 1996b). Although characterisation of NQO1 activity in primary cultures of mouse bone marrow stromal cells was found to be low, the enzyme was shown to be inducible and induction of the enzyme conferred protection against hydroquinone-induced toxicity (Twerdok et al, 1992).

Conjugation reactions, for example with GSH, can enhance the ability of hydroquinones to autoxidise. Glutathionyl hydroquinone, identified as a urinary benzene metabolite (Nerland & Pierce, 1990), was found by Brunmark & Cadenas (1988) to autoxidise at a rate 8-fold faster than hydroquinone. Rao (1996)

concluded that, in vitro, glutathionyl hydroquinone acted as a potent pro-oxidant based on its ability to degrade DNA.

Reactive oxygen species may also form due to the reduction of molecular oxygen by the action of cytochromes P450. Johannson & Ingelman-Sundberg (1983) observed that benzene could be directly oxidized to phenol by hydroxyl radicals derived from the reduction of molecular oxygen by microsomal cytochrome P450 activity or reconstituted enzyme systems. Similarly, Kahn et al. (1990) detected the presence of hydroxyl radicals during the NADPH-dependent metabolism of benzene by rat bone marrow microsomal preparations.

12.2 Reactivity of benzene metabolites

Results derived from in vivo and in vitro studies indicate that a number of mechanisms contribute to the cytotoxicity, genotoxicity and carcinogenicity of benzene metabolites. Cytotoxicity can arise due to depletion of intracellular GSH and changes in intracellular redox status (Ludewig et al, 1989; Rao & Snyder, 1995; Witz, 1985) and covalent binding of benzene metabolites to macromolecules (Latriano et al, 1989; Lutz and Schlatter, 1977; Mazzullo et al, 1989; Snyder et al, 1987). Metabolites suspected of contributing to the genotoxicity and carcinogenicity of benzene include benzene oxide, hydroquinone, catechol, 1,2,4-trihydroxybenzene and *trans,trans*-muconaldehyde. The effects induced by these metabolites comprise DNA base alterations, chromosome structural aberrations and aneuploidy. However, the metabolite concentrations at which many of these effects have been shown to occur in vitro are higher than those expected to occur in vivo.

12.2.1 Genotoxicity

Several studies have demonstrated the formation of DNA adducts after incubation of benzene metabolites with purified DNA. Hydroquinone when incubated with calf thymus DNA resulted in the formation of deoxycytidine (Pongracz et al, 1990), deoxyadenosine (Pongracz & Bodell, 1991) and deoxyguanosine adducts (Jowa et al, 1990). Gut et al. (1996) were able to demonstrate the formation of the N-7 guanine adduct on exposure of calf thymus DNA to benzene oxide under in vitro conditions while Latriano et al. (1989) found *trans,trans*-muconaldehyde to form adducts with deoxyguanosine. In addition to nuclear DNA, in vitro studies have shown mitochondrial DNA, derived from bone marrow mitoplasts, to undergo alkylation by benzene metabolites (Kalf et al, 1985; Snyder et al, 1987).

Under cellular conditions, a comparison of the ability of benzene metabolites to induce DNA adduct formation in HL-60 cells, a promyelocytic leukemia cell line, found hydroquinone to be 7-9 times more effective at inducing such adducts than catechol or 1,2,4-trihydroxybenzene and that a correlation existed between adduct formation and cytotoxicity. Co-incubation of hydroquinone with either catechol or 1,2,4-trihydroxybenzene produced a synergistic effect that was 3-6 times greater than the added effects of each metabolite. It was further observed that DNA adducts form in the presence of benzene metabolite mixtures which are not observed when cells are incubated with the individual metabolites, leading the authors to suggest that other processes leading to adduct formation may be involved (Lévay & Bodell, 1992; Lévay et al, 1991). Chenna et al. (1995) subsequently identified an enzyme with glycosylase activity that excises deoxycytidine and deoxyadenosine adducts of benzoquinone from DNA.

It is noteworthy that transfected HL-60 cells expressing a high level of NQO1 activity exhibited lower levels of DNA adduct formation when exposed to hydroquinone compared to non-transfected HL60 cells which are deficient in NQO1 activity. Similarly, C15 cells, a myeloperoxidase-deficient HL-60 subline, produced lower levels of DNA adducts with hydroquinone compared to HL-60 cells which normally express high levels of myeloperoxidase (Wiemels et al, 1999).

The ability of hydroquinone species to induce mutations has been demonstrated by Joseph et al. (1998). In a series of in vitro experiments, it was demonstrated that sequence-specific frame shift mutations could be caused by hydroquinone, but not semiquinone, benzoquinone or reactive oxygen species, in the supF tRNA gene. It was further demonstrated that BALBc/3T3 cells undergo transformation by hydroquinone (15 μM) and that the frequency of transformation could be increased by a tumour promoter. Such initiated cells produced tumours with 100% frequency when injected into severe combined immunodeficient (SCID) mice. Sakai et al. (1995) previously had shown that benzoquinone caused initiation in a two-stage model of carcinogenesis using BALB/3T3 cells.

Mueller et al. (1987) detected the alkylation product of benzene oxide, N-7-phenylguanine, in the urine of rats exposed to benzene (500 ppm) for 8 h while Norpoth et al. (1996) detected several benzene-derived urinary guanine adducts following the administration of benzene to rats. However, it should be noted that the presence of N-7-phenylguanine in the urine does not provide sufficient evidence that the adduct is derived from DNA excision-repair activities. The presence of benzene-induced DNA adducts has been detected in the tissues of rats dosed with [^{14}C]-benzene (Lutz and Schlatter, 1977; Mazzullo et al, 1989) although the nature of the adducts was not investigated. However, Reddy et al. (1989b) found only equivocal evidence for the in vivo formation of aromatic DNA adducts in the bone marrow, liver, kidney and mammary gland of benzene-treated female Sprague-Dawley rats. DNA isolated from Zymbal glands was found to contain 4 adducts per 10^9 DNA nucleotides, although the adducts did not correspond to major adducts described in in vitro studies. Thus it was concluded that DNA-quinone adduct formation in the rat is not extensive, possibly due to the efficient elimination of quinones by other mechanisms. In addition to forming DNA adducts in the bone marrow of experimental animals, benzene exposure produced DNA adducts in the livers of male mice (Lutz and Schlatter, 1977); however, liver tumours were not observed in 2-year carcinogenicity studies of these animals (NTP, 1986).

The mutation frequency of V75 Chinese hamster cells increased in a dose-dependent manner after treatment for 1 h with benzoquinone, an effect that was found to be independent of intracellular GSH status and observed at low (< 10 μM) concentrations. The frequency of micronucleated cells was also increased by benzoquinone but only at concentrations greater than 20 μM. In contrast, benzoquinone did not induce sister chromatid exchanges at any concentration up to 100 μM (Ludewig et al, 1989).

As described in Sections 10.6 and 11.5, several studies have demonstrated chromosomal aberrations in experimental animals and humans following exposure to benzene. While the administration of benzene to CD-1 mice resulted in micronuclei formation, treatment with either phenol, hydroquinone or catechol failed to induce micronuclei (Gad-el-Karim et al, 1985). Barale et al. (1990) demonstrated, in vivo, a synergistic effect on micronuclei formation in CD-1 mice bone marrow cells by the concurrent administration of hydroquinone and phenol.

Lewis et al. (1988) reported that hydroquinone, under in vitro conditions, caused DNA to form single- and double-strand breaks by a mechanism that was independent of reactive oxygen species. In contrast, catechol did not induce DNA damage. These investigators further observed that DNA could be degraded by 1,2,4-trihydroxybenzene, an effect inhibited by scavengers of reactive oxygen species. When tested together in vitro, hydroquinone and catechol produced a synergistic effect on micronuclei formation in human lymphocytes, possibly by interfering with mitotic spindle function and disturbing chromosome segregation (Robertson et al, 1991). Benzoquinone has also been reported to interfere with microtubule assembly by blocking a thiol-sensitive binding site (Irons et al, 1981).

12.2.2 Oxidative stress

The formation of reactive oxygen species is a normal part of cellular biochemistry and is considered to be an important component of intracellular signalling processes, including mediating signal transduction within haematopoietic cells initiated by growth factor signals (Sattler et al, 1999). However, exposure of biological systems to excessive levels of reactive oxygen species results in the induction of oxidative stress. Oxidative stress can induce oxidative modification of DNA bases and chromosomal abnormalities, depletion of intracellular GSH, changes in intracellular redox status, peroxidation of lipids, oxidation of proteins and modulation of cellular functions. The role of oxidative stress in benzene-mediated toxicity has been extensively reviewed by Subrahmanyam et al. (1991).

Rao & Snyder (1995) examined the effects of hydroquinone, benzoquinone and 1,2,4-trihydroxybenzene (50 µM) on several parameters of antioxidant defence function of HL-60 cells. The three metabolites did not induce the cells to generate superoxide anion or nitric oxide but did produce detectable levels of hydrogen peroxide. Intracellular GSH levels were depleted by hydroquinone and 1,2,4-trihydroxybenzene but not benzoquinone.

The presence of lipid peroxidation products was found to increase in rat tissues following the administration of benzene (Khan et al, 1984) while urinary levels of malondialdehyde, a biomarker of lipid peroxidation, were elevated in rats receiving hydroquinone (Ekström et al, 1988). The presence of intracellular peroxidation products has been detected in HL60 cells following treatment with either 1 µM benzoquinone or 10 µM hydroquinone (Hiraku & Kawanishi, 1996). Several studies have identified the presence of 8-hydroxydeoxyguanosine (8-OHdG) as a sensitive biomarker of DNA damage due to oxidative stress (Kasai & Nishimura, 1984, 1986; Shigenaga et al, 1989). In two occupational studies in workers known to have benzene exposure, a dose-response relationship was demonstrated between the exposure level and urinary 8-OHdG levels (Lagorio et al, 1994b, Nilsson et al, 1996). However, the presence of 8-OHdG in the urine is not conclusive evidence of DNA excision-repair activities in response to oxidative modification of DNA.

Benzoquinone species and *trans,trans*-muconaldehyde readily react with GSH (Brunmark & Cadenas, 1988; Rao et al, 1982) which can lead to depletion of intracellular GSH levels and changes in intracellular redox status. Treatment of V79 Chinese hamster cells with benzoquinone for 1 h resulted in decreased GSH, NADPH and nicotinamide adenine dinucleotide levels but only at cytotoxic concentrations at or above 100 µM (Ludewig et al, 1989). Ekström et al. (1988) found rat hepatic GSH levels to be depleted after administration of hydroquinone by gavage while the administration of *trans,trans*-muconaldehyde to mice for 10 or 16 days resulted in decreased hepatic sulfhydryl levels (Witz et al, 1985).

The growth of HL-60 cells was found to be stimulated by the presence of hydroquinone within the range of 10-40 μM. Similarly, the incorporation of [^{3}H]-thymidine was enhanced by hydroquinone, benzoquinone or 1,2,4-benzenetriol. However, the effects produced by the three metabolites could be eliminated if the cells were pre-incubated with catalase, an antioxidant specific for hydrogen peroxide. The effects of hydroquinone and benzoquinone could be mimicked by reactive oxygen species produced by a xanthine/xanthine oxidase system. It was further observed that while hydroquinone or benzoquinone did not reduce the cell cycle time they did increase the number of cells entering into S-phase from G_0/G_1 phase (Wiemels & Smith, 1999). The role of reactive oxygen species, and in particular hydrogen peroxide, has been further explored by Sattler et al. (1999). These investigators found haemopoietic growth factors to induce increased levels of reactive oxygen species in MO7e cells, a growth factor-dependent human megakaryocytic cell line. Treatment of these cells with either growth factors or hydrogen peroxide resulted in increased tyrosine phosphorylation of cellular proteins, a key step in intracellular signalling processes.

12.2.3 Modulation of cellular function

The mature macrophage produces interleukin-1 (IL-1), a cytokine essential for stem cell maturation. However, it has been observed that macrophages treated with hydroquinone (10 μM) produce less IL-1 than control cells (Thomas et al, 1989). This is due to the inhibition of calpain, a protease required for the conversion of pre-IL-1 to its active form, by hydroquinone (Renz & Kalf, 1991; Kalf et al, 1996). Treatment of isolated mouse bone marrow-derived macrophages with non-cytotoxic doses of hydroquinone (10 μM) resulted in a 10 to 30% reduction in total calpain activity (Miller et al, 1994). In contrast, the production of PGE_2 by bone marrow cells, in vivo, was enhanced by benzene exposure (Gaido & Wierda, 1987; Kalf et al, 1989) although it is uncertain how the release of arachidonic acid, the precursor of prostaglandins, from phospholipid stores is initiated under these conditions. However, hydroquinone and catechol have been shown to regulate protein kinase C (PKC) activity by producing a short term cytosol-to-membrane translocation of PKC (Gopalakrishna et al, 1994), a key step in the mobilisation of arachidonic acid. Da Silva et al. (1989) have further shown that benzene can directly activate PKC. PGE_2 has been identified as an inhibitor of granulocyte/macrophage progenitor cell proliferation (Gentile & Pelus, 1987).

The growth of granulocyte/macrophage colonies was stimulated in a synergistic manner by co-treatment of mouse bone marrow cells with low concentrations of hydroquinone (10^{-8} to 10^{-5} M) and recombinant granulocyte/macrophage colony stimulating factor (GM-CSF) compared to cells treated with GM-CSF alone. The maximal response was achieved with 1 μM hydroquinone but no effect was observed when phenol, catechol or *trans,trans*-muconaldehyde were substituted for hydroquinone (Irons et al, 1992). While treatment of HL-60 cells with hydroquinone at concentrations between 10-40 μM resulted in an increase in cell proliferation, at a concentration greater than 50 μM hydroquinone caused a decrease in cell viability (Wiemels & Smith, 1999). In a further study, Wiemels et al. (1999) demonstrated that 12 h after treatment with hydroquinone (50 μM) approximately 40% of HL-60 cells were apoptotic as determined by the terminal deoxynucleotidyl-transferase (TdT) assay. Apoptosis is a form of physiological cell death characterised by altered cell morphology including condensation of the cytoplasmic and nuclear compartments and internucleosomal DNA fragmentation. Apoptosis has been observed to occur in a dose-dependent manner when HL-60

cells are treated with hydroquinone and catechol (25 to 100 μM) but not by phenol. Similarly, hydroquinone or catechol induces $CD34^+$ human bone marrow progenitor cells to undergo apoptosis (Moran et al, 1996). These reports support an earlier study in which weak internucleosomal cleavage was observed in HL-60 cells following incubation for 4 h with 20 μM hydroquinone and 5 μM benzoquinone and pronounced cleavage observed at 50 μM hydroquinone and 10 μM benzoquinone using pulse-field gel electrophoresis (Hiraku and Kawanishi, 1996).

12.3 Critical biological effects

12.3.1 Bone marrow toxicity

The critical biological effect of benzene in all experimental species is bone marrow toxicity characterised by a reduction in bone marrow cellularity. Bone marrow consists of stromal cells (composed of macrophage and fibroblastoid cell populations) along with stem and progenitor cell populations that form a complex matrix within which are produced a number of essential regulatory growth factors. Stromal cells regulate stem and progenitor cell proliferation, differentiation and maturation by producing both inducers (colony stimulating factors (CSFs) and interleukins, particularly IL-1) and inhibitors (PGE_2) of cell growth. PGE_2 inhibits cell growth by suppressing the production of CSFs and IL-1. Benzene metabolites appear to disrupt the balance of these regulatory factors by inhibiting production of CSFs and IL-1 and increasing PGE_2 production, although low levels of hydroquinone can replace or augment, in vitro, the effects of growth factors (Wiemels & Smith, 1999). Evidence to support this hypothesis has been provided by experiments in which the co-administration of IL-1 abrogates the effects of benzene treatment. Similarly, if non-steroidal anti-inflammatory agents, which inhibit PGE_2 production and the cyclooxygenase-dependent oxidation of phenol and hydroquinone, are co-administered with benzene, haematotoxicity is not observed. Although increased apoptosis has been observed by exposing bone marrow cells to various benzene metabolites, these effects appear to occur only at high metabolite concentrations.

12.3.2 Leukaemia

Leukaemia is the progressive proliferation of abnormal and usually monoclonal leukocytes in hemopoietic tissues. Benzene-induced leukaemias are typically myelogenous in nature rather than lymphocytic. Currently, the mechanism(s) by which benzene induces leukaemia in susceptible individuals remains obscure. Clinical studies of therapy-related myelodysplastic syndromes and acute myeloid leukaemia have shown an increase in chromosomal aberrations particularly aneuploidy, long-arm deletions and translocations involving chromosomes 5, 7 and 8 (Pedersen-Bjergaard et al, 1995). Individuals with chronic exposure to benzene tend to exhibit similar changes in chromosomes 5 and 7 of peripheral blood lymphocytes (Zhang et al, 1998).

Chromosomal aberrations involving chromosomes 5, 7 and 8 of various cell lines, including blood $CD34^+$ progenitor cells, have been reported to occur, in vitro, in response to low-dose hydroquinone exposure (Smith et al, 2000; Stillman et al, 1997). In particular, $CD34^+$ bone marrow cells were observed to lose chromosome 7 accompanied by selective deletion of the long-arm of chromosome 5 (5q31) but no changes in chromosome 8 (Stillman et al, 2000). Stillman et al. (1999) have also

reported that while catechol does not alter cellular cytogenetics, a dose-dependent synergistic effect is observed between hydroquinone and catechol. The combination of metabolites induces changes in chromosome 5 not seen with hydroquinone alone, a result analogous to the synergistic effect on micronuclei formation in human lymphocytes described by Robertson et al. (1991).

A study of patients with therapy-related AML identified a close correlation between the use of drugs with DNA-topoisomerase inhibitor activity and aberrations in chromosomes 5, 7 and 8 (Super et al, 1993). Topoisomerases are a class of nuclear proteins (endonucleases) that convert one topological version of DNA into another by catalyzing the breakage and reformation of DNA phosphodiester linkages. They are involved in DNA replication and transcription, DNA repair, chromosome segregation and maintain genomic stability. Due to the sulfhydryl-dependent nature of topoisomerases and the ability of several benzene metabolites to modify sulfhydryl groups, inhibition of topoisomerase activity by benzene metabolites has been proposed as a mechanism for leukaemia formation. Chen & Eastmond (1995) found no evidence for topoisomerase I inhibition by phenol, catechol, hydroquinone, benzoquinone or 1,2,4-benzenetriol at concentrations up to 1000 μM. Similarly, topoisomerase II activity was not inhibited by benzene metabolites at concentrations less than 500 μM with the exception of 1,2,4-benzenetriol which was inhibitory at 250 μM. The activation of phenol by a peroxidase and hydrogen peroxide system resulted in inhibition at 50 μM and the products of this reaction, 2,2'-biphenol and 4,4'-biphenol were found to be inhibitory at 500 μM, whereas the peroxidase activation products of these compounds were inhibitory at 100 and 10 μM respectively. However, Parke and Williams (1953) failed to find any evidence for the in vivo formation of biphenol products after benzene exposure and there is evidence that these metabolites do not readily form in the presence of hydroquinone (Smith et al, 1989). In contrast, Hutt and Kalf (1996) found topoisomerase II activity to be inhibited by hydroquinone or benzoquinone at 6 and 3 μM respectively.

In addition to modulation of topoisomerase activity, benzene metabolites can modify other nuclear proteins including tubulin (Pfeiffer & Metzler, 1996) and produce DNA-protein cross-links (Schoenfeld & Witz, 1999) which may contribute to chromosomal aberrations and the development of leukaemia. It has been postulated that chromosomal aberrations could result in inactivation of tumour suppressor genes, such as p53, activation of proto-oncogenes and altered expression of growth-factor and growth-factor receptor genes on the aberrant chromosomes (Irons and Stillman, 1996; Smith, 1996). Similarly, the formation of apurinic sites due to depurination by N-7 guanine adducts of benzene oxide (Gut et al, 1996) could result in misreplication of DNA and contribute to the development of leukaemia, as could oxidative DNA base lesions due to benzene-induced oxidative stress.

12.3.3 Tumours in Zymbal, Harderian, lacrimal and mammary glands

In addition to haematopoietic abnormalities, rodents exposed to benzene develop solid tumours in the Zymbal, Harderian, lacrimal and mammary glands, although other organs and tissues may also be involved (Huff et al, 1989). The mechanisms by which benzene induces tumours in these glands have not been extensively investigated. Biochemical characterisation has revealed the presence of high levels of peroxidase enzymes which can activate phenolic metabolites of benzene to reactive species capable of modifying DNA and altering cellular functions as described above. Humans lack an anatomical equivalent of the Zymbal gland and

the human Harderian gland is only of rudimentary development and has not been characterised with respect to peroxidase activity.

Studies by Low et al. (1989) indicate that neither benzene nor its metabolites accumulate in the rat Zymbal gland, a sebaceous gland of the external ear duct of rodents. However, examination of Zymbal gland tissue after oral administration of benzene revealed phenol and hydroquinone to constitute 3% and 30% respectively of unconjugated metabolites. Phenyl glucuronide accounted for 35% of conjugated metabolites but phenylsulfate could not be detected. The absence of phenylsulfate was attributed to a lack of sulfotransferase activity in this tissue. In contrast, Osborne et al. (1980) found the Zymbal gland to exhibit a high level of peroxidase activity indicating that activation of phenolic benzene metabolites could occur in this organ. Reddy et al. (1989a) subsequently identified DNA adducts in excised Zymbal glands after incubation with benzene or its metabolites. The combination of low sulfotransferase and high peroxidase activity would appear to be conducive to the formation of reactive metabolites in the Zymbal gland, thus facilitating tumour formation.

Both lacrimal glands and the accessory lacrimal glands, the Harderian glands, develop tumours in response to benzene exposure. Biochemical characterisation of these glands has demonstrated the presence of high constitutive levels of lactoperoxidase (Morrison & Allen, 1966), which can activate phenolic metabolites of benzene to reactive species in the same manner as myeloperoxidase.

Mammary gland tumours have been observed in rodents in response to benzene (Huff et al, 1989) and limited epidemiological evidence suggests an association between exposure to benzene or benzene-containing products and mammary tumours in humans (Hansen, 2000; Petralia et al, 1999; see Section 11.6.2). The mechanism for the formation of these mammary tumours is uncertain. Reddy et al. (1989b) failed to detect DNA adducts associated with the mammary gland of female rats after 10 weeks of benzene exposure, suggesting an epigenetic mechanism may be involved. However, as stated in Section 9, Low et al. (1989) found the distribution of radiolabel in female rats (Sprague-Dawley) to vary depending on the dose of [^{14}C]-benzene administered. When comparing doses of benzene at 0.15, 1.5 and 15 mg/kg bw, the highest dose resulted in a substantial increase in the amount of radiolabel associated with the mammary gland and bone marrow compared to other tissues at the lesser doses. Mammary tissue is richly perfused with blood and has a high fat content which allows for the accumulation of benzene metabolites. It also contains lactoperoxidase which has been shown to metabolise phenolic compounds to reactive species (Monzani et al, 1997). Consequently, benzene metabolites may become activated within mammary tissue resulting in altered cellular function and carcinogenesis.

12.4 Interindividual variations in susceptibility

12.4.1 Gender effects

While several studies have reported gender-dependent differences in the metabolism and/or toxicity of benzene in mice, there are no reliable data to indicate that there are gender differences in humans with respect to either the metabolism of benzene or susceptibility to benzene toxicity.

Male Swiss (CD-1) mice exposed to benzene exhibited more severe benzene-related toxicity, including genotoxic effects, than females (Meyne and Legator,

1980; Ward et al, 1985). Similarly, suppression of bone marrow cellularity in male DBA/2 mice was greater than females after exposure to benzene (Luke et al, 1988a). Corti and Snyder (1996) found, using Swiss Webster mice exposed to benzene (10 ppm) for 6 h over 10 days, that the number of erythoid colony forming units (CFU-E) had decreased in the bone marrow of adult-exposed males, *in utero*-exposed males and foetal male livers compared to female adults and foetuses. It was further shown by Corti and Snyder (1998), in vitro, that isolated CFU-E derived from male mice were more susceptible to individual benzene metabolites then female isolates.

A marked gender-related difference was observed in the hepatic glutathione-S-transferase (GST) activity of CD-1 mice with the π isoform exhibiting approximately 25% greater activity towards *trans,trans*-muconaldehyde in the females compared to males (Goon et al, 1993). Investigations of gender-related differences in benzene metabolism by mouse bone marrow have not, as yet, been undertaken. Hu et al. (1993) observed that microsomes prepared from the kidneys (but not livers) of male mice (C3H/HeJ) possessed CYP2E1 activity up to 50-fold higher for acetaminophen metabolism compared to female mice. It was further observed that the administration of testosterone to female mice increased the CYP2E1 activity in the kidneys of females. Supporting evidence for the role of metabolic gender-differences was provided by Kenyon et al. (1995) who found that male mice ($B6C3F_1$) excreted more hydroquinone glucuronide when dosed with phenol compared to female mice. In a subsequent study, Kenyon et al. (1998) found bone marrow levels of phenol and hydroquinone to be higher in male mice ($B6C3F_1$) compared to female mice after exposure to benzene.

Attempts to demonstrate gender differences in benzene metabolism in humans by comparing urinary metabolites (*trans,trans*-muconic acid and phenylmercapturic acid) to benzene exposure levels have produced negative results (Inoue et al, 1989; Inoue, 2000).

12.4.2 Genetic polymorphisms

It has been observed that different strains of male mice (DBA/2, C57B1/B6 and $B6C3F_1$) exhibit differing sensitivities to benzene when exposed under identical conditions (Luke et al, 1988b; Pirozzi et al, 1989) and that the metabolic profile of urinary benzene metabolites is strain-dependent (Longacre et al, 1981). These data suggest that individual responses to benzene may be genetically determined. Johnson & Lucier (1992) concluded from an analysis of *trans,trans*-muconic acid biomarker assays in humans that genetic variability may account, in part, for the variance between benzene exposure and urinary *trans,trans*-muconic acid concentrations. Subsequently, it has been postulated that the presence of genetically determined differences in enzyme expression or activity, genetic polymorphisms, may partially account for the toxicity associated with benzene exposure (Aksoy, 1985; Moran et al, 1999; Rothman et al, 1997). Studies of cases involving familial susceptibility to benzene (Aksoy, 1985) tend to support this view. Genetic differences involved in the metabolism of benzene can modify its rate of metabolism, the profile of metabolites produced and metabolite activation/detoxification pathways. Such changes have been quantified by analysis of the urinary metabolites of benzene, phenylmercapturic acid and *trans,trans*-muconic acid (Rossi et al, 1999).

CYP2E1

The metabolism of benzene by hepatic CYP2E1 is the critical first step in the development of benzene toxicity as the enzyme is responsible for the formation of phenol and its secondary metabolism to hydroquinone (Guengerich et al, 1991). Genetic polymorphisms associated with CYP2E1 from different racial groups have been identified, with frequencies ranging from 2-27% (Kato et al, 1992) and changes in transcriptional activity of the enzyme in response to mutations have been described (Hayashi et al, 1991). Seaton et al. (1994) observed that the CYP2E1 activity of microsomes prepared from the livers of trauma victims varied 13-fold with respect to benzene metabolism. However, as DNA analysis was not undertaken, it is not known if the differences were genetically determined. Rothman et al. (1997) showed in a study of 50 workers exposed to benzene that CYP2E1 genetic polymorphisms were not associated with benzene toxicity. In another study of 59 workers exposed to benzene, although considerable variation in urinary metabolite markers was observed, the subjects did not exhibit polymorphisms associated with CYP2E1 (Rossi et al, 1999).

A cross-species analysis of the expression of CYP2E1 in the bone marrow of mice, rats and rabbits and human $CD34^+$ stem cells found the enzyme to be present in all species tested. While the intra- and interspecies variability between mice and rats was small with relatively low enzyme activities, rabbits exhibited enzyme activities an order of magnitude greater (Bernauer et al, 2000).

Glutathione-S-transferase

The enzymatic conjugation of GSH to a number of benzene metabolites, particularly benzene oxide, *trans,trans*-muconaldehyde and quinones, occurs via the action of glutathione-S-transferase (GST) (Goon et al, 1993b; Jerina et al, 1968). It has been postulated that GST genetic polymorphisms are positively correlated with increased risk of oxidative stress (Hayes & Strange, 1995) and cancer (Strange et al, 1998). Xu et al. (1998b) found a significant association ($p < 0.05$) between benzene exposure (0.71 ppm TWA), sister chromatid exchanges and the GSTT1 genotype in a study of 23 workers. Hsieh et al. (1999) examined the role of GST polymorphism in workers exposed to benzene and found that those with the GSTT1 and GSTM1 variants of the enzyme, which exhibit reduced enzymatic activity, were more likely ($p = 0.046$) to have reduced white blood cell counts on exposure to high levels of benzene.

Epoxide hydrolase

Epoxide hydrolase, which converts benzene oxide to benzene dihydrodiol, has the potential to regulate the formation of *trans,trans*-muconaldehyde. Analysis of 40 transplant-quality human liver samples for interindividual variation in epoxide hydrolase activity revealed an approximately 8-fold difference in enzymatic activity and microsomal epoxide hydrolase protein levels were highly correlated with that activity. In contrast, neither enzymatic activity nor microsomal epoxide hydrolase protein levels correlated with microsomal epoxide hydrolase RNA levels which varied by 49-fold. Polymorphisms in amino acid loci of epoxide hydrolase accounted, in part, for the differences in enzyme activity (Hassett et al, 1997).

NAD(P)H:quinone oxidoreductase (NQO1)

NQO1 catalyzes the two-electron reduction of quinones to their corresponding hydroquinone form (Lind et al, 1982). Twerdok et al. (1992) reported considerable

strain differences in the basal and inducible levels of NQO1 between C57B1/6 and DBA/2-derived mouse bone marrow stromal cells. The basal and maximal inducible activity of NQO1 in C57B1/6-derived stromal cells was approximately 3- and 5-fold greater respectively than that of DBA/2-derived cells.

Traver et al. (1992) identified a point mutation in the human NQO1 gene ($^{609}C \rightarrow T$) that results in loss of enzymatic activity in the protein. Thus individuals homozygous for the mutation possess no NQO1 activity, while heterozygous individuals exhibit reduced enzymatic activity. It has been estimated, using a reference population, that the frequency of the mutation is 13% (Rosvold et al, 1995). Analysis of several ethnic groups has shown that homozygous individuals range between 5-22% and heterozygous individuals from 34-52% of the population (Kelsey et al, 1997). The study of Rothman et al. (1997) demonstrated a correlation between NQO1 genetic polymorphism and benzene toxicity among 50 workers exposed to benzene. Rossi et al. (1999) identified a high frequency of NQO1 genetic polymorphism (42.7% reduced activity and 8.3% no activity) amongst 59 workers exposed to benzene and urinary excretion of S-phenylmercapturic acid was significantly lower in individuals lacking NQO1 activity. An increased prevalence of the $^{609}C \rightarrow T$ mutation has been found in a study of 104 patients diagnosed with myeloid leukemias (Larson et al, 1999). However, a study of a group of six related individuals predisposed to cancer showed that the NQO1 $^{609}C \rightarrow T$ transversion did not correlate with NQO1 activity in heterozygous individuals, suggesting that either the $^{609}C \rightarrow T$ transversion has no effect on NQO1 activity or that post-transcriptional regulation alters the activity of the modified enzyme (Kuehl et al, 1995).

Further investigations, in vitro, have found NQO1 to be inducible in wild-type (C/C) human bone marrow cells on exposure to the benzene metabolites hydroquinone and catechol. In contrast, cells homozygous for the $^{609}C \rightarrow T$ mutation (T/T) did not express NQO1 in response to hydroquinone treatment whereas heterozygous cells (C/T) exhibited intermediate induction (Moran et al, 1999).

12.4.3 Environmental influences

In addition to genetic influences, the susceptibility of an individual to benzene toxicity may also be influenced by environmental or lifestyle factors. Generally, the role of environmental factors in modifying benzene toxicity have not been adequately studied. Reviews of environmental influences on solvent toxicity, including benzene, have been published (Medinsky et al, 1994; Sato, 1991).

Alcohol

As discussed in Section 9, CYP2E1 is the initial enzyme responsible for the metabolism of benzene to phenolic metabolites. Studies have shown a number of substances including alcohol (ethanol) to induce hepatic CYP2E1 activity (Johansson & Ingelman-Sundberg, 1988; Koop et al, 1989). Alcohol consumption by rats and rabbits resulted in increased microsomal metabolism of benzene (Johansson & Ingelman-Sundberg, 1988; Nakajima et al, 1985) and increased benzene-mediated myelotoxicity in rats (Nakajima et al, 1985). Consequently, alcohol consumption by individuals exposed to benzene may result in enhanced metabolite formation and increased risk of myelotoxicity.

Toluene

Toluene acts as a substrate for CYP2E1 (Nakajima et al, 1992) and thus, in the presence of benzene, can act as an inhibitor of benzene metabolism. Andrews et al.

(1977) demonstrated the inhibition of benzene metabolism by the co-administration of toluene to male Swiss mice. Urinary benzene metabolites were significantly decreased ($p < 0.01$) and the amount of exhaled benzene increased in toluene- and benzene-treated animals compared to control benzene-treated animals. While the tissue concentration of benzene did not alter with toluene treatment, the concentration of total benzene metabolites was significantly reduced ($p < 0.05$) in various tissues including blood and bone marrow. Inoue et al. (1989) showed that workers exposed concurrently to benzene and toluene produced significantly less ($p < 0.01$) urinary *trans*,*trans*-muconic acid compared to workers exposed only to benzene. However, in a study in which urinary phenylmercapturic acid was used as a biomarker for workers exposed to benzene, no correlation with toluene exposure was found (Inoue et al, 2000).

Non-steroidal anti-inflammatory drugs

Cyclooxygenase activity within bone marrow contributes to benzene-mediated bone marrow toxicity by participating in the oxidation of phenolic metabolites to reactive species and by the conversion of macrophage-derived arachidonic acid to PGE_2, an inhibitor of stem cell proliferation. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin are potent inhibitors of cyclooxygenase activity (Randall et al, 1980; Roth et al, 1975). The administration of NSAIDs, prior to benzene exposure, has been shown to diminish the bone marrow toxicity associated with benzene in mice (Kalf et al, 1989; Pirozzi et al, 1989). The routine use of NSAIDs may confer some protection from the effects of benzene exposure.

12.5 Summary

Exposure to benzene can result in bone marrow toxicity in several species in addition to leukaemia in humans and solid tumours in other animal species. In order for bone marrow toxicity to occur, benzene must first be metabolised by the liver to intermediate metabolites. These metabolites become localised within the bone marrow where they undergo activation by peroxidase enzymes, particularly myeloperoxidase which is found in large amounts in bone marrow, and, to a lesser extent, by cyclooxygenase. While individual benzene metabolites appear not to induce bone marrow toxicity, the combination of phenol and hydroquinone have been shown to induce the same effects on bone marrow as benzene. This effect appears to be due to the ability of phenol to act as a co-oxidant in the activation of hydroquinone to the semiquinone and benzoquinone by myeloperoxidase. Subsequent changes in cellular function result in altered growth factor production with inhibition of bone marrow stem cell proliferation, differentiation and maturation. The oxidation of hydroquinone also results in the formation of reactive oxygen species. Damage to cells by these species can result from DNA adduct formation, DNA base modification, chromosomal aberrations and changes to intracellular redox status, particularly depletion of glutathione and oxidation of protein sulfhydryl groups. Damaged cells not deleted by apoptosis and which possess activated oncogenes or damaged tumour suppressor genes may begin to proliferate as clonal lines, which may result in leukaemia in humans or solid tumours in animals.

While a number of gender-related differences have been described in the response of rodents to benzene exposure, there is no evidence for such differences in the response of humans. However, humans do exhibit differences in the expression and

activity of several enzymes involved in the metabolism of benzene, the most notable of which occurs with NQO1, an enzyme which is responsible for converting quinones to their corresponding hydroquinones and affords protection against quinone-adduct and reactive oxygen species formation within cells. Thus the expression of genetic polymorphisms may modulate the sensitivity of an individual or ethnic group to the effects of benzene exposure.

13. Health Hazard Assessment

This section compares and integrates key data on animal toxicity and human effects in order to characterise the potential adverse human health effects of benzene and their dose-response relationships. The critical studies have been described in Sections 10-11. In integrating their findings, consideration has been given to quality of data, strength of evidence and consistency of outcomes.

13.1 Acute effects

13.1.1 CNS effects

In animals and humans, acute exposure to benzene has dose-dependent CNS depressant or anaesthetic effects which have a rapid onset of action and are reversible upon cessation of exposure (unless fatal), with limited evidence of neurobehavioural stimulation at sub-anaesthetic doses.

In mice, there are clinical signs of CNS depression at exposure levels ≥1000 ppm benzene.

In humans, clinical signs include generalised symptoms such as dizziness, headache and vertigo at levels of 250-3000 ppm, leading to drowsiness, tremor, delirium and loss of consciousness at 700-3000 ppm, whereas exposure to 25 ppm benzene for 8 h is not associated with any adverse signs or symptoms.

13.1.2 Skin, eye and respiratory tract irritation

Limited, but consistent animal data show that undiluted benzene is irritating to the skin and eye. Benzene vapours have also been reported to cause lacrimation in rats. In humans, aspiration of liquid benzene has been observed to cause pulmonary oedema and bleeding. Furthermore, human case reports show that benzene vapours may induce skin, eye and/or respiratory tract lesions that vary from slight to severe irritation, depending on the vapour concentration. As such, benzene can be characterised as irritating to the skin, eyes and respiratory tract. However, there are no reports of skin, eye or respiratory tract irritation in humans exposed to benzene vapour levels <33 ppm (TWA_8).

13.2 Repeated dose effects (other than carcinogenicity)

13.2.1 CNS effects

Repeated exposure to benzene has been shown to affect the dopaminergic system in both mice and rats and one study found a reduction in brain weight in mice exposed to high doses (350 mg/kg/day) for 30 days. Although a variety of neurological effects have been attributed to repeated occupational exposure to benzene, these were predominantly recorded in studies that did not include an unexposed control group. In the only available human study with an unexposed control group, there was a dose-dependent increase in the prevalence of dizziness and headache within a dose range that averaged 59 ppm benzene. As such, it would appear that any CNS effects in humans from long-term exposure to benzene are likely to be similar to those resulting from acute exposures and occur at exposure levels that are higher

than those associated with other human health effects (such as bone marrow depression).

13.2.2 Immunosuppression

Effects suggestive of an impairment of the ability of LC to respond to antigenic and mitogenic stimuli with rapid proliferation have been consistently observed in subacute oral and inhalation studies in mice and have also been found in a subacute inhalation study in rats. The corresponding NOAEL/LOAEL values are 0.44/10 ppm in mice and 200/400 ppm in rats. These were established in studies in which blood cells from animals exposed in vivo were tested in various in vitro systems. There are no reports of similar findings in humans, although a reduction in the number of LC in peripheral blood is common in benzene-induced bone marrow depression. Changes in the blood level of some immunoglobulin classes have been reported in workers exposed to 3-57 ppm benzene, but this finding has not been confirmed in other studies.

In mice and rats, the LOAEL for immunosuppresion is similar to that for bone marrow depression. Furthermore, whereas there is no evidence that benzene compromises LC function in humans, benzene is an established cause of reduced LC counts. Therefore, it is appropriate to characterise immunosuppression as a sign of LC toxicity that is an aspect of, and included in, the wider effect of bone marrow depression discussed below.

13.2.3 Bone marrow depression

Bone marrow depression (haematotoxicity, 'benzene poisoning') from exposure to benzene has been reported in all species examined, including mice, rats, guinea pigs, rabbits, pigs and humans. Its main manifestation is a reduction in the number of one or more of the formed elements of the blood (LC, Plt, RBC, WBC) and/or in Hb, and/or an increase or decrease in RBC size (MCV). The mechanistic studies discussed in Section 12 indicate that the toxicity of benzene to haematopoietic cells in the bone marrow is due to several of its metabolites that are formed *in situ* in relatively high concentrations and act in an additive or synergistic manner to disrupt a range of mechanisms that regulate blood cell formation. Further support for this notion is provided by the order of susceptibility of mice and rats to benzene haematotoxicity (male mice > female mice > rats), which parallels the rate of formation and tissue concentrations of reactive benzene metabolites.

In animals exposed to inhalation of benzene, abnormal blood counts and morphological abnormalities in blood forming organs have been found at exposure levels ≥10 ppm in mice (including mouse foetuses exposed *in utero*) and ≥100 ppm in rats. These effects were observed even at the lowest dose tested in all long-term studies. Therefore, a NOAEL cannot be established.

In humans, several occupational studies indicate that the incidence and severity of bone marrow depression is related to recent or current exposure to benzene. It is not possible to estimate the average latency period from the available human data; however, animal studies indicate that abnormal blood counts may develop in less than a month. As described in Section 11.4.4, a LOAEL for haematological effects in humans has been determined in a study in 44 Chinese workers with long-term exposure to benzene, in which the only haematological abnormality in the lowest exposure group (n = 11; median exposure (TWA_8) = 7.6 ppm; range 1-20 ppm) was a modest decrease (16%) in ALC (Rothman et al, 1996a, 1996b). The limitations of

this study include a relatively wide exposure range and a small number of subjects of an ethnic group that may express genetic polymorphisms modulating sensitivity to the effects of benzene exposure. On the other hand, the study had a well-matched control group, minimal exposure to other chemicals (toluene and xylenes) and a dose-response relationship was established between ALC and benzene exposure as measured by repeated personal monitoring as well as with benzene metabolites in the urine. Furthermore, the prevalence of polymorphisms known to increase the susceptibility to benzene-induced bone marrow suppression (the GSTT1 and NQO1 ($^{609}C \rightarrow T$) genotypes; see Section 12.4.2) is 3-5 times higher among Chinese than among Caucasians (Kelsey et al, 1997; Xu et al, 1998). Therefore, a LOAEL determined in Chinese subjects should also be valid for Caucasians. For these reasons, based on current human data, 7.6 ppm (TWA_8) is considered the best estimate for a LOAEL which may be close to the point of departure for the onset of haematological effects. The available human data are insufficient to establish an appropriate NOAEL, but studies with various limitations indicate that it is likely to be >0.5 ppm (TWA_8).

The only epidemiological study in the general population found an excess occurrence of anaemia and related disorders in a community whose tap water contained ≤66 μg/L benzene. However, as the equivalent dose in a 60-kg person with a daily water consumption of 2 L is <2.2 μg/kg/day or 450 times lower than the only oral NOAEL for haematotoxicity recorded in animal studies (1 mg/kg/day; Wolf et al, 1956), this finding may well have been heavily influenced by bias arising from public awareness of the pollution of the water with benzene and the health effects of the chemical.

In conclusion, there is a substantial body of animal, human and mechanistic data which supports the association between benzene exposure and bone marrow depression and indicates that this is a result of cytotoxicity and, therefore, a threshold effect. The available studies are insufficient to draw firm conclusions about the inhalation NOAEL, although human observations suggest that it is >0.5 ppm. The lowest inhalation LOAEL observed in animals (mice) is 10 ppm, which is comparable to the best estimate for a human LOAEL (7.6 ppm).

13.2.4 Fertility effects

A single oral dose of benzene has been shown to induce chromosome aberrations and have cytotoxic effects in mouse spermatogonia at high doses (≥220 and ≥880 mg/kg respectively). There is also evidence of degenerative changes in the testes (atrophy) and ovaries (atrophy or cystic lesions) of mice exposed to repeated inhalation or oral administration of high doses of benzene (300 ppm for 6 h/day and 25-50 mg/kg/day respectively). At these dose levels, there was evidence of concomitant haematotoxicity, but no mortality or other findings that would suffice to characterise the effects on the gonads as secondary to generalised toxicity.

Consistent with metabolic differences, benzene did not induce testicular or ovarian toxicity at similar exposure levels in rats. There were no fertility-related effects in female rats exposed to ≤300 ppm benzene for 6 h/day for 10 weeks prior to mating and on GD 0-20. Another study found that female rats exposed to 200 ppm benzene for 24 h/day produced no litters, but did not determine the cause of this.

In humans, there are several reports of menstruation disturbances in female and one of reduced semen quality in male workers exposed to benzene. However, the studies have several limitations and do not provide convincing evidence that benzene may have adverse effects on human fertility.

Based on a 13-week study in mice, the inhalation NOAEL for degenerative lesions in the testis and ovaries is 30 ppm, with a LOAEL of 300 ppm (Ward et al, 1985). Based on ovarian atrophy in a 2-year oral study in mice, the LOAEL is 25 mg/kg/day; a NOAEL was not determined (NTP, 1986). These effect levels are either higher than or similar to those at which there is also clear evidence of bone marrow depression.

13.2.5 Developmental effects

Based on the weight of evidence from a number of developmental toxicity studies in mice, rats and rabbits, benzene can be characterised as foetotoxic, but not teratogenic (see Section 10.5.2). The foetal effects observed in the absence of signs of maternal toxicity were a small reduction in foetal BW and an increase in the incidence of delayed ossification and other minor skeletal abnormalities. There is also limited evidence of a reduction in the number of stem cells in the blood forming tissues of mouse foetuses exposed *in utero* to benzene levels similar to those known to cause bone marrow depression in adult animals (10-20 ppm).

Studies of pregnancy outcome in humans have produced mixed results with regard to the risk for SAb. One study found an elevated SGA risk for fathers with occupational exposure to benzene. In another study, there was a marginally significant reduction in birth weight in infants whose mothers had been exposed to low levels of benzene at work. However, the studies have several limitations and do not provide convincing evidence that benzene may have foetotoxic effects in humans. There are no studies of the effect of maternal benzene exposure on the blood forming tissues of human foetuses.

In conclusion, animal and in vitro data indicate that benzene and/or its metabolites may inhibit normal foetal growth, skeletal development and possibly blood cell production. The available epidemiological data are insufficient to draw conclusions about the likelihood that benzene may have similar effects in humans.

Based on adequately reported studies in the rat, the inhalation NOAEL for foetal effects in the absence of maternal toxicity is 40 ppm, with a LOAEL of 100 ppm (Coate et al, 1984; Green et al, 1978). In other studies in the rat, 100 ppm is also the LOAEL for bone marrow depression.

13.2.6 Other non-neoplastic effects

Other non-neoplastic effects are inadequately documented to determine their significance for health hazard assessment.

13.3 Genotoxicity

The genotoxicity of benzene has been investigated extensively in a broad spectrum of in vitro and in vivo systems. Overall, the results are consistent with the conclusion that several benzene metabolites (particularly cathechol, hydroquinone and quinone) can induce a variety of lesions in genetic material, which range from DNA base alterations and single strand breaks to structural and numerical chromosome aberrations. Chromosome aberrations have also been identified in

peripheral blood cells of workers exposed to benzene, generally at exposure levels >10 ppm. Specifically, recent studies found an increase in the frequency of aneuploidy, long-arm deletions and translocations involving chromosomes 1, 5, 7, 8, 9 and 21 (see Table 11.3). As discussed below, these findings suggest that benzene exposure can lead to chromosome lesions which are similar to the specific abnormalities that are the hallmark of human leukaemia. However, there is no indication that an increase in the occurrence of such lesions in non-neoplastic peripheral blood cells is associated with any adverse health effects *per se*. Therefore, it is appropriate to characterise genotoxicity as a mode of action that is an aspect of, and included in, the wider effect of carcinogenicity addressed below.

13.4 Carcinogenicity

13.4.1 Leukaemia

In several of the occupational cohort studies reviewed in Section 11.6.1, past employment in an industry or job category with the potential for exposure to benzene was associated with a significant increase in the risk for cancer of the blood and lymphatic system and/or leukaemia. In addition, there was a significant trend with cumulative exposure, that is, a clear dose-time-response relationship in three out of four studies in which detailed exposure assessments were made. The strength of the association ranged from weak in the majority of cohorts to strong (SMR = 10-20) in Pliofilm workers with a cumulative exposure in excess of 500 ppm-years (Table 11.4; Table 11.5). With regard to leukaemia type, AML (ANLL) was found to account for most of the risk elevation and there was no evidence of a statistically significant dose-time-response relationship for CML, ALL or CLL in any of the cohorts. Several case-control studies also identified prior exposure to benzene or benzene-containing substances as a significant risk factor for a variety of lympho-haematopoietic cancers, including but not limited to acute leukaemia (see Section 11.6.2). As such, it is universally agreed that occupational exposure to benzene may induce leukaemia, specifically AML (ANLL). In the largest cohort studied to date, the latency period from first exposure to clinical diagnosis was estimated at 11-12 years, with a range from 10 months to 50 years (Yin et al, 1987b).

Human leukaemias are clonal diseases generally characterised by a large variety of acquired chromosome aberrations (including translocations, insertions, deletions and inversions) in individual bone marrow cells in the haematopoietic stem and progenitor cell compartment (Gilliland, 1998; Irons & Stillman, 1996).

As described in Section 12, although the mechanism of carcinogenesis of benzene is unknown, several benzene metabolites have been shown to cause DNA damage, including base alterations, chromosome structural abnormalities and aneuploidy.

In patients with AML secondary to treatment with alkylating agents or radiation (s-AML), there is a recurrent pattern of cytogenetic abnormalities involving loss of all or part of chromosomes 5 and 7. Furthermore, s-AML is generally preceded by a period of preleukaemia (also known as MDS) characterised by a persistent bone marrow dysplasia, which is believed to provide a microenvironment that increases the susceptibility of stem and progenitor cells to chromosome damage and/or enhances the survival and proliferation of cells with genetic abnormalities. The pattern of cytogenetic abnormalities involving chromosomes 5 and 7 is also observed in studies of leukaemia patients occupationally exposed to benzene or benzene-containing substances. It has therefore been speculated that benzene-

induced leukaemia is the result of a series of both epigenetic events that affect the microenvironment and genetic events that lead to the activation of oncogenes and/or the loss of tumour suppressor genes (Irons & Stillman, 1996) and, therefore, is a threshold rather than a non-threshold effect (CONCAWE, 1996). There is little documentation on the association between non-neoplastic bone marrow lesions such as MDS and leukaemia in benzene-exposed subjects. Of 18 incident cases of bone marrow disorders in the large cohort of benzene-exposed Chinese workers described in Section 11.6.1, 11 had bone marrow depression whereas 7 had MDS. Furthermore, in the same cohort, a diagnosis of bone marrow depression ('benzene poisoning') was associated with a 71-fold increase in the risk for ANLL/MDS which could not be attributed to cumulative benzene exposure. However, although these findings are consistent with the hypothesis that non-neoplastic bone marrow lesions precede frank leukaemia in some benzene-exposed subjects, they do not suffice to prove that the pathogenesis of benzene-induced leukaemia involves an epigenetic step.

As discussed in Section 11.6.1, only the Pliofilm cohort is suitable for the determination of the carcinogenic potency of benzene. In this cohort, the SMR for leukaemia was significantly elevated at cumulative exposures >50 ppm-years for two of the three available exposure estimates (Table 11.5), equivalent to a long-term exposure level of >1.25 ppm benzene over a working life of 40 years. However, these findings derive from a single study with insufficient statistical power to rule out the possibility of some increase in the SMR at lower exposures.

No observational studies were found which have examined the relationship between leukaemia incidence or mortality and the exposure of individual adults or children to non-occupational benzene levels.

13.4.2 Solid tumours

Lymphoma

Lymphomas are solid malignant tumours of lymphocytic origin. They include NHL and MM which are monoclonal and Hodgkin's disease, which may be either monoclonal or of mixed cellularity (Freedman & Nadler, 1998; Longo, 1998).

In mice, the incidence of lymphoma was elevated in several studies conducted in strains where this is a common spontaneous tumour.

In humans, some of the occupational cohort studies summarised in Table 11.4 link past employment in job categories with the potential for benzene exposure with a significant or marginally significant increase in the risk for all lymphoma (in Italian refinery workers employed prior to 1961 and Chinese workers in the painting, printing, footwear and chemical industries), NHL (in Finnish petroleum industry workers and Chinese workers in the painting, printing, footwear and chemical industries) or MM (in Australian petroleum industry workers). The strength of the association was weak in Australian and Finnish petroleum industry workers, intermediate in Italian refinery workers employed prior to 1961 and highest (RR = 4.7 for NHL) in Chinese workers with assessed (and probably underestimated) exposure levels ≥25 ppm benzene. However, a dose-time-response relationship has not been demonstrated. Some of the case-control studies reviewed in Section 11.6.2 also suggest an association between prior exposure to benzene or benzene-containing substances and the risk of NHL or MM.

Although it cannot be excluded that there is an association between benzene exposure and the risk for lymphoma, specifically NHL and MM, the evidence is not as conclusive as it is for leukaemia.

Mammary cancer

In female mice, there was a statistically significant, dose-related increase in the incidence of mammary gland carcinomas at dose levels ≥50 mg/kg/day in two oral carcinogenicity studies. The incidence was not increased in female rats dosed orally with up to 500 mg/kg/day for 2 years, or in a number of inhalation studies in mice and rats exposed to up to 300 ppm benzene for 2 years or longer.

In humans, the SIR for breast cancer was elevated in a cohort study including 1942 female workers in a Finnish petroleum company; however, the elevation was mainly due to cases among clerical workers and similar in magnitude to that found in other studies of Finnish women in office jobs. In addition, there is a single, but well controlled case-control study showing that the risk for breast cancer in women is weakly associated with duration of benzene exposure, probability of exposure and a crude estimate of cumulative exposure to the chemical. There was also a marginally elevated risk associated with employment as a car mechanic or petrol station worker in a case-control study of primary breast cancer in men. These findings are insufficient to determine the likelihood of a causal relationship between benzene exposure and breast cancer in humans, although it cannot be excluded.

Skin cancer

There was an increased incidence of epithelial (non-melanoma) skin tumours in male rats in two 2-year oral bioassays, but only at very high dose levels (200-500 mg/kg/day) that may have exceeded the maximum tolerated dose. Similar tumours were not seen in female rats, or in any of several carcinogenicity studies in the mouse.

In humans, the risk for melanoma or skin cancer (mainly melanoma) was elevated in three petroleum industry cohorts (Table 11.4). In addition, ever employment in the petroleum industry was a marginally significant risk factor for concurrent basal and squamous cell carcinoma in one of the case-control studies reviewed in Section 11.6.2. The risk for skin cancer (mainly melanoma) was also elevated in the Dow Chemical cohort, but there was no trend with either level or duration of exposure to benzene. As such, although these studies suggest that there may be an elevated risk for skin cancer among workers in the petroleum and chemical industries, there is no indication that this can be attributed to exposure to benzene.

13.5 Summary and conclusions

Human case reports indicate that acute exposure to benzene vapours can cause CNS depression and skin, eye and respiratory tract irritation. With regard to chronic exposure, it is well documented through numerous epidemiological studies that the principal human health hazards are bone marrow depression and leukaemia, particularly AML (ANLL). There is also some evidence of an association between chronic benzene exposure and the risk for lymphoma, specifically NHL and MM. At present, leukaemia and lymphoma must be considered non-threshold effects caused by exposure to a genotoxic carcinogen. With regard to bone marrow depression, it is reasonable to assume that this is a

threshold effect. Based on current human data, 7.6 ppm (TWA_8) is the best estimate of a LOAEL which may be close to the point of departure for the onset of haematological effects. An appropriate NOAEL has not been established; however, occupational studies with various limitations indicate that it is likely to be >0.5 ppm. Finally, it cannot be excluded that repeated exposure to benzene may be weakly associated with reproductive effects and mammary cancer in humans.

No data from human studies were found to indicate that children are more susceptible to benzene toxicity than adults or that benzene affects human males and females differently. As discussed in Section 12.4.3, experimental data indicate that alcohol consumption may increase the risk of adverse health effects from chronic exposure to benzene.

14. Classification for Occupational Health and Safety

This section discusses the classification of the health effects of benzene according to the NOHSC Approved Criteria for Classifying Hazardous Substances (the Approved Criteria) (NOHSC, 1999a) or, in the case of physicochemical hazards, the Australian Dangerous Goods (ADG) Code (FORS, 1998). The Approved Criteria are cited in the NOHSC National Model Regulations for the Control of Workplace Hazardous Substances (NOHSC, 1994c) and provide the mandatory criteria for determining whether a workplace chemical is hazardous.

Where adequate human data were unavailable, the classification for health hazards has been based on experimental studies (animal and in vitro tests). In extrapolating results from experimental studies to humans, consideration was given to relevant issues such as quality of data, weight of evidence, metabolic and mechanistic profiles, inter- and intra-species variability and relevance of exposure levels.

Benzene is currently listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) with the following classification: 'Flammable'; 'Carcinogen, Category 1' and 'Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed'.

14.1 Physicochemical hazards

Benzene meets the criteria of the ADG Code for classification as a flammable liquid, as it gives off flammable vapours at – 11°C and an atmosphere containing 1.4-7.9% v/v benzene is explosive (Table 5.1). Benzene is not chemically reactive under normal ambient conditions.

Classification. Benzene is already classified as 'Flammable'.

14.2 Health hazards

14.2.1 Acute toxicity

The available human data on the acute toxicity of benzene are anecdotal in nature.

As shown in Table 10.1, the 4-h inhalation LC_{50} in the rat is 13,700 ppm (43.8 mg/L). The oral LD_{50} values determined in the rat are inconsistent (810, 5600 and 9900 mg/kg). However, as the oral LD_{50} in the mouse is 4700-6500 mg/kg, the weight of evidence suggests that benzene has a low acute oral toxicity. The dermal LD_{50} in the rabbit is >8200 mg/kg.

Single exposure to benzene has been associated with CNS stimulation or depression in both animals and humans and with male germ cell toxicity in mice. However, observations indicate that these effects are reversible after a recovery period ranging from a few hours for CNS effects to several weeks for germ cell damage.

Classification. Benzene does not meet the Approved Criteria for classification for acute lethal effects or non-lethal irreversible effects after a single exposure.

14.2.2 Irritant and corrosive effects

Liquid benzene has been shown to cause skin and eye irritation in rabbits. Benzene vapours have been reported to cause eye irritation in humans and rats at concentrations ≥33 and ≥10 ppm respectively. In humans, vapour levels >60 ppm have been associated with irritation of the skin, including second degree burns, and of the mucous membranes of the nose, mouth, throat and lower airways, including signs of serious respiratory system effects such as dyspnoea, laryngitis, tracheitis, bronchitis and pulmonary haemorrhage.

Classification. Based on animal tests and practical observation in humans, benzene meets the Approved Criteria for classification as 'Irritating to skin' (risk phrase R38), 'Irritating to eyes' (R36) and 'Irritating to the respiratory system' (R37).

14.2.3 Sensitising effects

There are no animal studies or human case reports of skin or respiratory sensitisation to benzene.

14.2.4 Effects from repeated or prolonged exposure

According to the Approved Criteria, a substance is classified as hazardous when serious damage (clear functional disturbances or morphological changes which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route. In this context, haematological disturbances are considered to be particularly important if the evidence suggests that they are due to decreased bone marrow production of blood cells.

There is a substantial body of human evidence that repeated occupational exposure to benzene vapours at ≥ 7.6 ppm (0.024 mg/L) can cause bone marrow depression. This is usually a reversible condition, but may progress to aplastic anaemia or cancer (AML). Toxic effects on the blood and blood forming organs have also been found consistently in rats exposed to inhalation of benzene at concentrations ≥100 ppm (0.32 mg/L) for 6 h/day for 5 days/week, in mice exposed to inhalation of benzene at concentrations ≥10 ppm (0.032 mg/L) for 6 h/day for 5 days/week, and in rats and mice exposed to orally administered benzene at dose levels ≥25 mg/kg/day, in studies of a duration of 90 days (13 weeks) or longer.

There are no human or animal studies of the haematological effects of dermal exposure to benzene. However, as benzene is absorbed through the skin in humans, it is likely that bone marrow toxicity may also be caused by repeated or prolonged exposure by the dermal route.

Classification. Benzene meets the Approved Criteria for causing serious damage to health by repeated or prolonged exposure and is already classified as 'Toxic: Danger of serious damage to health by prolonged exposure by inhalation, in contact with skin and if swallowed' (R48/23/24/25).

14.2.5 Reproductive effects

Effects on fertility

The available human case reports and studies have several limitations and do not prove a causal relationship between benzene exposure and fertility effects in humans.

In a study of male mice, a single oral dose of 880-6160 mg/kg benzene had no effect on body or testis weight, but was toxic to differentiating spermatogonia. There is also evidence of degenerative changes in the testes (atrophy) and ovaries (atrophy or cystic lesions) of mice exposed to repeated inhalation or oral administration of high doses of benzene (300 ppm for 6 h/day and 25-50 mg/kg/day respectively). At these dose levels, there was concomitant haematotoxicity, but no mortality or other findings that would suffice to characterise the effects on the gonads as secondary to generalised toxicity.

Benzene did not induce testicular or ovarian toxicity at similar exposure levels in rats. There were no fertility-related effects in female rats exposed to ≤300 ppm benzene for 6 h/day for 10 weeks prior to mating and on GD 0-20. Another study found that female rats exposed to 200 ppm benzene for 24 h/day produced no litters, but did not determine the cause of this.

As such, benzene may have a toxic effect on the testes and ovaries in mice, but these effects were demonstrated only at high doses of doubtful relevance for humans. The available data on reproductive capacity in rats are limited and inconclusive.

Classification. The available evidence is insufficient to classify benzene as toxic to fertility under the Approved Criteria.

Developmental effects

The available human studies have several limitations and do not prove a causal relationship between benzene exposure and developmental toxicity in humans.

The available developmental toxicity studies in mice, rats and rabbits are summarised in Table 10.2 in Section 10.5.2. Based on the weight of evidence from these studies, benzene is foetotoxic, but not teratogenic. Foetotoxic effects were mainly found at dose levels associated with maternal toxicity. However, some studies in mice and rats found a small reduction in foetal BW or an increase in the incidence of delayed ossification and other minor skeletal abnormalities at dose levels at which no maternal effects were reported. These minor growth disturbances were found in the foetuses of dams exposed to ingestion or inhalation of benzene at high doses of doubtful relevance for humans (800-1300 mg/kg/day by mouth or 100-500 ppm by inhalation).

In two small studies, inhalation exposure of pregnant mice to 10-20 ppm benzene on GD 6-15 resulted in toxic effects on blood cells in haematopoietic tissue in the liver, bone marrow, or spleen of the offspring exposed *in utero*. These effects occurred in the absence of other signs of developmental toxicity and were consistent with lesions induced by benzene in the same tissue type in adult mice at similar levels of exposure. However, the studies comprised an insufficient number of animals to be entirely convincing.

Classification. The available evidence is insufficient to classify benzene as a developmental toxicant under the Approved Criteria.

Effects on lactation

Benzene has been found in human breast milk. In the rat, one study found small changes in body and organ weights in the offspring of rats exposed to inhalation of benzene during pregnancy and lactation, but did not establish whether these effects were lactational or the result of exposure *in utero*.

Classification. The available evidence is insufficient to classify benzene for effects on lactation.

14.2.6 Mutagenic effects

The Approved Criteria defines a mutation as a permanent change in the amount or structure of the genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism.

To be classified in Category 1 (Substances known to be mutagenic to humans) or Category 2 (Substances which should be regarded as if they are mutagenic to humans), a substance must be known or strongly presumed to cause heritable mutations in humans, that is, changes to the genetic material that occur in germ cells and can be transmitted to the offspring. If a substance has only been shown to induce mutations in somatic cells, it is classified in Category 3.

Benzene and/or its metabolites, particularly catechol, hydroquinone and quinone, have been shown to cause DNA damage in mammalian in vitro systems as determined by sensitive test methods. Furthermore, benzene has been shown to be genotoxic to somatic cells in a broad spectrum of in vivo models in which the chemical was administered to rodents by inhalation, oral gavage or parenteral injection. These include tests for SCE and MN induction in peripheral blood cells, bone marrow cells, foetal liver cells, lung fibroblasts and Zymbal gland cells; gene mutations in LC, lung and spleen cells; chromosome aberrations in LC, bone marrow cells and spleen cells; and DNA adducts in nucleated blood and bone marrow cells. Chromosome aberrations have also been identified in peripheral blood cells of workers exposed to benzene, generally at exposure levels >10 ppm.

Published documentation on mammalian germ cells appears to be limited to two studies in the male mouse. Spanò et al. (1989) found that a single oral dose of ≥880 mg/kg benzene caused a dose-dependent reduction in the relative cell count in the primary spermatocyte and spermatid fractions, indicating that benzene and/or its metabolites have the potential to reach the germ cells (see Section 10.5.1). Ciranni et al. (1991) subsequently showed that a single oral dose of ≥220 mg/kg benzene induced chromatid aberrations in differentiating spermatogonia in a dose-dependent manner (see Section 10.6 and Figure 10.1). However, no evidence could be found in the open literature that these results have been replicated by other laboratories or are supported by findings in other appropriate tests. As such, the experimental data available at present do not satisfactorily demonstrate heritable genetic damage.

Classification. Based on the above, benzene meets the Approved Criteria for classification as a mutagenic substance in Category 3 (R40: 'Possible risk of irreversible effects').

14.2.7 Carcinogenicity

The Approved Criteria provides for the classification of carcinogenic substances into three categories. Category 1 includes substances known to be carcinogenic to humans, whereas Categories 2 and 3 in general are used where there is more or less convincing evidence from appropriate long-term animal experiments indicating that human exposure to the chemical may result in the development of cancer.

A substance is included in Category 1 if there is sufficient evidence from epidemiological studies to establish a causal association between human exposure and the development of cancer. The existence of a causal relationship would be any of the following:

- an increased incidence of one or more cancer types in an exposed population compared with a non-exposed population;
- evidence of dose-time-response relationships, that is, an increased cancer incidence associated with higher exposure levels or with increasing exposure duration;
- an association between exposure and increased risk observed in more than one study;
- demonstration of a decline in risk after reduction of exposure; and
- specificity of any association, defined as an increased occurrence at one target organ or of one morphological type.

For benzene, the strongest evidence is provided by the finding of an excess mortality from cancer of the blood and lymphatic system and a significant trend with cumulative benzene exposure in the Chinese, CMA and Pliofilm cohorts described in Section 11.6.1 (Hayes et al, 1997; Paxton et al, 1994a; Wong et al, 1987b). Further evidence is provided by two case-control studies which found a significantly elevated risk for blood and lymphatic system cancer at relatively high, but not at lower levels of exposure to benzene (Health Watch, 1998; Richardson et al, 1992). Finally, the increase in AML risk with cumulative exposure in the Pliofilm cohort is evidence of cell type specificity of the association between benzene exposure and human cancer (Wong, 1995).

Classification. Benzene meets the Approved Criteria for classification as a carcinogenic substance in Category 1 and is already classified as such and assigned risk phrase R45: ‘May cause cancer’.

14.3 Summary

Benzene is currently listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) with the following classification: ‘Flammable’; ‘Carcinogen, Category 1’ and ‘Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed’. Based on the information available at this time, benzene also meets the Approved Criteria for classification as ‘Irritating to eyes, respiratory system and skin’ (R36/37/38) and as a mutagenic substance in Category 3 (R40: ‘Possible risks of irreversible effects’).

15. Environmental Exposure

In this section, environmental benzene levels and major sources of entry will be discussed separately for the outdoor and indoor environment. Given the brief residence time of benzene in surface water and soil, the main emphasis is on benzene in the atmosphere.

Benzene will be released through many different activities in both a point source and diffuse manner. As such, outdoor air levels have been considered under several different scenarios for point source releases, whereas diffuse releases are addressed in the context of estimating a predicted environmental concentration (PEC) in air for urban environments.

Air monitoring data exist for several areas within Australia, both for urban and point source releases. While monitored point source releases are discussed in their relevant sections, they cannot be compared directly to predicted levels, as these are determined for points at 100 m from the point source, while the monitoring data are from a range of distances.

With regard to the indoor environment, there is documentation from studies conducted in Australia and New Zealand of the concentration of benzene in motor vehicles. However, there are few Australian measurements of benzene levels in indoor air in homes and non-residential buildings. In consequence, these have been assessed on the basis of both Australian and overseas studies and the estimated concentration of benzene in air in a model Australian urban environment.

The environmental concentration estimates developed in this section must be interpreted cautiously as they have been derived by the application of numerous assumptions and approximations to inherently uncertain databases such as the NPI.

15.1 Point source releases to air

This section will consider several different industries. The primary end use of benzene is as a component of petrol (Section 7) and as such the petroleum industry is of major importance when assessing this chemical. Additionally, other specific industries have been identified as releasing significant quantities of benzene, including but not limited to the steel, aluminium and chemical industries.

15.1.1 Petroleum industry

Section 7.2.1 provides a brief overview of the refining process. More detailed information is available from the AIP website (AIP, 2000).

Petroleum refineries

Benzene emissions from petroleum refineries can be grouped into five main categories, namely process vents, storage tanks, equipment leaks, transfer operations, and wastewater collection and treatment. USEPA (1998b) provides techniques for estimating emissions of benzene through leak emissions from refineries, which essentially consist of multiplying equipment counts, equipment leak factors and the benzene concentration in each process. While data exist on the concentration of benzene in various refinery streams, no information is available on

equipment counts and leak factors. Furthermore, leak factors are estimations in themselves so the final result would need to be treated with caution. As such, the USEPA method has been disregarded for the purposes of this assessment.

The Technical Guidance Document (TGD) (EC, 1996) may be used to estimate releases. However, production of benzene *per se* is not the objective of the refinery. It is to produce marketable petrochemical products, of which benzene is a component in various grades. As such, it is difficult to apply the correct scenario from TGD. Nevertheless, if a refinery is considered an operation that produces substances (other than intermediates) in dedicated equipment (category 1b), TGD indicates that 0.01% of available benzene will be emitted during the refining processes (based on the vapour pressure of benzene at 25°C).

AIP (1997) provides data on refinery capacity for the eight Australian refineries. For the purposes of this assessment, data from these refineries have been averaged to create a 'model refinery' with a refining capacity of 3871 kt crude oil per annum.

Benzene is expected to be available for emission during distillation activities, catalytic reforming and catalytic cracking. In order to determine the quantity of benzene available for release, the annual quantity of material passed through each of the processing stages has been averaged and multiplied by the maximum expected percentage of benzene at each stage (0.1% for crude oil undergoing distillation, 2% for material undergoing catalytic cracking and 8% for material undergoing catalytic reforming, as discussed in Section 7.2.1). It was assumed that refining operations are conducted on 300 days per annum. The release estimate of 0.01% was applied to the annual amount of benzene available for emission and converted to an expected daily release.

The following results were obtained for the 'model' refinery:

Total benzene in crude oil refined (kt/y)	Benzene in catalytic cracking (kt/y)	Benzene in catalytic re-forming (kt/y)	Total benzene production (kt/y)	Benzene release per year (kg)	Benzene release per day (kg)
3.9	22.4	72.7	99	9900	33

The Australian refineries have provided estimates of their benzene emissions from 1 July 1999 to 30 June 2000 to NPI and these appear similar to values reported for the previous year.

Table 15.1 shows that reported releases (average of 43 kg per day) are comparable with those estimated above (33 kg per day). When benzene production is calculated based on a benzene concentration of 0.1%, 2% and 8% in crude distillation, catalytic cracking and catalytic reforming processes respectively, the release percentages of benzene from Australian refineries range from 0.006 to 0.039%, with an average release of 0.016%. This compares with 0.01% used for the model refinery. These data suggest that the model underestimates releases. Therefore, when determining predicted concentrations in air, reported release figures will be used.

The PEC in air will be determined following the procedure in TGD (EC, 1996). Estimates are at 100 m from the point source and are derived as follows: PEC_{air} (mg/m^3) = emission x $Cstd_{air}$, where emission = emission rate to air (kg/d) and

$Cstd_{air}$ = standard concentration in air at source strength of 1 kg/d = 2.78 x 10^{-4} mg/m^3.

Following this calculation, the atmospheric PECs for all eight Australian refineries range from 1.6-5.5 ppb at 100 m from the point source (Table 15.1).

Table 15.1: Release of benzene from Australian petroleum refineries and predicted environmental concentrations in air at 100 m from the source

State	Refinery	Benzene release (kg/y)*	Benzene release (kg/day)	Benzene production (kt/y)	Release (%)	PEC_{air} (mg/m^3)	PEC_{air} (ppb)
NSW	Shell	11000	30	91	0.01	0.008	2.6
	Caltex	18000	49	131	0.01	0.014	4.2
QLD	BP	18000	49	59	0.03	0.014	4.2
	Caltex	5600	15	108	0.01	0.004	1.3
SA	Mobil	10000	27	82	0.01	0.008	2.4
VIC	Mobil	7000	19	120	0.01	0.005	1.7
	Shell	15000	41	129	0.01	0.011	3.5
WA	BP	19000	49	71	0.03	0.014	4.2

* As reported to NPI. N.B. BP from Western Australia is for the 1998-1999 reporting period as later results are not yet available.

In their review of studies of hazardous air pollutants performed in Australia and New Zealand, the Victorian EPA summarised measurements near two oil refineries at Lytton, Brisbane in 1992 (EPA Victoria, 1999). The mean of half-hour average measurements is stated as 0.0168 mg/m^3, or 5.2 ppb, which is within the range of the above estimated atmospheric concentrations. The highest 20 half-hour averages ranged from 0.108-1.365 mg/m^3 (or 33.5-423 ppb).

Petrol terminals

Once refined, petroleum product is transferred to the Terminals in the capital cities via pipelines, while it is shipped to Coastal Bulk Plants. The product is transferred by road to small inland bulk plants, and this is from the main terminals. Emissions reported to NPI during 1999-2000 have been recorded as fugitive emissions and tend to have been estimated rather than measured. However, the emission estimation techniques used have been stated as acceptable in the NPI database and these figures will be used to predict concentrations in air at points 100 m from the terminal sites.

When interrogating the NPI database, emissions were only considered for those sites readily identified as terminals, of which there were 28 (WA data not provided). Emissions per annum ranged from 18,000 kg from the largest terminal to 250 kg from the smallest. The average emissions from the terminals were 2706 kg per annum (with only eight of the terminals actually reporting emissions higher than this). To ensure conservatism in the assessment, two scenarios will be considered, one using the average of the full sample size (including the highest emitting terminal), and one for the highest emitting terminal. The same calculation is used as described above and it is assumed emissions occur over 365 days per annum. The resulting PECs in the atmosphere are shown in Table 15.2.

Table 15.2: Predicted environmental concentrations in air at 100 m from Australian terminals

Terminal	Release (kg/y)	Release (kg/day)	PEC_{air} (mg/m^3)	PEC_{air} (ppb)
Largest terminal	18,000	49.3	0.014	4.2
Average terminal	2,706	7.4	0.002	0.6

15.1.2 Steel and associated industries

Coke making operations

Coal is converted to coke in coking ovens. Benzene is contained in coke oven gas and, as such, may be emitted during charging of coke in ovens. Coke ovens are arranged in batteries, with operating processes as described in Section 7.2.2.

Of the two steelworks in Australia, the Port Kembla coke ovens are significantly larger. Data provided by the applicants show that in the order of 2700 kt/y of coke were produced at Port Kembla in 1994-1996, whereas at the Whyalla plant in the order of 891 kt (dry weight) coal was processed during 1999.

NPI data for 1999-2000 are available for both steel works. Port Kembla reported release of benzene to the atmosphere of 99,000 kg. This was a combination of stack emissions (24,000 kg determined through direct measurement) and fugitive emissions (75,000 kg determined through engineering calculations). Whyalla reported release of benzene to the atmosphere of 24,000 kg, a combination of stack emissions (1,100 kg determined through direct measurement) and fugitive emissions (23,000 kg determined through engineering calculations).

The PEC_{air} is calculated following the methodology described above. It was determined based on atmospheric release as reported by the Port Kembla steelworks for the 1999-2000 NPI reporting period. Based on this, 99,000 kg benzene will be expected to be released in a year. For 365 days of operation per annum, this equates to a daily release of 271 kg. Applying the formula described above, the PEC_{air} at 100 m from the coke ovens is 0.076 mg/m^3, or 23.3 ppb.

Coal gas by-product plants

A second benzene production site at an integrated steelworks is the by-product plant where BTX and coal tar are recovered from coke oven gasses as described in Section 7.2.2.

The USEPA (1998b) summary of benzene emission factors for furnace and foundry coke by-product recovery plants, covers all aspects including naphthalene separation; tar interception, dewatering, decantation and storage; light oil storage; flushing liquor circulation tank; and wash oil decanter and circulation tank. While it is expected foundry coke is used in the coking operations at Port Kembla and Whyalla, as a worst case it will be assumed that furnace coke is used. Emission factors are provided for both controlled and uncontrolled circumstances. As the level of control is uncertain, both scenarios are considered. Table 15.3 provides details (with all emission factors combined to provide a total emission factor). As described above, the Port Kembla steelworks produces in the order of 2700 kt of coke per annum. This is assumed to be the input for the determination of benzene release from the by-product plant.

Table 15.3: Estimated benzene emissions from a coal gas by-product plant

	Controlled	Uncontrolled
Emission factor	14.7 g/t	343.1 g/t
Benzene emission per annum	40 t	927 t
Benzene emission per day	133 kg	3090 kg
PEC_{air}*	11 ppb	270 ppb

* Follows methodology described above and is for points 100 m from the point source.

BHP has provided emission estimates and monitoring data from their gas processing plant at Port Kembla. Annual benzene emissions were estimated at 443 t in 1995, but are predicted to fall to 70 t once an ongoing project to control tank vent releases to air has been completed. The monitoring data show an average concentration of 174 ppb next to the plant, decreasing to 58 ppb at 200 m and suggest a concentration at 100 m from the plant to be in the order of 120 ppb. These estimates and monitoring data are within the range expressed above (Table 15.3).

In addition, ambient air benzene monitoring results are available from measurements taken from September 1996-January 1997 at several points around the by-product plant at the Port Kembla steelworks (Westley-Wise et al, 1999). Highest average concentrations of 1.08 ppb were found closest to the plant (26 samples at 1.1 km). At 1.2 km, averages were significantly less at 0.42 ppb, but higher again at 1.4 and 1.6 km (0.66 and 0.67 respectively). Control sites situated at 3.8, 5.5 and 12 km from the steelworks showed mean benzene levels of 0.68, 0.73 and 0.28 ppb respectively. These readings suggest that at distances of >1 km from the point source, levels may be expected to be close to background readings.

Coal tar distillation

Tar produced at the coal gas by-product plants at Port Kembla and Whyalla is shipped to Koppers in Newcastle for processing, as described in Section 7.2.2. Koppers has provided information showing that they receive tar in the order of 96,000 t/y from Port Kembla and 27,000 t/y from Whyalla, containing 0.107% and 0.157% benzene respectively. This equates to 145 t/y of benzene.

Koppers states that the only source of benzene emission to air is from the fume scrubbing systems' stacks. Koppers operates under a NSW EPA licence requiring the concentrations of emissions from all fume systems to be analysed each year. Annual releases of benzene from these stacks were provided for the last five years. As only concentrations were reported, stack velocities of 1 m/s and operating temperatures of 30^0C were assumed to calculate mass emissions of benzene per annum.

15.1.3 Aluminium industry

Aluminium is produced from bauxite, from which alumina (aluminium oxide) is extracted by a refining process, followed by the electrolytic reduction of the oxide to the metal in aluminium smelters.

Alumina refining

Alumina refining involves four basic stages: (1) digestion of bauxite in hot caustic soda; (2) removal of residues from the liquor stream; (3) precipitation of alumina hydrate from the clarified liquor; and (4) calcination of the precipitate to produce anhydrous aluminium oxide.

Benzene emissions from the alumina refinery at Kwinana reported to NPI are the result of 'liquor burning' processes which treat the liquor residues referred to above (Alcoa, 2000). This is presumably due to thermal degradation of organic impurities in the bauxite. Liquor treatment processes differ from plant to plant mainly due to bauxite quality differences. There are six alumina refineries in Australia, two of which have liquor burning facilities. Kwinana has the oldest liquor burning plant and does not have volatile organic chemicals (VOC) reduction equipment fitted, hence the reported benzene emissions. The other refinery with liquor burning facilities at Wagerup, Western Australia has a catalytic thermal oxidiser which removes most VOCs from the off-gas. As a result, the levels of benzene emission do not trigger NPI reporting.

Currently, the largest refinery in Australia, QAL in Gladstone, does not have liquor burning facilities. It is reasonable to assume that new technology when put in place will have VOC reduction equipment. So in determining a PEC in air, the Kwinana plant will be used as the model.

Benzene emissions reported for Kwinana were 21,000 kg during the first year of reporting to the NPI. The site produced 1900 kt of alumina indicating benzene emissions are around 0.001% of alumina production. Emissions were determined through a mixture of direct measurement (at the air stack) and engineering controls to estimate fugitive emissions and are considered reliable.

Applying the above calculation to determine a PEC_{air} at points 100 m from the point source and assuming operation on 300 days per annum, the concentration is estimated to be 0.019 mg/m^3, or 6.1 ppb.

Aluminium smelting

Metallic aluminium is produced from alumina by electrolysis. During the process, oxygen is deposited on and consumes the cell's carbon anodes, which are made from coal tar pitch and petroleum coke.

Benzene is not a component of coal tar pitch or petroleum coke, but could be released as part of the VOCs produced during smelting operations. However, it currently appears that no estimation techniques are available to predict emissions of VOCs. None of the six aluminium smelters provided releases of benzene (or VOCs) in their NPI reports. Because data were provided on other releases, it is likely that benzene was produced in quantities <10 t/y, which does not trigger reporting. Due to a lack of information, no meaningful estimations can be made with regard to benzene emissions from aluminium smelting plants.

15.1.4 Chemical industry

Bulk benzene storage

Locally produced BTX and imported benzene are stored in bulk at the Terminals Pty Ltd bulk storage facility, Coode Island - Melbourne, then distributed to the major end user of benzene feedstock, Huntsman Chemical Company in Melbourne. Emission levels sourced from the NPI database for the reporting period July 1999 to June 2000 indicated that 8.2 t of benzene were released by this facility.

Butadiene rubber manufacture

Qenos' Altona facility uses about 40 t of benzene per annum as a solvent component in the manufacture of butadiene rubber. The butadiene is polymerised in an enclosed system, as briefly described in Section 7.2.3. The benzene is a minor component in the cyclohexane based solvent and is not consumed during the reaction. Instead, the solvent is removed from the rubber-solvent solution by steam stripping, condensed, purified and recycled. No data are available to confidently predict emissions of benzene during rubber manufacture.

USEPA (1998b) does not provide any in-depth discussion on the emissions of benzene when used as a solvent as this use is expected to be eliminated in the next few years, although process vents, dryer vents and building ventilation systems are identified as emission points. However, TGD (EC, 1996) may be used to estimate emissions. Based on its vapour pressure, TGD predicts that 0.01% of benzene will be emitted to the atmosphere when used for chemical synthesis in a continuous process. With 40 t per annum, this corresponds to an annual release of 4 kg, with a daily release over 300 days of 0.013 kg, resulting in a predicted concentration in air at points 100 m from the point source of 0.004 $\mu g/m^3$, or 0.001 ppb.

Releases to water can also be predicted. Based on the solubility of benzene, TGD estimates that 0.05% will be released with wastewater. This equates to 20 kg per annum, or 0.07 kg per day.

Styrene manufacture

The Huntsman plant in Melbourne converts in the order of 80 kt benzene per annum to ethyl benzene for processing into styrene (see Section 7.2.3).

USEPA (1998b) has provided emission factors based on a controlled 300 kt/y capacity integrated ethyl benzene/styrene plant (Table 15.4). Major process emission sources are the alkylation reactor area vents, atmospheric and pressure column vents, vacuum column vents and the hydrogen separation vent. These emission factors will be used for this assessment, although actual emission factors may vary with throughput and control measures.

Table 15.4: Benzene emission factors during manufacture of styrene and phenol in a controlled 300 kt/y capacity model plant (USEPA, 1998b)

Plant	Product	Source	Emission factor (kg/t)*
Styrene plant	Ethyl benzene	Alkylation reactor vent	0.0003
		Benzene drying column	0.012-0.48
		Polyethylbenzene recovery column	0.002-0.005
		Benzene-toluene vacuum vent	0.03-1.2
	Styrene	Hydrogen separation vent	0.00003-0.0012
	Total		0.04433-1.6865
Phenol plant	Cumene	Benzene drying column	0.001
		Catalyst mix tank scrubber vent	0.00795
		Wash decant system vent	0.000392
		Benzene recovery column	8.5×10^{-4}
	Phenol	Cumene oxidation	5.82×10^{-5}
	Total		0.01025

* These emissions do not consider equipment leaks and fugitive emissions through storage and handling.

As mentioned above, in the order of 80 kt per annum benzene is used in the manufacture of styrene. By weight, benzene accounts for around 74% of styrene, that is, around 28 kt per annum ethylene is required for styrene manufacture. This indicates an annual capacity through the plant of 108 kt of materials. Applying the above emission factors to an environment where control technology is in place, between 4.8 and 182 tonnes per annum benzene would be emitted.

Annual benzene emissions from the Huntsman plant are reported to have fallen from 70 t in 1996 to 7 t in 1998 following the installation of a vapour recovery system to control emissions from tanks in the styrene plant (Huntsman, 1999). These emissions are within the range estimated above. Therefore, as estimated emissions from the phenol plant are much smaller (see below), the PEC_{air} will be calculated from the most recent Huntsman emission data, that is, 7 t/y. Assuming 365 days per annum of manufacture, this equates to 19.2 kg per day, corresponding to a PEC_{air} at 100 m from the styrene plant of 0.0054 mg/m^3, or 1.6 ppb.

Phenol manufacture

Huntsman uses up to 15 kt benzene per annum in the production of cumene (isopropyl benzene), which is then split to phenol and acetone (Section 7.2.3).

USEPA (1998b) provides emission factors for cumene and phenol production. Major process emission sources are process vents, equipment leaks, storage vessels, wastewater collection and treatment systems and product loading and transport operations. These emission factors are presented in Table 15.4.

As mentioned above, up to 15 kt per annum benzene is used in the phenol manufacture. By weight, benzene accounts for around 65% of cumene, meaning around 8 kt per annum propylene is required for the cumene manufacture. This indicates an annual capacity through the plant of 23 kt of materials. Applying the above emission factors, in an environment where control technology is in place, 235 kg per annum of benzene can be expected to be emitted. Assuming manufacture on 365 days per annum, this equates to 0.64 kg per day, corresponding to an estimated air concentration at 100 m from the plant of 0.16 μg/m^3, or 0.06 ppb.

Australian monitoring data

In their review of studies of hazardous air pollutants performed in Australia and New Zealand, the Victorian EPA summarises measurements taken from the Altona chemical complex in 1995 (EPA Victoria, 1999). Benzene-emitting industries in the area include a petroleum refinery, a petroleum terminal and the Qenos and Huntsman chemical plants. The summarised results for 3-min average measurements show an average of 2.7 ppb with a maximum 3-min average of 39 ppb. The maximum hourly average is given as 30 ppb. Measurements from four other locations show averages of 0.7 (0.2-2.5); 0.7 (0.2-1.2); 0.9 (0.3-1.6); and 0.7 (0.3-1.6) ppb (timing not specified).

Unpublished data from the Victorian EPA show benzene concentrations from 0.3-8.1 ppb in 58 air samples collected within 400-2200 m from the Huntsman facility in April-June 1997. In samples collected with a wind switch directional sampling system on four separate days at a point 600 m from the plant, benzene levels ranged from 1.5-6.4 ppb during downwind periods, with upwind (background) concentrations ranging from 0.5-4.2 ppb.

These monitored results are higher than those estimated above for butadiene rubber and phenol manufacture, but are within the range estimated for other benzene-emitting industries in the area.

15.1.5 Fossil fuel burning for power generation

The greatest sources of fossil fuels for electricity generation are black coal, brown coal and natural gas (NPI, 1999d). Electricity generation in Australia for 1996/97 saw 26% come from burning of brown coal and 58.5% from black coal (ESAA, 1999).

The combustion processes in fossil fuel power generation lead to the coincidental production of a number of NPI category 1 substances, including benzene. Generally, this coincidental production will be below NPI threshold levels. However, in the NPI emission estimation technique manual for fossil fuel electricity power generation, some emission data are available (NPI, 1999d). This manual provides an emission factor for benzene of 6.5×10^{-4} kg/t coal burnt for electricity generation.

On this basis, the NPI has estimated emissions for the largest Australian power station sites utilising black and brown coals. The largest Australian power stations utilising black coal are Eraring and Bayswater in New South Wales. These power stations use 5-6 million t of coal per annum. In estimating the emissions, a conservative assumption of 10 million t per year black coal was adopted, providing a maximum site emission estimation of 6.5 t benzene (NPI, 1999d). For brown coal, the largest single facility is Loy Yang Power, located in Victoria. This site uses an average of around 20 million t of brown coal per annum. The total emissions estimated by NPI assumed consumption of 25 million t brown coal per annum, resulting in an estimated emission of 16.3 t benzene (NPI, 1999d).

Table 15.5 shows the estimated concentrations assuming emissions occur on 365 days of the year and applying the usual formula to determine a local PEC_{air} at points 100 m from the above model power plants.

Table 15.5: Predicted environmental concentrations of benzene in air at 100 m from fossil fuel power generation plants

Fuel type	Coal consumption (kt/y)	Benzene emitted (kg/y)	Daily release (kg)	PEC (mg/m^3)	PEC (ppb)
Brown coal	25,000	16,300	45	0.013	3.9
Black coal	10,000	6500	18	0.005	1.6

15.1.6 Other point sources

Landfills

USEPA (1998b) provides an emission estimation technique for determining benzene emissions from municipal solid waste landfills. The rate of benzene emissions from a landfill is governed by gas production and transport mechanisms. Production mechanisms for benzene will include biological decomposition or chemical reaction. Transport mechanisms include transportation of benzene in its vapour phase to the surface of the landfill, through the air boundary layer above the landfill and into the atmosphere.

Uncontrolled benzene emissions from a landfill may be estimated by determining the uncontrolled methane generation rate, using this to determine the uncontrolled benzene emission rate and finally, using this to calculate the uncontrolled benzene mass emission rate.

The uncontrolled methane volumetric generation rate may be estimated for individual landfills by using a theoretical first-order kinetic model of methane production (developed by USEPA), from the equation $Q_{CH4} = L_0R(e^{-kc}-e^{-kt})$, where Q_{CH4} = methane volumetric generation rate at time T, m^3/y; L_0 = methane generation potential, m^3 methane per t refuse; R = average annual acceptance rate of degradable refuse during active life (t/y); k = methane generation rate constant, yr^{-1}; c = time since landfill closure (0 for active landfill); and t = time since initial refuse placement (years). Default values for L_0 and k are provided by USEPA. An L_0 value of 125 m^3/t refuse is stated as appropriate for most landfills. Values for k depend on moisture levels, with higher values (a suggested value is given of 0.05/y) appropriate for areas with normal or above normal precipitation. For landfills with drier waste, a k value of 0.02/y is more appropriate. For the US, an average k value is 0.04/yr. This will be used as a default value.

Information from the Australian Waste Data Base (EA, 1999a) provides average waste generation per person for selected states. The highest waste producing state was Western Australia with an average of 1.61 kg/person/day municipal waste generated over the 1995-1997 period. This compared to 1.12 kg/person/day over a six-year period (1990/91-1995/96) in New South Wales, and 1.07 kg/person/day over a 4-year period (1992/93-1995/96) in Victoria. Only municipal wastes have been considered as they are expected to be highest in degradable material.

For a worst case 'model' landfill, it will be assumed the landfill services a population of 150,000 and disposal is at a rate of 1.6 kg per person per day, 365 days of the year, giving an annual waste input into the landfill of around 88,000 t municipal waste. The landfill will be assumed to have commenced operation 10 years ago and still be in operation.

Applying these inputs to the above formula, the methane volumetric generation rate can be estimated to be 3,630,000 m^3 per annum.

Based on the methane volumetric generation rate, a volumetric emission rate for benzene can now be estimated using the equation $Q_{BZ} = 2Q_{CH4} \times C_{BZ}/(1 \times 10^6)$, where Q_{BZ} = benzene volumetric emission rate (m^3/y); Q_{CH4} = methane volumetric emission rate (m^3/y); and C_{BZ} = benzene concentration in landfill gas in ppm (USEPA, 1998b).

This model assumes that approximately 50% of landfill gas is methane. USEPA provides emission concentrations of benzene based on a landfill site's history of co-disposal with hazardous wastes. Their analysis indicates that benzene emissions vary with the amount of hazardous waste co-disposed and provides the following emission concentrations:

Type of waste disposed	Emission concentration (ppm)
Municipal waste co-disposed with hazardous waste	24.99
Municipal waste, unknown history of co-disposal with hazardous waste	2.25
Municipal waste only	0.37

With the exception of incinerators for hospital waste, there are no incinerator facilities in Australia for disposing of hazardous or municipal waste, so the main route for disposal of hazardous waste is to landfill. For this assessment, as a worst case, it is assumed that municipal waste is co-disposed with hazardous waste. Thus, a benzene emission concentration of 24.99 ppm will be used.

Applying this to the benzene volumetric emission formula above, the 'model' landfill is estimated to produce 181 m^3 benzene per annum. Based on this, the uncontrolled emission rate of benzene in kg/y can be estimated by the equation $I_{BZ} = Q_{BZ} \times 78.11/(8.205 \times 10^{-5}\ m^3.atm/(mol.°K))(1000\ g)(273 + T)$, where I_{BZ} = uncontrolled benzene mass emission rate, kg/y; Q_{BZ} = benzene volumetric emission rate, m^3/y; T = temperature of landfill gas (°C) with a default value of 25°C; and 78.11 = molecular weight of benzene (USEPA, 1998b). This gives an estimated annual emission of benzene from the 'model' landfill of 580 kg per annum.

Assuming emission over 365 days per annum, and applying the formula to determine a PEC_{air}, then at points 100 m from the landfill, the concentration of benzene in air can be expected to be 4.4×10^{-4} mg/m^3 or 0.14 ppb. As very little hazardous waste is likely to be co-disposed in Australia, this is very much a worst-case estimate.

Monitoring undertaken at the Castlereagh Waste Management Centre revealed mean benzene concentrations of 0.4-1.5 ppb at 7 sampling areas. The minimum reading was 0.3 ppb with a maximum level of 2.3 ppb detected (Dean et al, 1996). These readings are higher than the PEC determined above. However, these measurements fall within the expected urban background concentration levels for benzene (Section 15.2.2).

Waste incinerators

In the absence of data on benzene emissions from waste incinerators such as those used for hospitals and of relevant emission estimation techniques, meaningful calculations cannot be performed.

15.1.7 Summary

Table 15.6 summarises the predicted environmental concentrations of benzene in air at points 100 m from the point sources discussed above.

Benzene release from point sources is highest for coal gas by-product and coke oven plants. Coal tar distilleries and petroleum and alumina refineries may also be expected to show significant levels of benzene in surrounding air.

Table 15.6: Summary of predicted environmental concentrations of benzene in air at 100m from various point sources

Point source	PEC (mg/m^3)	PEC (ppb)
Petroleum industry		
• refineries	0.004-0.014	1.3-4.2
• terminals	0.002 (average) 0.014 (maximum)	0.6 (average) 4.2 (maximum)
Steel and associated industries		
• Coal coking	0.076	23.3
• Coke gas processing	0.04-0.86	11-270
• Coal tar distillation	0.025	7.7
Aluminium industry	0.019	6.1
Chemical industry		
• Butadiene rubber manufacture	4×10^{-6}	0.001
• Styrene manufacture	0.0054	1.6
• Phenol manufacture	1.6×10^{-4}	0.06
Fossil fuel burning for power generation	0.005-0.013	1.6-3.9
Landfills	4.4×10^{-4}	0.14

15.2 Diffuse releases to urban air

15.2.1 Emissions estimation

Within an urban environment, there will be many sources contributing to benzene levels in the atmosphere. These include point source releases as well as diffuse emissions from cars, service stations, solid fuel burning and lawn mowing.

Monitoring data for various Australian cities is considered further below. To represent other urban areas of Australia, concentrations will be modelled based upon releases to the atmospheric air column above an Australian model city located inland, with a population of 300,000, at a population density corresponding to Australia's largest city, Sydney.

To determine the land area the urban centre will cover, population density is required. The New South Wales EPA provides a 1996 population for Sydney of around 3,820,000 people. The Sydney area covers 1548 km^2 (EPA New South Wales, 1999), giving a population density approaching 2500 people/km^2. The method for determining the volume of atmospheric air columns is described in Connell & Hawker (1986). With a population of 300,000 , the urban centre used for this calculation would cover a land area of 120 km^2, with an atmospheric air column volume of 7.38×10^{11} m^3.

Service stations

According to AIP (2000), there are 8233 service stations in Australia. The model population of the model urban environment is around 2% of the Australian total. Assuming a *pro rata* allocation for service stations, this equates to around 165 service stations in the urban centre.

The NPI draft emission estimation technique manual has been used to estimate benzene emissions from service stations in the urban area (NPI, 1999c). This document provides emission rates for various stages including underground tank filling, tank breathing and emptying, vehicle refuelling and spillage. Different emission rates are suggested for tank filling and vehicle refuelling depending on methods and technology. Based on the NPI manual, this assessment will use the emission rate for submerged filling of 880 mg/L throughput and assume that displacement losses during refuelling are uncontrolled giving an emission rate of 1320 mg/L. These emission factors are for total emissions of VOCs and result in the estimation of aggregated emissions from service stations in the model urban centre shown in Table 15.7.

Table 15.7: Estimated emission of volatile organic chemicals (VOC) from service stations

Emission source	Emission factor (mg/L)	Throughput (ML/y)	VOC emissions (kg/y)
Underground tank filling	880		
Tank breathing/emptying	120		
Vehicle refuelling	1320		
Spillage	80		
Total	2400	360	864,000

NPI speciation data for VOCs emitted at service stations show benzene to be 0.9% by weight of petrol vapour. Therefore, of these emissions, 7776 kg per annum will be emitted as benzene.

Petrol engine exhaust

Benzene in petrol engine exhaust emissions is a combination of unburned benzene originally present in fuel and benzene produced as a result of incomplete combustion of other petrol components. Non-benzene aromatics in fuels can cause around 70-80% of the exhaust benzene formed and some also forms from engine combustion of non-aromatic fuel hydrocarbons (USEPA, 1993). As such, vehicles using benzene-free fuel such as LPG and diesel may still release benzene in exhaust emissions.

The quantity of benzene in exhaust varies depending on control technology and fuel composition. A catalytic converter is a device that uses a catalyst such as platinum and palladium to more fully complete the burning or oxidation of the fuel as it leaves the engine. These unburned exhaust emissions comprise hydrocarbons including benzene (in the form of unburned petrol), carbon monoxide (formed by the combustion of fuel) and nitrogen oxides (created when the heat in the engine forces nitrogen in the air to combine with oxygen). The catalyst helps to convert carbon monoxide into carbon dioxide. It also converts the hydrocarbons into carbon dioxide and water and the nitrogen oxides back into nitrogen and oxygen.

Based on the 1996 census, Canberra, which has a population similar to the model urban centre, has 118,700 households and 188,900 registered motor vehicles (predominantly passenger vehicles, but includes light commercial vehicles). These figures will be assumed for the model urban environment. Data collected by the Australian Bureau of Statistics in 1995 indicate an average distance travelled of 15,200 km per annum (including vehicles which did not travel any distance). Duffy et al. (1999) provide measurements of benzene emissions from Australian cars and state that pre-1986 cars have an average emission of 132 mg/km, while post-1985 cars average 41 mg/km benzene emission.

The Motor Vehicle Census for Australia (ABS, 2000a) was used to determine the number of vehicles expected to have control technology (catalytic converters) to those that do not. This census gives data up to the end of October 1999, and lists vehicles by fuel type, vehicle type and age. The data were divided into various age classes with any vehicle in or before the 1983-1986 age group being assumed to not have control technology.

Considering figures for petrol driven passenger motor vehicles and light commercial vehicles (these two vehicle types accounted for around 92% of the vehicle fleet), it was determined that in the order of 35.3% of the vehicles in the model urban centre would not have control technology (that is, we assume they will produce emissions in line with pre-1986 cars given above). The following emissions were calculated:

Catalytic converters	No. of vehicles	Total km/y	Emissions (kg/y)
Yes	122,218	1.86×10^9	76,166
No	66,682	1.01×10^9	133,790
Total			209,956

Under the *Fuel Quality Standards Act 2000*, the Commonwealth Government is establishing national standards prescribing a range of characteristics for petrol and diesel. Federal Cabinet has agreed that there will be a maximum benzene concentration in petrol of 1% v/v from January 1 2006. Modelling, based on an earlier proposal to reduce benzene content to 1% by 2005, predicted this would lower total benzene emissions (evaporative + exhaust) by 29% in the year 2010 (Environment Australia, 2000). Reducing the benzene content of petrol by two-thirds does not equate to a similar reduction in total benzene emissions because benzene exhaust emissions are to a large extent independent of benzene levels in petrol.

Lawn mowing

It is assumed for worst case purposes that all dwellings have lawns. NPI has an emission estimation technique manual for aggregated emissions from domestic lawn mowing (NPI, 1999a). This document provides averages for percentages of 2-stroke and 4-stroke machines and mowing times per annum per household depending on fuel type. Estimated emissions of benzene are provided for each fuel type. Based on 118,700 households, the following emissions of benzene from domestic lawn mowing can be estimated following the NPI guidelines. As for petrol engine exhaust above, the anticipated lowering of benzene in fuel to 1% will lead to expected reductions in benzene emissions.

Engine type	Petrol type	Per cent of mowers	No. of mowers	Mowing time (h/y)	Emission factor (g/h)	Emission (kg/y)
2-stroke	Leaded	22	26,114	443,938	17	5330
	Unleaded	27	32,049	512,784	17	8720
4-stroke	Leaded	18	21,366	384,588	2.3	885
	Unleaded	26	30,862	462,930	2.3	1065
Total						16,000

Industry benzene emissions

The model urban centre will be assumed to have benzene emitting industries such as a power generator and a petrol terminal. According to the estimated releases shown in Tables 15.2 and 15.6, these sources would provide an average yearly emission of around 30 t, based on the highest values. While this obviously depends on industry type and control factors, it will be used for this assessment as a worst case assumption.

Domestic solid fuel burning

While estimation techniques have been developed (NPI, 1999b), as yet no survey data appear available to determine quantities of wood burnt in different heater types or consumption of timber for heating purposes. UK data indicate that the combustion of fuels contributes around 2% of total benzene emissions (Wadge & Salisbury, 1997). This will be assumed to hold for the current calculation. Total annual emissions from other uses estimated above amount to around 273 tonnes, indicating a further 5580 kg are released through domestic solid fuel burning.

15.2.2 Predicted environmental concentration in urban air

The calculated daily releases within the model urban centre are summarised in Table 15.8.

Table 15.8: Predicted daily releases of benzene within a model urban centre

Emission source	Approximate annual emission (kg)	Average daily release (kg)	Average daily release (%)
Service stations	7800	21	2.9
Vehicle exhaust	209,956	575	78
Lawn mowers	16,000	44	6
Industry	30,000	82	11.1
Domestic solid fuel burning	5600	15	2
Total	269,356	737	100

The atmospheric component for the model urban centre is defined as 7.38×10^{11} m^3. With 737 kg entering the atmosphere daily, this equates to a concentration of 1 $\mu g/m^3$, or 0.31 ppb. This applies to a ground area of 120 km^2, with a population density of 2500 people/km^2.

This calculation only provides a daily contribution to the atmosphere and does not account for breakdown and dispersion of benzene or accumulation in the atmosphere through release occurring every day. Assuming an atmospheric half-life of 8 days (Section 8.2.1) and no dispersion from the atmospheric column above the urban centre to the surrounding atmosphere, the concentration of benzene in the atmosphere is calculated to stabilise at around 3.4 ppb. This may be considered an

overestimation, as dispersion from the atmospheric column above the urban centre will occur. However, for the purposes of this assessment it will be used as a worst case average urban atmospheric PEC.

As explained above, under the *Fuel Quality Standards Act 2000*, the maximum benzene concentration in petrol will be lowered to 1% from January 1 2006. This will lead to a significant reduction in benzene emissions, due to lower emissions from vehicles and lawn mowers and reduced releases from petroleum refineries and terminals, which will affect the PEC calculation for benzene in urban air.

Australian monitoring data

Table 15.9: Reported concentrations of benzene in urban air in Australia (from EPA Victoria (1999) and DEP Western Australia (2000))

	Concentration (ppb)	
Location and period*	**Average**	**Maximum**
Adelaide, Edwardstown (industrial) 1994	19	77
Adelaide, North Terrace (CBD) 1994	8	26
Brisbane, 3 residential areas	0.62	1.67
	0.502	1.41
	0.328	0.78
Goat Island, NSW, downwind of refinery 1979	2.6	No data
Latrobe Valley, VIC 1987/88 (summer)	~1	No data
Melbourne, Altona 1991	7.9	20
Melbourne, CBD 1983/84[1]	22.3	37.8
Melbourne, CBD 1990	15.7	19.8
Melbourne, CBD 1991 (?)	~16	No data
Perth and Kwinana, urban background 1993/94	1.63	No data
Perth, Darling Scarp 1993/94	0.45	No data
Perth, Gooseberry Hill 1997/98	0.15	0.21
Perth, Kwinana, plume 1993/94	4.7	No data
Perth, metropolitan area 1997/98	1.44	17.6
Perth, North Fremantle 1997/98	0.37	0.54
Perth, smog 1993/94	1.9	No data
Sydney, Cahill Tunnel (peak hour) 1991 (?)	7-38	38
Sydney, George Street, summer 1994	4.1	5.2
Sydney, George Street, winter 1994	7.6	9.5
Sydney, near point sources 1992 (summer)	2.5	6.8
Sydney, suburban 1995:		
• Castlereagh Llandilo Road	0.4	No data
• Castlereagh Northern Road	0.5	No data
• Earlwood	4.72	No data
• Lidcombe	1.63	No data
• North Ryde	0.90	No data
• Randwick	2.40	No data
• Rozelle	1.29	No data
• Westmead	4.90	No data

*Results may not be comparable because of differences in sampling and analytical methodology

[1] CSIRO, 1995

The Victorian EPA has undertaken a review of monitoring studies performed in Australia and New Zealand on hazardous air pollutants, which was published in 1999 (EPA Victoria, 1999). In addition to this, a recent document provides monitoring for various air toxics including benzene in Perth (DEP Western Australia, 2000). The studies outlined in these documents are summarised in Table 15.9. All figures have been converted to ppb.

Comparison of modelled urban atmospheric PEC to monitored data

The level of 3.5 ppb for a model urban centre derived above is within the range of results reported through monitoring studies in Australian urban centres.

15.3 Indoor air concentrations

15.3.1 Homes

In general, benzene concentrations in the home are higher than the corresponding outdoor level. Table 15.10 summarises the results of several studies comparing average airborne concentrations of benzene in homes with corresponding outdoor levels.

Table 15.10: Summary of studies comparing average airborne concentrations of benzene in homes with corresponding outdoor levels

Location	Region or area	Benzene (ppb)		Ratio	Reference
		Indoors	Outdoors		
Alaska, USA	Remote	6.2	2.5	2.5	Goldstein et al. (1992), as cited in Wallace (1996)
Antwerp, Belgium,	Urban	9.4	4.4	2.1	Cocheo et al. (2000)
Arizona, USA	State-wide	0.5	0.4	1.3	Robertson et al. (1999)
Athens, Greece	Suburban	10.1	20.7	0.5	Cocheo et al. (2000)
Bristol, England	Urban	2.5	1.6	1.6	Brown & Crump (1996)
California, Maryland and New Jersey, USA	State-wide	3.1	1.8	1.7	Wallace (1996)
California, USA	Rural	1.1	0.4	2.8	Sheldon et al. (1991), as cited in Wallace (1996)
Copenhagen, Denmark	Urban	4.5	3.1	1.5	Cocheo et al. (2000)
Erfurt, Germany	Urban	1.2	0.9	1.4	Schneider et al. (1999)
Hamilton, Canada	Urban	1.7	1.2	1.4	HAQI (1997)
Hannover, Germany	Urban	1.0	2.9	0.3	Levsen et al. (1996)
	Semi-rural	0.7	0.3	2.3	
Hertfordshire, England	Semi-rural	3.7	2.2	1.7	Brown & Crump (1996)
Huddersfield, England	Suburban	0.5	0.4	1.4	Kingham et al. (2000)
Melbourne, Australia	Suburban	1.0	0.6	1.7	Brown (2000)
Mumbai, India	Urban	11.6	13.5	0.9	Srivastava et al. (2000)
Munich, Germany	Urban	0.8	0.8	1.0	Gebefügi et al. (1995)
Murcia, Spain	Urban	12.3	11.7	1.1	Cocheo et al. (2000)
Nancy, France	Urban	3.3	1.4	2.4	Gonzalez-Flesca et al. (1999)
Padua, Italy	Urban	7.0	8.0	0.9	Cocheo et al. (2000)
Rouen, France	Urban	9.5	4.7	2.0	Cocheo et al. (2000)
Rotterdam, Holland	Urban	2.0	0.9	2.2	Lebret et al. (1986)
Windsor, Canada	Urban	1.0	0.8	1.3	Bell et al. (1994)

The predominant finding of higher benzene levels indoors than outdoors is attributed to specific sources located within or in the immediate vicinity of the

home and/or the inability of these emissions to escape (Wallace, 1989). These include environmental tobacco smoke (ETS), heating and cooking systems, cooking fumes, evaporation from products and materials used in the home, and drift of vapours from attached garages or external sources of benzene.

Longitudinal studies of individual homes have shown that contributions from domestic sources are overlaid on those from outdoor air, which generally account for most of the seasonal and diurnal variations in indoor benzene levels (Gebefügi et al, 1995; Lioy et al, 1991; Thomas et al, 1993). However, indoor air levels also depend on the proximity to road traffic and the degree of ventilation, which in turn is dependent on diurnal, seasonal and climatic conditions (Levsen et al, 1996; Gilli et al, 1996; Cocheo et al, 2000). Ambient air concentrations are lowest during the night. However, if houses are closed up at night, either for safety reasons or in colder climates, especially during winter, benzene levels acquired during the day are unable to escape. Therefore, the total exposure over 24 h is increased relative to outdoor levels. During summer, and in warmer climates, when ventilation is greater, indoor concentrations are similar to outdoor concentrations.

In addition to ventilation patterns, the types of furnishing materials may influence the amount of benzene retained in the home. A study of benzene exposure in European cities found that, while urban pollution levels increased from north to south, the ratio of indoor to outdoor air levels were lower in southern European urban areas than in the north (Cocheo et al, 2000). One explanation proposed by the authors is that volatile organic pollutants, including benzene, from both indoor and outdoor sources may be trapped in absorbent fabrics and other materials, resulting in higher residual levels in houses that have more carpets, wood, linoleum and soft furnishings, as do houses in cold climates.

In the absence of localised sources inside the home (such as proximity to an attached garage, room with smokers), there are no significant differences in benzene concentrations between kitchens, living rooms and bedrooms, height above floor level, or older versus newer apartments (Schneider et al, 1999).

Approximately 85% of ETS comprises sidestream smoke emitted by the smouldering end of a cigarette (cigar or pipe, as the case may be), with lesser contributions from the mainstream smoke that active smokers directly inhale and exhale. The emission factor for sidestream smoke is in the range of 300-500 μg benzene per cigarette, with little variability between brands (Daisey et al, 1998; Miller et al, 1998). In two studies conducted in 200-300 homes with and without smokers in Germany and USA respectively, the average increase in benzene levels in homes with one or more smokers was 4.0 $\mu g/m^3$ or 1.2 ppb (Wallace, 1996). Surprisingly, an international study of exposure to tobacco smoke reported that fixed-site measurements in an unspecified number of homes in Sydney found slightly higher indoor air concentrations of benzene (median: 1.1 ppb) in non-smoking houses than in those where cigarettes, pipes or cigars were smoked within the communal areas (median: 0.9 ppb) (Phillips et al, 1998).

Herbal cigarettes, marijuana, incense sticks and mosquito coils produce benzene emissions similar to cigarettes, about 0.4-0.5 mg/g material burnt (Löfroth et al, 1991). However, the frequency of burning such articles is much less than for tobacco cigarettes and their contribution to indoor benzene levels is expected to be minimal.

Combustion of wood produces approximately 400 mg benzene for every kg dry wood burned or 114 μg benzene per kJ heat produced compared to 9 μg/kJ for

kerosene and 2 μg/kJ for LPG. Per-meal emissions from unflued cookstoves, such as a caravan or enclosed barbecue, are estimated to be 36 μg.h/m^3 (LPG), 124-268 μg.h/m^3 (kerosene), 316 μg.h/m^3 (charcoal) and 1220 μg.h/m^3 (wood) (Zhang & Smith, 1996). In actively burning fires, most of the combustion products go up the chimney. However, even well constructed open fireplaces are subject to downdrafts and smoke drift, especially when the fire is low. In addition, high outdoor benzene levels in smoke produced by wood fires can re-enter homes, particularly in areas subject to temperature inversions during winter.

Volatile emissions from cooking oils have been studied by Pellizzari et al. (1995) and Shields et al. (1995) who found that emissions of benzene in wok cooking vapours were higher from unrefined rapeseed oil than from peanut, soybean and canola oils (2.4 compared to 0.2, 0.5 and 0.7 ng/mL respectively in one experiment). Wok cooking is generally carried out at very high temperatures (275-280°C). Reducing the temperature of cooking from 275°C to 185°C reduced benzene emissions by sevenfold (Shields et al, 1995). However, given the average use of cooking oil in the home (about 50 mL per day), this source would not contribute measurably to benzene levels in the indoor atmosphere.

Some petroleum-based domestic products such as oil-based paints, particleboard and adhesives may contain very low concentrations of benzene as an impurity. The contribution to indoor air levels of benzene from these sources has not been measured, but is expected to be low. In New Zealand, Stevenson & Narsey (1999) found that redecorating activities increased the indoor concentrations of toluene and xylenes, but not benzene. Brown (2000) did not identify significant sources of benzene release in new and renovated buildings in Melbourne.

Indoor air levels of benzene are significantly increased in houses with an attached garage (Brown, 2000; Gebefügi et al, 1995; Levsen et al, 1996; Thomas et al, 1993). Sources of benzene in garages include vapours from cars and lawn mowers and stored petrol or other solvents. In New Zealand, the highest indoor air level for any site investigated (16.6 ppb or 20 times typical ambient air levels) was in a home with smoker occupants and an internal double garage housing two cars (Stevenson & Narsey, 1999). Sampling of 52 private flats in Munich revealed one unusually high indoor concentration (>31 ppb, or >37 times the outdoor concentration) which was attributed to infiltration from a garage (Gebefügi et al, 1995). Benzene concentrations in four attached garages in the USA ranged from 1-61 ppb; the mass transfer from sources in the garage to living areas in three of these homes ranged from 730-26,000 μg/h (Thomas et al, 1993). In Alaska, where petrol contains 5% benzene compared to ≤1.5% in other US states, garages were found to have benzene air levels ranging from 19-350 ppb (Gordian & Guay, 1995). Removal of a car, lawn mower, petrol canister and solvents from a garage in Hannover, Germany, reduced the benzene concentration in the garage from 25 ppb to 0.4 ppb (Levsen et al, 1996).

The measured indoor air levels shown in Table 15.10 refer to one Australian and a number of overseas localities which are difficult to compare, let alone extrapolate to the Australian continent as a whole, because of differences in a number of factors such as ambient benzene levels, climate, construction methods, heating systems, ventilation practices, smoking occupancy and the prevalence of homes with attached garages. It is nonetheless reasonable to assume that the average indoor to outdoor ratio in urban environments in Australia is close to the median of the available Australian and overseas data excluding remote, rural and semi-rural regions and areas, or 1.4 (range: 0.3-2.4).

The PEC_{air} in the model Australian urban environment described in section 15.2.2 is 3.4 ppb. Therefore, the estimated indoor air level taken forward for public exposure assessment is 1.4 x 3.5 = 4.8 ppb.

15.3.2 Non-residential buildings

Measurements of benzene in offices, shops, classrooms, hotels, bars, restaurants, theatres and other non-residential indoor environments are limited compared to homes. Available literature data giving indoor to outdoor concentration ratios are presented in Table 15.11. The highest ratios were due to specific sources such as petrol vapours and engine exhaust at a motocross event or tobacco smoke in bingo halls and taverns. Of these, emissions from indoor use of motor vehicles are not expected to contribute measurably to average indoor air levels of benzene, whereas tobacco smoke may have a significant impact, depending on smoking policies and occupancy, volume of space, rate of ventilation, heating, air-conditioning and air cleaning systems.

Table 15.11: Benzene air concentrations in non-residential buildings

		Ppb			
Location	**Building or venue**	**Indoors**	**Outdoors**	**Ratio**	**Reference**
California, USA	Portable classrooms	0.5-0.6	0.5-0.6	1	SUSD (1999)
Manila, Philippines	Office	0.4	1.1	0.4	Reverente et al. (1996)
	Restaurant	5.3	14	0.4	
	Shopping centre	1.2	3.9	0.3	
Melbourne, Australia	Gymnasium	0.6-1.9	0.8	0.8-2.4	Brown (2000)
Mumbai, India	Offices, smoking	15.1	9.3	1.6	Srivastava et al. (2000)
	Research library	10.7	11.4	0.9	
Sydney, Australia	Entertainment centre (motocross event)	209-334	2.3*	90-150	Angove et al. (2000)
Washington DC, USA	Library of Congress	2.1	1.9	1.1	NIOSH (1996)
Windsor, Canada	Offices, non-smoking	1.0	0.8	1.3	Bell et al. (1994)
	Hotel rooms	1.2	0.8	1.5	
	Bingo halls	6.4	0.8	8.0	
	Taverns	10.7	0.8	13	

* Sample taken inside building prior to the motocross event.

Other Australian data include a study conducted in Hobart, Tasmania, which found indoor air levels of benzene ranging from 0.9-7.8 ppb in eleven office buildings in the central business district (Mesaros, 1998). However, these buildings were selected for investigation because a very high number of their occupants suffered from typical sick building syndrome symptoms.

In the absence of sufficiently representative measured data, it is reasonable to assume that the concentration of airborne benzene in non-residential buildings in Australia is similar to the estimated indoor air concentration in Australian homes, except in restaurants, bars and the like with high levels of ETS.

As benzene and nicotine are both found in the vapour phase of cigarette emissions, nicotine concentrations can be used as an indicator of relative benzene exposures. A recent review of ETS exposure quoted typical nicotine air levels of 1-3 $\mu g/m^3$ in residences, 3-8 $\mu g/m^3$ in restaurants, and 10-40 $\mu g/m^3$ in bars (Hammond, 1999). As such, the additive effect of ETS in restaurants and bars where smoking is

permitted could be higher than in the homes of smokers by a factor of 2.7 (8/3) and 13 (40/3) respectively. The indoor air concentration of benzene in Australian homes is estimated at 4.8 ppb (Section 15.3.1) and the average additive effect of ETS in homes with smokers at 1.2 ppb (Wallace, 1996). Therefore, the estimated benzene levels in restaurants and bars with smoking occupancy are 8.0 and 21 ppb respectively. These are higher than the measured values shown in Table 15.11, but are considered reasonable worst case estimates.

15.3.3 Motor vehicles and other means of transportation

Several studies conducted in a number of locations have consistently found that road users including drivers and passengers in all kinds of vehicle are exposed to higher levels of benzene than background air quality data may suggest (Taylor & Fergusson, 1997).

In parked vehicles, the excess benzene concentration is due to evaporative emissions from the vehicle itself. Among others, these depend on the benzene content and vapour pressure of the fuel, the fuel system, engine temperature, ambient weather conditions, and the degree of enclosure of the passenger cabin. In vehicles in traffic, however, part of the excess is due to the intake of exhaust fumes from the tailpipes of preceding vehicles. As such, it depends not only on the above factors, but also on traffic level, flow, and mix in terms of cars with or without catalytic converters, trucks, buses and motorcycles. Generally, the excess would be minimal in new cars with fuel injection travelling at high speed in light traffic on a windy day with vents, windows and sunroof tightly closed and the air-conditioning on. Conversely, it would be maximal in old, carburetted, poorly maintained cars that travel slowly in congested traffic on a still day with vents and windows open and fans on. High benzene levels may also build up in vehicles left in undercover car parks or transiting tunnels and during refuelling at petrol stations (Duffy & Nelson, 1997; Taylor & Fergusson, 1997).

Table 15.12 summarises the available Australian and New Zealand studies that have measured the concentration of benzene inside moving vehicles during city commutes.

Table 15.12: Summary of Australian and New Zealand studies of in-vehicle benzene air concentrations during city commutes

Location	Conditions	No. of commutes	Mean benzene level (ppb)	Reference
Private cars				
Auckland	Catalyst-equipped car, summer	2	12	Stevenson & Narsey (1999)
	Catalyst-equipped car, winter	2	20	
Melbourne	Post-1986 car	1	13	Torre et al. (1998)
	Post-1986 cars	5	10	Torre et al. (2000)
Sydney	Pre-1986 car	4	48	Duffy & Nelson (1997)
	Post-1986 cars	8	22	
Public transport				
Melbourne	Tram	1	7.7	Torre et al. (1998)
	Train	5	1.6	Torre et al. (2000)
Sydney	Diesel bus, air-conditioned	3	5.9	Duffy & Nelson (1997)
	Diesel bus, not air-conditioned	4	8.8	

Average air levels were approximately 15 ppb and 48 ppb in cars with and without catalytic converters respectively. Weighting the latter according to the estimated number of post-1985 vehicles in the model urban environment described in Section 15.2.1 gives an estimated average benzene concentration in motorcars of about 28 ppb. This is higher than levels measured in the USA where the car fleet is newer and petrol contains less benzene than in Australia, but within the range reported from Europe and Korea (Jo & Park, 1999; Rodes et al, 1998; Taylor & Fergusson, 1997).

In trams and buses, benzene levels averaged 7.5 ppb. The lowest level was found in trains, indicating that rail commuters are unlikely to be exposed to benzene levels exceeding those in ambient air.

In Melbourne, personal monitoring of two individuals commuting by foot or bicycle showed benzene exposure levels of 4.4 and 12.2 ppb respectively, compared to a concentration of 6.0 ppb at a roadside point along their route (Torre et al, 1998). Overseas data reviewed by Taylor & Fergusson (1997) suggest that pedestrians and cyclists typically are exposed to two times ambient air levels. This would equate to an average roadside concentration of 6.8 ppb in the model Australian urban environment described in Section 15.2.2, where the predicted atmospheric concentration of benzene is 3.4 ppb.

15.4 Concentrations in water and soil

15.4.1 Water

Predicted environmental concentration (local PEC)

Some release to wastewater may be expected to occur during benzene production. Within the sewage treatment plant (STP), 86% of benzene will be removed in the following manner, assuming benzene is inherently biodegradable and based on the SIMPLETREAT tables provided in TGD (EC, 1996): 70% in air, 1% in sludge and 15% by degradation. This leaves 14% available in the water column on release to receiving waters. This level of removal is supported by a report in IUCLID where benzene levels in the influent and effluent from a municipal STP in The Netherlands in 1989-1991 averaged 3.9 and <0.5 µg/L respectively. This suggests removal of >87%.

By far the highest producer of benzene (excluding incidental production through petrol combustion in motor vehicles) is the petroleum industry. Table 7.3 shows that in Australia in the order of 440 kilotonnes per annum benzene is either extracted, manufactured or imported. NPI data for the 1998-99 reporting year show that only two refineries reported releases to water, namely 1100 kg from the Mobil refinery in South Australia and 120 kg from the BP refinery in Queensland. The calculated benzene production at the Mobil refinery in South Australia is 82 kt per annum (Table 15.1). As such, the release of 1100 kg (which was derived through a combination of measured data, engineering controls and emission estimation) suggests a release of 0.0013%

Using the maximum reported release of 1100 kg per annum and assuming release to a sewage treatment plant with a daily outflow of 250 ML and production on 300 days per annum, the $PEC_{local\text{-}surfacewater}$ can be estimated as follows: Production = 82,000 t; days of operation per annum = 300; daily production = 273 t; daily release

to STP = 273,000 kg x 0.000013 = 3.7 kg; removal from STP = 3.15 kg; concentration in STP = 2 μg/L; $PEC_{local\text{-}surfacewater}$ = 0.2 μg/L (dilution of 10:1).

A continental PEC will not be considered for this assessment, as there are insufficient data to estimate the full extent of incidental benzene production and release around the country. However, the continental PEC would be expected to be lower than that derived for local conditions.

Comparison with measured data

Due to its high volatility and low residence time in water, benzene would not be expected to be detected at significant levels in surface waters. The 1996 Australian drinking water guidelines state that benzene has not been detected in Australian drinking water (NHMRC, 1996).

International data provided in IPCS (1993) are summarised in Table 15.13.

Table 15.13: International data on benzene levels in water (IPCS, 1993)

Source	Country	Concentration (μg/L)	Comments
Rainwater	UK	87.2	Appears high for unknown reason(s)
	Germany	0.1-0.5	
Surface water	USA	0.004-0.9	Downriver chemical plant outfall
	USA (13 locations)	1-13	Both upstream and downstream near industrial outfall
	USA (Potomac River)	<2	Detection limit 2 μg/L
	Switzerland (Lake Zurich)	0.03	
	UK (80 water bodies)	7.2	Average of 61of 154 samples above the detection limit of 0.1 μg/L
	Netherlands (Rhine River)	<0.1	Sampling in 1979
	Germany	<0.1-1	Occasionally up to 200 μg/L
Sea water	Gulf of Mexico	0.005-0.015	Unpolluted waters, sampling in 1977
	USA (Brazos River estuary)	0.004-0.2	Flows into Gulf of Mexico
	Atlantic Ocean	0.06×10^{-3}	Open sea
	Baltic Sea	$0.1\text{-}4.6 \times 10^{-3}$	Open sea
Ground water	USA	1.6	63 private wells, 3.2% of samples contained benzene
	Germany	0.02-0.005	
	USA	30-300	Contaminated well water
	Netherlands	0.005-0.03	Unpolluted areas

Compared to these overseas river water measurements, the calculation for an Australian PEC in surface water may be slightly less than expected. However, it is considered realistic for the purposes of this assessment.

Benzene was detected in 37 of 987 bottom sediments in Japan at levels of 0.5-30 μg/kg. Lake Pontchartrain in USA showed sediment levels of 8-21 μg/kg in 1985. Between 1980-82, benzene was detected in 9% of sediment samples taken from 335 observation sites in USA, the median level being <5 μg/kg (IPCS, 1993).

15.4.2 Soil

NPI data show that the highest reported benzene release to soil is 45 kg per annum from a bulk petroleum storage facility. The top five sites where benzene release to land was reported total <80 kg per annum throughout the country. While it is not possible to predict a concentration in soil that would have any meaning, the NPI data indicate that benzene release to soil is likely to be marginal and not result in significant soil contamination.

Some exposure may result though application of sewage sludge, although the full extent of this is not known in Australia. However, it is understood that Sydney Water sends >90% of their sludge (possibly up to 200,000 tonnes per annum) to beneficial use. Some goes to agricultural use and is soil incorporated, while some goes to compost and horticulture where surface application may occur. Measurements of benzene in sewage sludge or its subsequent soil concentration after application to land could not be identified. Additionally, as described above, only in the order of 1% benzene released to a STP is expected to bind to sludge, so sludge application to land is unlikely to provide a high exposure route.

Most measured data on benzene in soil were obtained to determine the extent of direct contamination by spillage or leakage. In soils in the vicinity of five industrial facilities using or producing benzene in USA, benzene levels ranged from <2 to 191 μg/kg, whereas the concentrations in unpolluted soils in The Netherlands were less than those found in ground water, that is <0.005-0.03 μg/L (IPCS, 1993).

15.5 Summary

Table 15.14 summarises the predicted environmental benzene concentrations in air and water, based on the assessment findings discussed above.

Table 15.14: Approximate predicted concentrations of benzene in air and water

			Benzene concentration	
Environment	**Source type**	**Description**	**μg/m³**	**ppb**
Outdoor air	Point*	Petrol refineries	17.6	5.5
		Petrol terminals	13.4	4.2
		Coal coking plants	91	28.4
		Coal gas by-product plants	860	270
		Coal tar distilleries	25	7.8
		Alumina refineries	19	6.1
		Chemical industry	6.5	2.0
		Fossil fuel burning power plants	13	3.9
		Landfills	0.44	0.14
	Diffuse	Urban atmosphere	11	3.4
		Urban roadside air	22	6.8
Indoor air	Diffuse	Homes and other buildings	16	4.8
		Restaurants, smoking	26	8.0
		Bars, smoking	67	21
		Cars with catalytic converters	48	15
		Cars without catalytic converters	154	48
		Buses and trams	24	7.5
Surface water	Point	Treated oil refinery wastewater	200	0.20

* Maximum predicted concentrations at 100 m from source.

16. Public Exposure

16.1 Direct exposure

Active smoking

In Australia, 23.8% of the adult population are smokers; 27.4% are ex-smokers and 48.9% have never smoked (ABS, 2000b). In a survey conducted in Victoria in 1996-97, the self-reported number of factory-made cigarettes smoked per day averaged 17.8 in regular smokers aged 16 years and over (Trotter et al, 1998).

The quantity of benzene emitted in mainstream cigarette smoke varies from 0.4-104 μg/cigarette; it is proportional to the tar level and is not reduced by cigarette filters (Smith et al, 1997). In 26 brands on the UK market, the yields ranged from 3-60 μg/cigarette, with over half the brands yielding 45-55 μg (Darrall et al, 1998). Based on a value of 50 μg/cigarette, the daily benzene intake of an average smoker (17.8 cigarettes per day) is increased by 0.89 mg per day. For an adult person with a respiration rate of 22 m^3/day, this corresponds to the continuous inhalation of ambient air containing 12.5 ppb of benzene.

Petrol

In Australia, the benzene content of petrol can range from 1-5% v/v. Members of the public may be exposed directly to petrol used as fuel in private vehicles, lawn mowers, outboard engines etc. Although skin contact can occur from accidental drips or spills or the use of petrol for cleaning purposes, it is likely to be infrequent and of short duration. Direct exposure to benzene vapours occurs in garages and undercover parking stations, during petrol pumping at self-service petrol stations and inside parked cars with hot-soaked engines. Reported air levels in these locations vary widely depending on local circumstances, but are typically in the order of 10-100 ppb (Duffy & Nelson, 1996; Leung & Harrison, 1998; Nordlinder & Ljungkvist, 1992; Nordlinder & Ramnäs, 1987; Thomas et al, 1993) and are consistent with Australian data reported in Section 17.1.1.

Other consumer products

Paints, primers, paint strippers, lubricants, abrasives, model and hobby glues and other consumer products may contain organic solvents which in turn may contain very low concentrations of benzene as an impurity (Rastogi, 1993). The contribution to public exposure to benzene from these sources has not been quantified, but is expected to be very low.

16.2 Indirect exposure via the environment

Air

Although benzene is not persistent, it is ubiquitous in ambient air because of its widespread sources of release.

In Australia, measured levels of benzene in air range up to 77 ppb for outdoor urban environments (Table 15.10), 25 ppb in residential buildings (Brown, 2000) and 343 ppb inside petrol-fuelled vehicles (Duffy & Nelson, 1997).

The average atmospheric concentration of benzene in a model Australian urban environment is estimated at 3.4 ppb, with indoor/in-vehicle air levels ranging from 4.9-48 ppb (Table 15.15). These levels would be higher in homes, workplaces and vehicles with smoking occupancy. The contribution of ETS to indoor benzene levels is poorly documented, but is likely to vary considerably depending on local circumstances. In two large studies in Germany and USA, the average increase in benzene levels was 1.2 ppb in homes with one or more smokers (Wallace, 1996).

Drinking water

Contamination of surface water and groundwater can result from removal of benzene from the air in rain, leakage of underground storage tanks, and leaching of oil well and landfill sites.

A number of US studies have reported benzene at levels in the order of 5 ng/L in surface and well waters (Wallace, 1996). In Canada, benzene (detection limit 1 μg/L) was found in 50-60% of drinking water samples from 30 treatment facilities in a national survey, although in provincial monitoring programs it has rarely been detected at concentrations >1 μg/L (Government of Canada, 1993). In Germany, drinking water has been found to contain 18-45 ng/L benzene (GDCh, 1988).

To date, benzene has not been detected in drinking water in Australia (NHMRC, 1996).

Soil

Benzene has been detected in soil as a result of direct contamination by spillage or leakage, at concentrations ≤191 μg/kg (IPCS, 1993). The contribution from traffic emissions is likely to be negligible, because of the rapid volatilisation of benzene to air. Therefore, exposure of young children to benzene by ingestion of soil not directly contaminated by petrol is likely to be negligible.

Food

As discussed in Section 8.2.5, benzene does not accumulate in the food chain. However, the chemical may enter foods as a result of equilibration with surrounding media or through migration from cooking utensils and food packaging materials.

There are early reports of benzene being found in butter (0.5 ng/g), irradiated beef (19 ng/g), rum (120 ng/mL), eggs (500-1900 ng/g), fish (3-88 ng/g) and clams and oysters (220-260 ng/g) (IARC, 1982a; IPCS, 1993). More recent studies reviewed by Wallace (1996) found insignificant amounts in most of 107 foods (including raw eggs). Exceptions included preserved jams and sauces, shelled peanuts and fried eggs, which contained 5-38 ng/g benzene. A 1993 survey in the UK found low levels of benzene (1-18 ng/g) in carcass meat, offal, meat products, poultry, fish and nuts but not in dairy products, bread, cereals, sugar, vegetables, fruit or beverages (MAFF, 1995).

Benzene was, however, detected at low concentrations (27-56 ng/g) in the peel of three (apple, kiwi fruit and orange) of 24 fruit and vegetable samples purchased from local shops in Poland (Górna-Binkul et al, 1996); it was suggested by the authors that the likely source was absorption of benzene from the air by lipophilic components of the peel. The chemical was also found in olive oil produced from fruit stored in a shed housing harvesting machinery (Biedermann et al, 1996). Parking a small grass mower in the shed caused air levels within the shed to

increase from 0.1 to a maximum of 1.9 ppb in 3 h. The average benzene concentrations in oil obtained from olives stored in such sheds at three different locations were 3, 19 and 40 ng/g.

The mean airborne benzene levels in two petrol station kiosks in UK were 3.4 and 27 ppb (CONCAWE, 1998b). A survey of fatty foods sold from petrol stations or roadside stalls in the UK found benzene present in less than half of 114 packages of butter, margarine, lard and bacon (MAFF, 1996). Mean benzene levels were generally in the order of 10-20 ng/g. The pattern of distribution throughout the food samples indicated that the contamination was the result of either road transport or diffusion from the air and that penetration of products protected by impermeable packaging was negligible. Of 221 food products purchased at petrol service stations in Germany, only one (ice cream) contained benzene in detectable amounts (8 ng/g) (Eikmann et al, 1992). A recent, comprehensive review of studies conducted on hydrocarbon contamination of foods sold at petrol stations and shops situated near busy roads concluded that the levels of hydrocarbons (including benzene) in foods from these outlets was comparable to those found in food sold from shops remote from hydrocarbon sources (CONCAWE, 2000).

Benzene has been found in non-stick and thermoset polyester cookware, expanded polystyrene food packaging articles, polyvinyl chloride water bottles exposed to sunlight, containers made from contaminated recycled polyethylene terephthalate bottles, and in microwave heat susceptors packaged with foods such as pizzas and chips (Fayad et al, 1997; Gramshaw and Vandenburg, 1995; Jickells et al, 1990; Komolprasert et al, 1997; McNeal & Hollifield, 1993). However, in no case was migration considered likely to result in concentrations in foods exceeding 10 ng/g.

The daily dietary intake of benzene in the UK population is estimated at 0.5-2.4 μg/day (MAFF, 1995). There is no indication in the published or unpublished literature that food is an important source of exposure to benzene, accounting for at most 2.5% of total daily intake (CONCAWE, 2000).

16.3 Exposure assessment

Method and assumptions

It is widely agreed that inhalation is the predominant pathway for benzene exposure in humans, with <1-3% of total intake apportioned to skin contact and ingestion of food and water (Government of Canada, 1993; IPCS, 1993; Wallace, 1996; WHO, 2000). It has also been shown that the main microenvironments contributing to inhalation exposure are the home, the workplace, road use and tobacco smoke, while infrequent activities of short duration such as car refuelling have little impact on total intake (Leung & Harrison, 1998; MacIntosh et al, 1995). In consequence, this assessment of public exposure to benzene will disregard non-inhalation exposure and focus on the key environments of the home, the workplace and the road, and on active and passive smoking. In addition, although benzene has been detected in human breast milk (Section 9.2.2), quantitative data are not available and intake via this route is not included for the purposes of this report.

Exposures at home, at work and on the road are assumed to occur within the setting of the model urban environment described in Section 15.2. The corresponding air concentrations are those estimated in Section 15.3 and summarised in Table 15.15. Daily and cumulative exposures are estimated for four different age groups comprising 6 years of childhood, 14 years of education, a working life of 40 years

and 18 years of retirement (ABS, 2000b) and for lifestyles identified as non-ETS exposed, passive smoking and, in adults, active smoking. The estimated time spent in relevant environments by each age group is given in Table 16.1, based on data quoted in Langley et al. (1996). All age groups are assumed to spend 20 h/day in residential and other buildings. Non-ETS exposed persons are assumed to avoid all exposure to ETS and all schools and means of public transportation are assumed to be smoke-free. ETS exposure is assumed to entail an increase in indoor/in-vehicle air levels of benzene of 1.2 ppb, as described in Section 16.2. Finally, it is assumed that active smokers consume 17.8 cigarettes a day, equivalent to the inhalation of 12.5 ppb benzene for 24 h/day from the age of 21 and are exposed to ETS throughout.

Table 16.1: Public exposure scenarios

	Age group (years)			
Environment	**0-6**	**7-20**	**21-60**	**61-78**
Outdoors	4 h/day	4 h/day	4 h/day	4 h/day
Homes	19½ h/day	13 h/day for 190 days/year 19 h/day for 175 days/year	11 h/day for 225 days/year 19 h/day for 140 days/year	19 h/day
Schools	-	5½ h/day for 190 days/year	-	-
Workplaces	-	-	8 h/day for 225 days/year	-
Car transport	½ h/day	½ h/day for 190 days/year	1 h/day	-
Other road use*	-	1 h/day	-	1 h/day

* Walking along urban roads and bus, tram and bicycle riding.

Results

Table 16.2 summarises the estimated daily and cumulative exposures per age and lifestyle group calculated in accordance with the above assumptions.

Table 16.2: Estimated 24 h benzene exposures (in ppb) and cumulative exposures at the top of each age bracket (in ppb-years, rounded to the nearest 5) of the general population in a model Australian urban environment

	Non-ETS exposed		Passive smokers		Active smokers	
Age group	**Ppb**	**Ppb-years**	**Ppb**	**Ppb-years**	**Ppb**	**Ppb-years**
0-6 years	5.1	30	6.0	35	-	-
7-20 years	4.9	100	5.7	115	-	-
21-60 years	5.5	320	6.5	375	19.0	760
61-78 years	4.7	405	5.6	485	18.1	1086

Based on the assessed cumulative exposures, the lifetime weighted 24-h exposure is approximately 5.2 ppb in non-ETS exposed persons, 6.1 ppb in passive smokers and 15.2 ppb in active smokers. The daily intake in a 10-year old child with a bodyweight of 30 kg and a respiratory volume of 15 m^3/day is 8.0 µg/kg/day in the absence and 9.3 µg/kg/day in the presence of ETS exposure. In adult males aged 21-60 years with a bodyweight of 70 kg and a respiratory volume of 22 m^3/day, the

estimated intake is 5.6 μg/kg/day in non-ETS exposed persons, 6.6 μg/kg/day in passive and 19 μg/kg/day in active smokers. In adult females aged 21-60 with a bodyweight of 60 kg and a respiratory volume of 22 m^3/day, the estimated intake is 6.6 μg/kg/day in non-ETS exposed persons, 7.7 μg/kg/day in passive and 22 μg/kg/day in active smokers.

In terms of apportionment, indoor air, road use and outdoor air account for 73, 16 and 11% respectively of the estimated lifetime exposure to benzene in non-ETS exposed persons. In ETS exposed persons, passive smoking accounts for 15% of lifetime exposure. In smokers, 6% of lifetime exposure is attributable to ETS and 60% to the inhalation of mainstream smoke.

Population groups likely to be exposed to extreme benzene levels

The estimates given in Table 16.2 refer to a cross-section of the population in the model urban environment described in Section 15.2. Individual exposure levels may, of course, be vastly different, depending primarily on where people live and work, what car they drive, how much time they spend outdoors, on the road, or in smoky environments, and, in active smokers, on the quantity and type of tobacco they consume.

As a rule, exposures would be considerably below average in people who live in semi-rural or rural areas, work outdoors and spend little time on the road. Conversely, they would be well above average for a person who lives in a house with an attached garage, spends several hours a day commuting in a pre-1986 car, and works in an office or shop in a heavily trafficked street.

Comparison with overseas monitoring data and exposure estimates

Extensive monitoring studies conducted in 1980-87 by USEPA in about 800 subjects representing a cross-section of the populations of California, Maryland and New Jersey found a global average personal exposure level of 4.7 ppb (Wallace, 1996). In subsequent, smaller US studies, the average level was 1.6 ppb in a rural community in California and 7.4 ppb in a remote township in Alaska (Goldstein et al, 1992; Sheldon et al, 1991; both as cited in Wallace, 1996). In a mixed urban and rural subset of the Californian studies referred to above, the 24 h exposure level averaged 3.7 ppb in non-ETS exposed persons and 4.6 ppb in passive smokers (Miller et al, 1998). In Singapore, the measured personal exposure level in 20 persons with no known occupational exposure to benzene averaged 7 ppb (Foo, 1991). In Turin, Italy, the mean personal exposure level was 21.9 ppb in non-ETS exposed subjects and 28.6 ppb in passive smokers (Gilli et al, 1996). In a small study of students, homemakers and pensioners in Birmingham, UK, the measured personal exposure levels averaged 4.7 ppb during the day and 3.4 ppb during the night (Leung & Harrison, 1998). In nine council road and park workers in Nancy, France, who were monitored continuously from Monday morning to Friday evening, the mean personal exposure was 790 ppb-hours, corresponding to an average of about 7.6 ppb (Gonzalez-Flesca et al, 1999). In 100 office workers from Milan, Italy, the mean 24 h personal exposure amounted to 6.6 ppb (Carrer et al, 2000). In a large study in continental Europe, the annual average personal exposure level was 4.4 ppb, based on more than 1500 samples collected from 50 non-smokers in each of six cities (Cocheo et al, 2000). It was lowest in the northernmost city of Copenhagen (2.0 ppb) and highest in the southernmost cities of Athens (5.8 ppb) and Murcia (7.2 ppb). A study conducted in 1990-91 of 113 persons representing a cross-section of the adult Western German population found a mean

personal exposure level of 4.2 ppb, with 95% of the sample population exposed to ≤9.9 ppb (Hoffmann et al, 2000).

In Canada, public exposure in the general environment has been assessed under the Priority Substances Program (Government of Canada, 1993). The estimated intake by 5-11-year old, non-ETS exposed children was 2.7 μg/kg/day, compared to 4.0 μg/kg/day in passive smokers. In 20-70-year old adults, the estimated intake was 2.4 μg/kg/day in non-ETS exposed persons, 3.3 μg/kg/day in passive and 29.3 μg/kg/day in active smokers. Benzene intake in adults in UK has been estimated at 1-12 μg/kg/day depending on lifestyle and geographical factors (IEH, 1999), whereas CONCAWE (1999) arrived at an estimated airborne intake in non-smokers which was equivalent to approximately 2-4 and 7-8 μg/kg/day in urban and inner city environments respectively.

Ultimately, benzene intake in non-smokers derives primarily from vehicle and petrol emissions. The estimated Australian intake is higher than the measured data from California, Maryland and New Jersey in USA and the estimated intake in Canada, where the car fleet is newer and petrol contains less benzene than in Australia. However, it falls within the range measured in Alaska, Singapore and several European countries, where the age of the car fleet and/or the composition of petrol are more relevant to the Australian scenario.

As such, the estimated lifetime 24-h exposure level of 5.2-6.1 ppb in non-smokers in the Australian model urban environment is considered sufficiently realistic to serve as a point of reference for the assessment of public health risks from exposure to benzene in the general environment.

16.4 Summary and conclusions

Inhaled tobacco smoke contains about 50 μg benzene per cigarette, corresponding to a daily intake of 0.89 mg benzene by the average smoker (17.8 cigarettes/day). Non-smoking members of the general public are exposed to benzene through the inhalation of indoor, in-vehicle and outdoor air contaminated with the chemical through releases that predominantly derive from petrol evaporation, vehicle exhaust and tobacco smoke. Skin contact with benzene-containing products such as petrol and ingestion of contaminated water or food contribute minimally to human intake. There is no evidence that industrial emissions are a significant source of public exposure.

The 24 h average lifetime exposure in the Australian urban population is estimated at 5.2 ppb in non-ETS exposed persons. It is approximately one-fifth higher in passive smokers exposed to ETS at home, at work and in their cars (6.1 ppb) and almost three times as high (15.2 ppb) in the average smoker. The average 24 h exposure of the overall population of the model urban centre described in Section 15.2 can be estimated as follows:

Twenty-four per cent of the adult Australian population smokes (ABS, 2000b). At the 1996 census, about 71% of the population of Canberra was aged 18 years and over and the average household size was 2.7. Therefore, in the model city population of 300,000, there would be 300,000 x 0.24 x 0.71 = approximately 51,000 active adult smokers. In a survey of 887 active smokers in Victoria in 1997, 28% reported that they always smoked outside (Trotter & Mullins, 1998). Therefore, 51,000 x (1 – 0.28) = about 37,000 smokers would smoke indoors and thus potentially expose other people to their sidestream smoke. Given the average household size of 2.7, each indoor smoker is likely to expose about 1.7 other people

to his or her sidestream smoke, corresponding to 1.7 x 37,000 = approximately 63,000 ETS-exposed people. As such, the population of the model urban environment is composed of 186,000 non-ETS exposed inhabitants, 63,000 ETS-exposed inhabitants and 51,000 active smokers, which gives a fraction of 62, 21 and 17% respectively. Based on the average 24 h lifetime exposure levels mentioned above, this results in an average exposure level for the population as a whole of 0.62 x 5.2 + 0.21 x 6.1 + 0.17 x 15.2 = 7.1 ppb. Of this, 54% can be attributed to ETS-free indoor air, 22% to active smoking, 11% to road use, 8% to other outdoor activities and 5% to passive smoking.

The above exposure estimate is crude, but may nevertheless give guidance to the relative importance of the various sources that contribute to public exposure to benzene.

17. Occupational Exposure

Workers in the petroleum, steel, chemical and associated industries may be exposed to benzene during bulk manufacture, use, storage or distribution of the chemical or products that contain the chemical, such as crude oil, petrol, BTX and coal tar (see Section 7). Exposure may also occur in laboratories where benzene is used for research or analysis. In addition, the contamination of workplace environments with petrol vapours, engine exhaust or tobacco smoke may result in benzene exposures that exceed the population average, for example, in vehicle mechanics, professional drivers and hospitality workers.

Inhalation is the predominant route of occupational exposure to benzene, with the possible exception of workers having prolonged skin contact with petrol, such as mechanics during work on vehicle fuel systems (Laitinen et al, 1994). Incidental dermal contact may occur as a consequence of spills or leaks and the occasional use of petrol to clean tools or car parts, but would be infrequent and is unlikely to result in significant absorption because of the rapid evaporation of benzene applied to the skin (OECD, 2000). Pipetting and siphoning of benzene-containing liquids by mouth may result in ingestion of the chemical, but nowadays would be very rare.

Occupational exposure to benzene often occurs outdoors, where daily breathing zone levels may vary 10-fold depending on wind speed and other weather conditions (Kromhout et al, 1993).

17.1 Petroleum industry

The petroleum industry comprises an upstream segment involved in getting oil and gas out of the ground and a downstream segment involved in the refining, distribution and marketing of petroleum products.

Information on the number of petroleum industry workers in jobs with the potential for exposure to benzene was not available from applicants. However, it is known that there were about 6400 upstream employees in 1999 (APPEA, 2000). Petroleum refining is estimated to employ over 3000 people (DISR, 1999). As there are more than 40 terminals (Glass et al, 1998) and 8000 petrol stations (AIP, 2000), the number of workers engaged in petrol distribution and marketing is probably in the order of 20,000-30,000.

17.1.1 Petroleum production and refining

The production of crude oil and its refining to petrol and other end products comprise a series of continuous, fully enclosed processes which take place in naturally ventilated, open-air facilities. As such, the principal sources of exposure are fugitive emissions, waste streams, transfers resulting in vapour displacement, and situations where there is a need to break open or enter the system, such as sampling, cleaning and maintenance. All other things being equal, the potential for exposure is proportional to the concentration of benzene in the process stream. This is about 0.1% in crude oil, 0.5-2% in straight run gasoline, Avgas and cracked gasoline, 1-5% in blended petrol, and 4-8% in reformate (Section 7.2.1).

Australian exposure data have been culled from the retrospective exposure assessment for benzene conducted by Health Watch in the course of the nested

case-control study reviewed in Section 11.6.2 (Glass et al, 1998, 2000). This assessment primarily used local monitoring data from the participating petroleum companies to arrive at exposure estimates for a range of job categories and tasks. The available monitoring data were checked for correctness, completeness and consistency and analysed across sites by standard statistical methods. Personal samples taken over <180 min were excluded, except in the case of fitters whose overall exposure was calculated as the mean of a reasonable cross-section of short-term tasks that a fitter may perform. Non-detectable results were assigned a value of half the detection limit. For some job categories, exposure levels were normalised to a benzene concentration of 0.1% in crude oil and 3% in petrol.

Relevant summary statistics (arithmetic mean and range) that relate to current processes and technologies are shown in Table 17.1[9].

Table 17.1: Measured personal benzene exposure levels in the Australian petroleum industry (adapted from Glass et al, 1998)

Job category or task	Sample count	Benzene exposure levels in ppm (TWA)			
		Mean	Minimum	Maximum	$UTL_{95\%,95\%}$*
Crude oil production					
Fitter	12	0.04	<0.01	0.09	1.6
Operator	43	0.05	<0.01	0.53	0.6
Refining					
Catalytic cracking operator	295	0.16	0.02	5.52	0.5
Crude distillation operator	404	0.11	0.00	4.63	0.5
Crude storage tank cleaning†§	13	8.01	0.14	28.21	350
Fitters	369	0.62	0.01	39.00	4.8
Gas testing of storage tanks†§	12	9.08	0.09	58.21	620
Instrument fitter	42	0.48	0.01	10.60	1.7
Laboratory worker	65	0.15	0.01	1.13	1.3
Petrol blending	11	0.42	0.11	2.19	4.0
Plant-wide operator	25	0.08	0.01	0.31	0.7
Reformer operator	263	0.69	0.01	54.05	2.6
Separator cleaning	14	0.12	0.05	0.33	0.5
Slop tank cleaning*†	46	75.15	0.05	1043.89	2000
Sour water treatment	28	0.06	0.05	0.22	0.2
Tank farm workers	104	0.12	0.01	2.30	0.9
Distribution					
Drum filling§	24	1.55	<0.01	6.15	38
Fitter	13	0.67	0.02	5.80	23
Road tanker bottom loading§	31	0.55	<0.01	7.85	8.7

* Calculated for a lognormal distribution from the mean and standard deviation of the logtransformed data included in the Health Watch report.
† Respiratory protective equipment would have been worn.
§ Normalised to a concentration of 0.1% benzene in crude oil and 3% in petrol.

Table 17.1 above and some of the tables below also give the upper tolerance limit of the distribution's 95th percentile ($UTL_{95\%,95\%}$), which is a measure of the true maximum exposure level in the population the samples were drawn from. It is 95%

[9] Glass et al. (1998) tested their data for normality and, as expected, found that they generally showed a lognormal distribution; however, the arithmetic mean is considered the best measure of average long-term exposure.

certain that 95% of all members of a given exposure group are not exposed to levels that exceed the $UTL_{95\%,95\%}$.

Additional Australian monitoring data are included in a report on crude oil published by the European petroleum industry association, CONCAWE (1998a). These data, which are reproduced in Table 17.2, were taken from a petroleum company database covering the 1991-96 period. Some of them may have been included in the Health Watch statistics presented in Table 17.1.

Table 17.2: Personal monitoring at an Australian crude oil production unit (CONCAWE, 1998a)

		Measured exposure levels (ppm)			
Job category or task	Sample count	Duration (min)	Mean	Minimum	Maximum
Full-shift exposure					
Crude tanker loading	1	720	<0.01	-	-
Maintenance worker	7	600	0.03	<0.01	0.09
Platform operator	6	720	0.02	<0.01	0.06
Shutdown technician	4	720	<0.01	-	-
Stabilisation plant operator	25	720	0.03	<0.01	0.19
Storage tank cleaner	21	480	0.09	<0.01	0.34
Storage tank maintenance worker	3	480	0.01	<0.01	0.09
Short-term exposure					
Ballast tank cleaning, inside*	18	50-263	4.90	<0.03	34.10
Ballast tank cleaning, outside*	7	67-310	2.82	0.01	5.89
Crude tank cleaning*	7	158-378	0.31	<0.01	0.93
Inlet separator cleaning	2	104	<0.02	-	-
Manhole opening	2	21	0.62	0.12	1.12
Pipeline monitoring	8	50-200	0.34	<0.01	1.9
Plant equipment steaming	2	48-88	<0.01	-	-

* Respiratory protective equipment was worn.

The available Australian exposure data are in agreement with a number of Canadian, European or US surveys which generally report long-term exposure levels <0.1 ppm in crude oil production personnel and <1 ppm in petroleum refinery workers (CONCAWE, 1997, 1998a; Verma et al, 2000).

17.1.2 Petrol distribution and marketing

The delivery of petrol involves a series of transfers between stationary and mobile tanks, interrupted by storage periods that vary from hours to months. The main sources of release are tank breathing, vapour displacement during tank loading operations, and evaporation of minor spills. There is also the potential for exposure from vapour-filled pipework and tanks that are broken open or entered into during cleaning or maintenance operations.

The Health Watch exposure assessment described above provides some data on the exposure of workers at distribution terminals (Table 17.1). There are no Australian monitoring data for road tanker drivers and shipping tanker crew.

Overseas documentation on the exposure of workers involved in the distribution of petroleum products is limited. In Europe, exposure levels in drum fillers averaged 8.4 ppm (TWA_8) in a 1987 industry survey (CONCAWE, 1997). A US study from the 1970s found exposure levels <0.5 ppm in 126/128 pipeline maintenance workers, with levels ≤1.5 ppm in the remaining two (Domask, 1978, as cited in Weaver et al, 1983). In drivers of bottom-loaded road tankers, average short-term exposure levels during unloading ranged from 0.43-1.56 ppm benzene, with average full-shift exposure levels from 0.04-0.37 ppm (CONCAWE, 1997; Kawai et al, 1991; Weaver et al, 1983). Studies conducted in Europe in the 1980s and early 1990s found average TWA_8 levels ranging from 0.07-2.0 ppm in jetty workers and ship or barge crew involved in closed or open petrol loading operations (CONCAWE, 1997).

Data on Australian petrol station workers have been published by AIP (1996). Limited measurements in 1982 showed benzene exposure levels <1 ppm (TWA_8). This was followed up in 1993 with a study of 10 high volume petrol stations in Adelaide, Brisbane, Melbourne, Perth and Sydney, half of them self-service. Personnel monitored included attendants working in the pump area as well as managers, office and workshop staff. Area samplers were placed adjacent to the pumps. Non-detectable results were assigned a value of 0.707 times the detection limit. The results shown in Table 17.3 include the minimum variance unbiased estimate of the arithmetic mean (estimated arithmetic mean) and $UTL_{95\%,95\%}$ calculated from individual measurements by means of a commercially available spreadsheet (Mulhausen & Damiano, 1998).[10]

Table 17.3: Personal and area monitoring at 10 Australian petrol stations (benzene levels in ppm (TWA_8))

	Sample count	Estimated arithmetic mean	Range	$UTL_{95\%,95\%}$
Full-service stations				
• Attendants	25	0.21	0.03-0.61	0.86
• Other staff	18	0.09	0.02-0.62	0.59
• Area	40	0.15	0.02-0.60	0.69
Self-service stations				
• Attendants	9	0.08	0.05-0.12	0.22
• Other staff	9	0.05	0.03-0.09	0.15
• Area	43	0.06	0.03-0.13	0.14

The exposure levels of attendants and the area levels were significantly higher at full service than at self-service stations ($p < 0.05$). The difference in area levels may be due to attendants having a higher spill rate than motorists (AIP, 1996).

Overseas studies of exposure levels in petrol station attendants have been summarised by CONCAWE (1997) and Lagorio et al. (1993, 1997). The exposure levels shown in Table 17.3 are comparable to those in USA (0.03-0.31 ppm) and Europe (0.04-0.80) and lower than in India (1.16-1.44 ppm).

[10] The minimum variance unbiased estimate is the preferred point estimate of the arithmetic mean of a lognormal distribution (Mulhausen & Damiano, 1998).

17.1.3 Petroleum and petrol cleaning operations

Emergency crew and contractors may be exposed to evaporative emissions from petroleum or petrol spills, or from residues in leaking fuel storage tanks. In workers cleaning a beach after a major crude oil spill, full-shift personal exposure levels were <0.1 ppm benzene in 343/350 samples, with levels ranging from 0.16-0.81 ppm in the remaining seven (NIOSH, 1991, as cited in CONCAWE, 1998a). In contractors engaged to remove or repair leaking underground petrol tanks, benzene exposure levels ranged up to 18.8 ppm during short-term tasks, but remained ≤1 ppm for the shift as a whole (Kramer, 1989; Shamsky & Samimi, 1987).

17.1.4 Conclusions

In conclusion, mean TWA_8 exposure levels in the Australian petroleum industry are expected to be <0.1 ppm in crude oil production workers and <0.7 ppm in refinery and downstream distribution workers. A mean exposure of 1.55 ppm has been recorded for petrol drumming, but this activity is rarely undertaken and is not expected to result in long-term exposures ≥0.7 ppm. Higher individual full shift exposure levels have been measured in reformer operators (up to 54 ppm) and in distribution terminal workers (up to 7.9 ppm), but are not expected to be of regular or frequent occurrence. Although high to very high breathing zone levels have been measured during tank cleaning operations, actual exposures are likely to be much lower because of the routine deployment of respiratory protective equipment in confined spaces.

17.2 Steel and coal tar distillation industries

Workers in the steel industry may be exposed to benzene contained in coke oven gas and its by-products, BTX and coal tar (Section 7.2.2).

Monitoring data were obtained from the steelworks at Port Kembla, New South Wales, and Whyalla, South Australia, which recover BTX and coal tar from the gas. Data were not available for coke works that burn the oven gas as is, or from Koppers Coal Tar Products, who process coal tar to various end products.

17.2.1 Coke ovens

Coke oven workers are exposed to gas emissions through oven door leaks and when the doors are opened to remove coke and recharge the ovens. Information was not available on the number of workers employed at Australian coke ovens. Personal monitoring data collected in 1995-97 were provided for a number of cab drivers (30), oventop hands (6) and door adjusters (2) at Whyalla steelworks. The results are shown in Table 17.4.

In the 1980s, the average exposure level was 0.3 ppm (TWA_8) in British coke oven workers, with individual exposures at 27 coke works ranging from <0.2-8 ppm (Hurley et al, 1991). In a more recent study in Polish workers, the average level was 0.14 ppm (TWA_8), with a range from 0.02-0.42 ppm (Bienik, 1998). These findings are in overall agreement with the levels at Whyalla.

Table 17.4: Personal monitoring of coke oven and by-product workers at the Whyalla and Port Kembla steelworks (benzene levels in ppm (TWA))

Site and job category	Sample count	Duration (min)	Estimated arithmetic mean*	Range	$UTL_{95\%,95\%}$*
Whyalla					
Coke ovens	38	365-445	0.12	<0.01-1.04	0.74
By-product plant	27	350-420	0.72	<0.01-11.10	8.20
Port Kembla					
BTX (gas) operator	30	405-485	0.12	<0.01-0.26	0.25
BTX (liquid) operator	30	295-485	0.35	0.02-8.10	3.86
Tar operator	26	395-485	0.16	<0.01-1.04	1.02
Maintenance worker	53	No data	0.48	<0.01-4.50	4.57

* Calculated according to Mulhausen & Damiano (1998), with non-detectable results assigned a value of 0.7 times the detection limit.

17.2.2 Coal gas by-product plants

A coal gas by-product plant is designed to recover BTX from coal gasses and condense tar from gas wash oil and flushing liquor, as described in Section 7.2.2. BTX systems, which are fully enclosed, process streams containing up to 80% benzene. Tar systems are semi-enclosed, but handle streams with a much lower content of benzene (0.00003% in flushing liquor and <0.2% in the end product). Within the plant, the main sources of benzene exposure are fugitive emissions, evaporation from decanters and sumps, and maintenance work on vessels and pipework. At Whyalla, the final BTX product is re-injected into the gas system and burnt as fuel. At Port Kembla, it is piped to storage tanks for subsequent transport to Huntsman Chemical Company by road tanker (see below). The potential for exposure during loading is low, as the tankers are bottom-loaded and equipped with vapour return systems. The maximum number of exposed BTX and tar workers is in the order of 30-50 persons per site.

The results of personal monitoring conducted at Whyalla in 1995-97 and Port Kembla in 1997-99 are shown in Table 17.4 above.

At a US integrated steelworks, mean exposure levels in the by-product plant were estimated at 10.5 ppm over the 1957-1977 period (Hancock & Moffitt, 1984). However, the mean of 897 personal monitoring samples collected in 1978-83 by the American Iron and Steel Institute was only 1.35 ppm (TWA_8), with 25% of measurements in the 1-5 ppm range (Runion & Scott, 1985). In the 1980s, the average exposure level was 1.3 ppm (TWA_8) in British BTX workers, with individual exposures at 27 plants ranging from <0.2-12 ppm (Hurley et al, 1991). In a recent study in a Polish plant, the average level (TWA_8) was 0.63 ppm in BTX (gas) operators and 1.04 ppm in BTX (liquid) operators, with a range from 0.05-3.04 ppm (Bienik, 1998). The exposures measured in Australian workers fall within the ranges reported from Poland and UK.

17.2.3 Coal tar distillation

Crude coal tar from the steelworks at Port Kembla and Whyalla is transported to Koppers Coal Tar Products in Newcastle, where it is separated into various fractions in a series of fully enclosed, outdoor systems (see Section 7.2.2). The distillery employs 65 people, including fitters, laboratory chemists and operators. The crude tar and distillation products contain 0.11-0.16% and 0-4% benzene

respectively. The potential for exposure is limited to releases during unloading of the crude tar, fugitive emissions, and situations where there is a need to access the enclosed system, for example, to dip tanks and scrubber systems, collect and analyse samples, or carry out cleaning and maintenance.

Workers at Koppers are not routinely monitored for exposure to benzene. Overseas data on the exposure of coal tar distillation workers to benzene could not be identified. However, the coal tar and petroleum industries handle process streams with similar benzene content in similar, enclosed systems. By analogy, therefore, exposure levels among coal tar distillation workers are probably of the same order of magnitude as in petroleum refinery workers, that is, generally <0.7 ppm.

17.2.4 Conclusions

Based on the available data, mean benzene exposure levels are expected to be ≤0.7 ppm (TWA_8) in the steel and coal tar distillation industries. Higher individual full shift exposure levels have been measured in by-product plant operators (up to 11 ppm), but are not expected to be of regular or frequent occurrence. Mandatory changes have since been introduced to personal protective equipment requirements.

17.3 Chemical industry

17.3.1 Ethane and naphtha (gas oil) cracking

The Qenos petrochemical plants in Altona and Botany Bay produce a by-product known as pyrolysis gasoline which may contain from 6-36% benzene (Section 7.2.3). The pyrolysis gasoline stream is produced and contained in a fully enclosed, outdoor system. At the Altona plant, it is transferred in closed pipework to a neighbouring petroleum refinery, which stores the pyrolysis gasoline in floating-roof tanks and eventually ships it overseas. At the Botany plant, it is stored in a floating-roof tank until piped to Port Botany and shipped overseas for further processing. In consequence, the potential for exposure is limited to fugitive emissions at pumps and valves and to sampling and maintenance requiring access to the closed system. Potentially exposed workers comprise a maximum of 85 operators, supervisors and maintenance personnel per site.

According to a summary of personal monitoring data provided by Qenos, long-term full-shift exposure levels in a total of 14 job categories at the Altona and Botany pyrolysis plants did not exceed 0.10 ppm benzene in 1998-99, based on 7-11 samples per similar exposure group. This is in agreement with Tsai et al. (1983) who reported a mean exposure level of 0.11 ppm in 32 samples collected in the ethylene unit of an integrated US refinery in 1978-1983. Furthermore, at the Altona site, full-shift personal exposure levels were consistently <0.07 ppm in 32 fitters and operators involved in a turn-around operation in 1998 and <0.05 ppm in 9 maintenance contractors who were sampled in 2000. Qenos also provided personal monitoring data from a small number of contract surveyors and wharf operators involved in a shore to ship transfer at Port Botany of pyrolysis gasoline containing about 35% benzene. Full-shift exposure levels ranged from 0.1-0.4 ppm, which is comparable to the levels measured in workers engaged in ship to shore transfer of benzene feedstock (Table 17.5).

17.3.2 Bulk distribution

The predominant end user of benzene feedstock is Huntsman Chemical Company in Melbourne, with an approximate annual consumption of 20 kt BTX (see above) and 80 kt 95-99% pure benzene imported through Terminals Pty Ltd on Melbourne's waterfront (Section 7.2.3). About 0.05% of the imported quantity is diverted to the Qenos butadiene rubber plant in Altona, Victoria. There are no other users of bulk benzene in Australia.

BTX is transported from Port Kembla to Melbourne by road. The potential for exposure is low, as the product is transferred via dedicated, closed lines and transport takes place in bottom-loaded road tankers equipped with vapour return systems. Loading and unloading last 30-40 min each and the volume transported is equivalent to 2-3 trucks/day. The number of potentially exposed workers would be <10.

Benzene is delivered to Terminals by ship about 30 times a year. There is the potential for exposure from drips and spills when making and breaking the line connections for ship to shore transfer. A pump onboard the ship moves the cargo into one of six nitrogen-blanketed benzene storage tanks, which are vented to air through a carbon bed system, minimising the potential for exposure to displaced vapours. The time taken to connect, disconnect and pig the lines is <60 min. The transfer itself lasts from 12-26 h depending on the size of the cargo. The transfer requires a manning level of 4-5 operators. There is limited potential for exposure during subsequent transfer to Huntsman, as the chemical is transported in dedicated, bottom-loaded road tankers equipped with a vapour return system. Dedicated pipelines are used for loading and unloading, which last 25-30 min each.

The results of personal monitoring conducted at Terminals in 1997-1999 and at the Huntsman styrene plant in 1997 are shown in Table 17.5.

Table 17.5: Personal monitoring during road tanker loading/unloading of benzene feedstock and ship to shore transfer (benzene levels in ppm (TWA))

Process or task	Sample count	Duration (min)	Estimated arithmetic mean*	Range	$UTL_{95\%,95\%}$*
Terminals					
Road tanker loading	8	Full-shift	0.11	0.10-0.20	0.24
	6	Short-term	0.51	0.10-1.00	14.28
Ship to shore transfer	12	Full-shift	0.25	0.10-5.60	3.36
	12	Short-term	0.76	0.10-11.60	25.37
Huntsman					
Road tanker loading/ unloading	4	465-690	0.14	0.03-0.20	10.36

* Calculated according to Mulhausen & Damiano (1998).

The data indicate that short-term exposures during road tanker loading rarely exceed 1 ppm, whereas ship to shore transfer of bulk benzene may result in short-term exposures ≤12 ppm. Measured full-shift exposures are consistently <0.25 ppm in the case of road tanker loading/unloading. Wharf operators may occasionally be exposed to higher full-shift levels, but their average exposure over the year would remain <0.5 ppm as Terminals only receive about 30 benzene shipments/year. Wharf operators also wear a full face respirator mask with an organic canister while disconnecting hoses and hence personal exposure levels will be lower.

In 1978-83, the mean exposure level among 426 chemical industry workers loading unspecified road tankers with benzene was 0.42 ppm (Runion & Scott, 1985). There are no published data on the exposure of shipping tanker crew or wharf operators during the unloading of bulk benzene.

17.3.3 Butadiene rubber manufacture

The Qenos elastomer plant in Altona uses pure benzene as a component of a solvent employed in the manufacture of butadiene rubber in a fully enclosed batch process, as described in Section 7.2.3. There are approximately 20 operators, maintenance and laboratory workers in the rubber plant. These are potentially exposed to benzene released through fugitive emissions or when the system is opened for sampling or maintenance.

According to a summary of personal monitoring data provided by Qenos, long-term breathing zone levels at the elastomer plant in 1998-99 ranged from 0.01-0.51 ppm across a total of 11 job categories, based on 25-30 full-shift samples per similar exposure group. The highest breathing zone levels were observed in workers involved in the collection of samples of the rubber-solvent mixture and in the cleaning of a strainer system that separates rubber particles from the recycled solvent. However, these tasks require the use of respiratory protective equipment and actual exposures are therefore likely to be <0.5 ppm in all cases.

Most published data on benzene exposure in the rubber industry refer to outdated processes and workplace control measures. However, the Qenos findings are in reasonable agreement with a recent assessment of chemical exposures at US styrene-butadiene rubber plants which reported current benzene exposure levels in the order of 0.5-0.7 ppm (Macaluso et al, 1996).

17.3.4 Styrene and phenol manufacture

At Huntsman, the styrene and phenol plants convert large quantities of BTX and benzene to various intermediates in a series of interconnected, fully enclosed, outdoor systems. The processes are described in Section 7.2.3. The principal sources of exposure are fugitive emissions and maintenance operations such as the periodic replacement or regeneration of catalysts. There is little potential for exposure from transfers between systems, as these take place in closed pipework and all benzene holding and storage tanks are connected to an organic vapour recovery system. The potential exposure of quality assurance personnel is limited through the use of closed sampling systems and fume cupboards. There are approximately 100 workers in the styrene and phenol plants and about 30 laboratory and other service staff who may be exposed to benzene.

Full-shift personal monitoring data collected during routine operations in the styrene and phenol plants in 1994-98 and in the main quality control laboratory in 2000 are shown in Table 17.6.

Table 17.6: Personal monitoring in the Huntsman styrene and phenol plants and main quality control laboratory (benzene levels in ppm (TWA))

Site and job category	Sample count	Duration (min)	Estimated arithmetic mean*	Range	$UTL_{95\%,95\%}$*
Styrene plant					
Outside operator	28	420-685	0.16	<0.01-0.82	1.21
Plant engineer	4	340-545	0.39	0.05-1.52	-
Technical process leader	4	540-660	0.05	0.01-0.10	-
Phenol plant					
Day co-ordinator	3	330-435	0.07	<0.01-0.10	-
Outside operator	13	320-700	0.10	0.05-0.21	0.27
Main laboratory					
Technician	5	560-600	0.03	0.01-0.04	0.23

* Calculated according to Mulhausen & Damiano (1998), with non-detectable results assigned a value of 0.7 times the detection limit.

Short-term or instantaneous monitoring of workers engaged in maintenance tasks in the styrene and phenol plants in 1990-99 showed breathing zone levels from 0.2-4200 ppm benzene. The median result was 1.9 ppm in the styrene plant (83 readings) and <0.5 ppm in the phenol plant (199 readings). In a few instances, short-term breathing zone levels ranging up to 6.25 ppm have been recorded in workers collecting or disposing of quality control samples. In almost all cases, respiratory protection was worn where benzene levels in the presence of other hydrocarbons were unknown or exceeded 3 ppm and where benzene in the absence of other hydrocarbons was present in unknown concentrations or exceeded 1 ppm.

Personal monitoring (11 samples) of maintenance workers during turnaround of the phenol plant in 1994 indicated 6 to 12-hour TWA exposures of 0.02 to 0.38 ppm. Static monitoring (3.5 – 18 hour sampling) of benzene in the phenol plant conducted over three months in 1992-93 indicated that of 353 results, 161 were < 0.5 ppm, 104 were 0.5 – 1.0 ppm, 88 were > 1.0 ppm. The geometric mean was 0.73 ppm. Of the 88 results > 1.0 ppm, 25 were due to abnormal plant conditions which the plant personnel were aware of at the time. The company stated it has made some improvements in preventative maintenance and operating procedures since 1993.

There is limited documentation on the exposure of styrene and phenol workers to benzene. Based on 620 samples collected in 1990-94, average full-shift benzene exposure levels at three German styrene/phenol plants varied from 0.10-0.60 ppm, depending on job category (OECD, 2000). These findings are in reasonable agreement with those reported by Huntsman.

17.3.5 Conclusions

Based on the above, mean benzene exposure levels are expected to be <0.5 ppm (TWA_8) in the chemical industry. Higher individual full shift exposure levels have been measured in workers involved in ship to shore transfer of benzene feedstock (up to 5.6 ppm) and in chemical plant engineers (up to 1.5 ppm), but are not expected to be of regular or frequent occurrence. Although breathing zone levels up to 4200 ppm benzene have been recorded during short-term maintenance tasks, actual exposures would have been much lower because of the routine deployment of respiratory protective equipment in such situations.

17.4 Laboratory use for research or analysis

In telephone interviews conducted for this assessment with 55 laboratories identified as having purchased reagent grade benzene within recent years, 38 stated that they currently use benzene for research or analysis, 5 stated they no longer use the chemical, while a further 7 claimed not to be using it and 5 laboratories could not be contacted. The survey identified up to 620 potentially exposed laboratory staff with a median value of 4 (range: 1-116) staff per laboratory. These numbers do not include undergraduate students in university teaching laboratories but do include post-graduate students. The typical amounts used at any one time were as follows:

Volume (mL)	Percentage of laboratories
≤5	29
6-100	42
101-1000	24
>1000	5

Although the potential for exposure is expected to vary considerably depending on circumstances such as the quantity of benzene used, the opportunity for evaporation, the size of the laboratory and the air shift rate, the survey revealed that, in general, benzene is currently used in a manner likely to minimise the risk of exposure. This is achieved by confining the use of benzene to fume cupboards (95% of laboratories), providing other exhaust ventilation (29% of laboratories), the limited amount and duration of use, and appropriate procedures for the disposal of contaminated materials. However, some laboratories reported procedures that may increase the risk of exposure. These include the practice of decanting benzene from large bottles into measuring cylinders or beakers where splashing or spills are likely to occur; the disposal of contaminated pipette tips into open general purpose waste bins; and the storage of small quantities of benzene on work benches or shelves in containers that are permeable to benzene.

As relevant monitoring data were not identified, the Estimation and Assessment of Substance Exposure (EASE, 1997) model (version 2.0) was used to predict exposure levels. Based on the survey information, pure benzene was assumed to be handled directly in a non-dispersive manner, at room temperature and in the presence of local exhaust ventilation. According to this inherently conservative model, exposure levels of 10-20 ppm may be expected. As benzene typically is used for <1h/week, the corresponding long-term average would be 0.25-0.50 ppm. This is higher than the mean exposure levels measured in industrial laboratory workers, which range from 0.03 ppm in the chemical industry (Table 17.6) to 0.15 ppm in petroleum refineries (Table 17.1).

17.5 Contaminated workplace environments

17.5.1 Petrol vapours and vehicle exhaust

Occupational exposure to petrol vapours and vehicle exhaust fumes may occur in vehicle mechanics, professional users of petrol-fuelled implements such as gardeners and loggers, and people who work on or in the immediate vicinity of busy roads, such as professional drivers, road labourers, staff at fast food drive-in outlets, toll collectors and traffic wardens. Detailed information on the number of workers in such jobs was not collected. However, there were in the order of

150,000 vehicle tradespersons, 60,000 amenity horticultural tradespersons, 10,000 forestry and logging and 200,000 road transport workers in the Australian labour force in 1996 (ABS, 1996).

Australian monitoring data were not available for any of the above occupations. However, the Australian and New Zealand studies reviewed in Section 15.3.3 indicate that professional city drivers would be exposed to full-shift breathing zone levels of approximately 7.5 ppb in non-petrol fuelled vehicles such as buses, taxis and trucks, 15 ppb in post-1986 and 48 ppb in pre-1986 petrol-fuelled cars and vans. Furthermore, the exposure of roadside workers is likely to be similar to that of pedestrians and cyclists, that is, approximately 7 ppb (TWA_8) in the model Australian urban environment described in Section 15.2.

Overseas monitoring data are available for bus drivers, loggers, traffic wardens and vehicle mechanics, as shown in Table 17.7.

Table 17.7: Personal monitoring of bus drivers, loggers, traffic wardens and vehicle mechanics (full-shift benzene levels in ppm (TWA))

Occupation	No. of workers	Arithmetic mean	Range	Reference
Bus drivers	59	0.03	0.01-0.05	Rossi et al. (1999)
Loggers*	22	0.15	0.02-0.74	Nilsson et al. (1987)
Traffic wardens	20	0.02	<0.01-0.03	Fustinoni et al. (1995)
Vehicle mechanics	54	0.17	0.01-1.70	Foo (1991)
	65	0.15	<0.01-2.89	Javelaud et al. (1998)
	70†	0.14	0.01-1.77	Muzyka et al. (1998)

* Loggers using two-stroke chainsaws in sparse to thick pine forest stands at an ambient temperature of –16 to 8°C and wind speeds of 0-4 m/s.
† Workers in a garage servicing buses running on a particular diesel blend containing 2.1% benzene.

With regard to bus drivers and traffic wardens, the exposure levels shown in Table 17.7 are 3-4 times higher than those estimated above. However, they were recorded in Bologna and Milan in Italy, where traffic congestion in narrow streets is likely to result in in-vehicle and roadside benzene air concentrations that are substantially higher than in urban environments in Australia.

With regard to vehicle mechanics, the findings summarised in Table 17.7 are consistent with an average exposure level <0.2 ppm (TWA_8). This is in accordance with the personal exposure levels measured in car repair shops in Germany in 1996-97 (OECD, 2000). Tasks that require the fuel system to be broken open may result in short-term breathing zone levels ≤15 ppm benzene and may also entail a component of dermal exposure (Laitinen et al, 1994; Nordlinder & Ramnäs, 1987).

Although the concentration of benzene in jet fuel is very low, static air monitoring has shown benzene levels ≤1.3 ppm in a freshly drained commercial aircraft tank and ≤15 ppm in military aircraft tanks equipped with explosion suppression foams (Carlton & Smith, 2000; Yeung et al, 1997). However, entry into such tanks would be subject to confined space regulations and entrants would wear suitable respiratory protective equipment.

17.5.2 Environmental tobacco smoke

Occupational exposure to benzene contained in ETS may occur in waiters and other staff in restaurants and bars. Detailed information on the number of workers in such

jobs was not collected, however, there are about 150,000 employees in the Australian clubs and pubs, taverns and bars industries (ABS, 2000b).

Monitoring data for these occupations could not be identified. However, based on the indoor air levels in restaurants and bars with smoking occupancy assessed in Section 15.3.2, personal exposure levels are estimated at 8-21 ppb benzene (TWA_8).

17.5.3 Conclusions

Based on overseas studies, benzene exposure in professional users of petrol-fuelled implements and vehicle mechanics is estimated at <0.2 ppm (TWA_8). Occupational exposure to benzene in air contaminated with vehicle exhaust or ETS is estimated at 7.5-48 ppb (TWA_8) in professional city drivers, 7 ppb (TWA_8) in roadside workers and 8-21 ppb (TWA_8) in hospitality staff.

17.6 Aluminium industry

There are no published studies of benzene exposure in the aluminium industry and epidemiological studies do not indicate an excess incidence of benzene-related diseases. However, data reported to NPI show that one aluminium refinery is emitting benzene to the atmosphere in a quantity corresponding to 0.001% of alumina production (Section 15.1.3). Moreover, it has been hypothesised that benzene could form from coal tar pitch used at smelter facilities in the preparation of carbon anodes and smelting pot bases. In consequence, the industry was asked to provide any data in its possession that could clarify the potential for occupational exposure to benzene at aluminium refineries and smelters.

There is no routine personal or area monitoring for benzene in the aluminium industry. Some refineries reported that benzene had been determined at normal background levels in the course of broader studies of the release of volatile organic chemicals. Three smelter operations reported *ad hoc* monitoring projects in the anode manufacturing and baking departments and/or during the relining of smelting pot bases. In one case, benzene was not detected. The results obtained in the other two cases are shown in Table 17.8.

Table 17.8: Personal monitoring during anode manufacturing and pot construction at two Australian aluminium smelter facilities (benzene levels in ppm (TWA))

Process or task	Sample count	Duration (min)	Estimated arithmetic mean*	Range	$UTL_{95\%,95\%}$*
Smelter A					
Anode baking	11	300-585	0.94×10^{-3}	0.16×10^{-3} - 9.39×10^{-3}	14.53×10^{-3}
Anode manufacturing	12	360-645	0.75×10^{-3}	0.01×10^{-3} - 2.70×10^{-3}	18.26×10^{-3}
Smelter B					
Potlining cathode rodding	21	240-360	0.06	0.31×10^{-3} - 0.43	1.06
Potlining slotting/ sidewalling	10	330-415	4.03×10^{-3}	$<0.01 \times 10^{-3}$ - 8.99×10^{-3}	0.32

* Calculated according to Mulhausen & Damiano (1998).

Although liquor burning at aluminium refineries may result in the release of benzene, there is no evidence that this results in any measurable occupational exposure to the chemical.

Monitoring data collected at two aluminium smelters show that the preparation of anodes and smelting pots produce levels consistently <0.01 ppm benzene. At one smelter, cathode rodding was associated with exposures that averaged 0.06 ppm but ranged up to 0.43 ppm. However, a subsequent biological monitoring study found no increase in benzene breath levels in workers exposed to potlining fumes (Brown, 1996). Overall, these findings indicate that coal tar pitch is unlikely to be a significant source of occupational exposure to benzene.

17.7 Summary

The estimated average benzene exposure levels across various Australian industries and industry sectors discussed above can be summed up as follows:

- Long-term occupational exposures are estimated to range from 7-48 ppb benzene in people who work in roadside, indoor or in-vehicle environments contaminated with vehicle exhaust fumes or tobacco smoke;
- Workers in the upstream petroleum industry are generally exposed to benzene levels <0.1 ppm (TWA_8);
- Vehicle mechanics and professional users of petrol-fuelled implements are estimated to be exposed to benzene levels <0.2 ppm (TWA_8);
- Workers in the chemical industry are generally exposed to benzene levels <0.5 ppm (TWA_8) with some maintenance workers in phenol manufacture potentially exposed to levels of < 0.7 ppm (TWA_8), as indicated by static monitoring;
- Laboratory workers using benzene for research or analysis are estimated to be exposed to benzene levels from 0.25-0.50 ppm (TWA_8);
- Workers in the downstream petroleum industry are generally exposed to benzene levels <0.7 ppm (TWA_8);
- Workers in the coal tar distillation industry are estimated to be exposed to benzene levels <0.7 ppm (TWA_8);
- In the steel industry, coke oven and coal gas by-product workers are generally exposed to benzene levels ≤0.7 ppm (TWA_8);
- Occasional short-term exposures to benzene levels ranging from 10-20 ppm may occur in wharf operators involved in ship to shore transfer of benzene feedstock, in laboratory workers using pure benzene for research or analysis, and in vehicle mechanics with tasks that require fuel systems to be broken open; and
- Higher breathing zone levels may occur during maintenance tasks, particularly in confined spaces, but are generally short-term and limited to work situations that require the use of respiratory protective equipment.

18. Risk Characterisation

This section integrates the information on the biological effects of benzene presented in Sections 8-13 with the environmental, public and occupational exposure estimates developed in Sections 15-17, in an overall estimation of the incidence and severity of the adverse effects the chemical may cause on the environment and people of Australia. This process provides the basis for identifying areas of concern and evaluating risk management strategies, including the setting of ambient air quality and occupational exposure standards.

There is very little documentation on adverse human health effects in people exposed to benzene at non-occupational levels. Therefore, the risks to human health are first assessed with regard to occupational exposures and then extrapolated to the general public.

18.1 Environmental risks

Benzene is a volatile and water-soluble chemical. Its major release in Australia is expected to be to the atmosphere, predominantly through fumes released during petrol combustion in motor vehicles. Direct release to the aquatic compartment is expected to be minor by comparison and removal through degradation and volatilisation from sewage treatment plants is likely to greatly reduce the amounts of benzene reaching receiving waters. Monitoring data from around the world confirm the widespread transport of this chemical with substantial detections obtained in air and surface waters overseas. No surface water monitoring data is available in Australia , while international results show that where benzene was detected in surface waters, it was generally less than 10 μg/L.

18.1.1 Atmospheric risk

Limited experimental data on environmental organisms exposed through the gas phase are available. Exposure to benzene in the vapour phase exhibited toxic action on the grain weevil, but the concentration of benzene was not reported. At concentrations >50 mg/m^3 (>15.5 ppm), lethal effects may be expected in plants. It appears plants recover from sublethal effects, and plants are not expected to be exposed to concentrations at the level reported above, so a minimal risk to terrestrial plants is predicted when exposed through the gas phase.

Abiotic effects can also be assessed. While direct photolysis is not considered to be a significant removal process, the atmospheric half-life is relatively short (expected to be <20 days) due to reaction with photochemically produced hydroxyl radicals. The chemical contains no halogenated substituents and due to its short residence time is not expected to have a potential effect on stratospheric ozone.

Webster et al. (1998) state that transport times to the Arctic can be measured in weeks. With a half-life of up to 3 weeks for benzene, it can be expected that the chemical could undergo significant transport in the atmosphere and may migrate to the poles. No measurements appear to be available from these regions.

For chemicals to be considered persistent organic pollutants (POPs), they need to meet certain criteria with respect to persistence, bioaccumulation and the potential for long-range transport. Benzene meets the criteria for persistence in air (half-life

>2 days) and, therefore, possibly the criterion for long-range transport. Half-lives in soil and sediments need to be >6 months. There are no measurements in this area so no conclusions can be drawn, although benzene is not likely to remain associated with soil for extended periods as it is likely to be mobile (relatively low log K_{oc}), and is also expected to be removed significantly through volatilisation. Benzene fails the criteria of persistence in water for >2 months. While a small number of bioaccumulation results indicate a BCF >5000, the vast majority of results are much less than this and benzene also fails the bioaccumulation criterion of BCF>5000. Therefore, benzene cannot be considered a POP.

18.1.2 Aquatic risk

PEC/PNEC ratios for the aquatic compartment can be calculated using the worst case local scenario, in this instance, the PEC_{local} of 0.2 µg/L (see Section 15.4.1), and the derived PNEC of 17 µg/L (Section 8.3.2).

The ratio of PEC/PNEC has been calculated for local and continental compartments as follows: $PEC/PNEC_{local} = 0.01$.

In order to predict a low potential for an environmental hazard, the PEC/PNEC ratio must be <1. The PNEC has been conservatively determined by taking the lowest chronic effect from a large data source and applying a further safety factor of 10.

In determining the PEC/PNEC ratio, the PEC may be slightly underestimated as more than one major benzene emitting plant may be found in a local situation. However, surface waters in heavily industrialised areas of USA and UK show detections of benzene <10 µg/L, which would still result in a PEC/PNEC <1.

International measurements of benzene in sediments show a maximum concentration of 20.4 µg/kg (dry weight) in surface sediment. However, no benthic tests are available from which to conduct a meaningful risk assessment for sediments. It is reasonable to assume that benzene associated with the sediments is in fact adsorbed and so not bioavailable. If this were not the case, the chemical would be expected to volatilise. Based on this, the hazard to benthic organisms is anticipated to be low. However, anaerobic degradation studies indicate that benzene may be relatively resistant to biodegradation under the conditions expected in sediments.

This evidence supports a conclusion of a low expected risk to the aquatic environment. This assessment has not taken into account the environmental effects of large accidental releases of benzene.

18.1.3 Terrestrial risk

While a PEC was not determined (Section 15.4.2), measured data from contaminated sites overseas could be used as an approximation. Benzene in soil is usually the result of direct contamination through spillage or leakage, with the highest level found being 191 µg/kg in the US. Soil concentrations in the Netherlands are reported as less than those found in ground water (<0.005-0.03 µg/L).

The only soil dwelling terrestrial organism for which tests were available was the earthworm, and the only test performed in this regard was a contact test from benzene application to filter paper where an LC_{50} of 98 $\mu g/cm^2$ was determined. As such, a PNEC was not able to be determined.

However, for an industry to pollute soil surface at the reported LC_{50} concentration, it would be required to release around 100 kg of the chemical over a 1 ha area at the lethal concentration (10 kg to cover a 100 m^2 area) at any one time. The highest reported annual release to land in the NPI database is 45 kg from a petroleum bulk storage facility. While it is not known what area this applies to, it is highly unlikely that enough chemical would be released at any one time to cause an adverse impact on terrestrial organisms.

Therefore, a low risk to the terrestrial environment is expected.

18.2 Occupational health risks

Occupational exposure to benzene is predominantly by inhalation and may occur in workers in the petroleum, steel, chemical and associated industries, in laboratories where benzene is used for research or analysis, and in workplace environments contaminated with petrol vapours, engine exhaust or tobacco smoke (Section 17). Dermal absorption may be of significance for workers who have prolonged skin contact with petrol, such as mechanics during work on vehicle fuel systems.

18.2.1 Acute effects

For acute occupational effects, the risk characterisation process considers likely exposure patterns to assess whether single exposures are high enough to indicate a health concern.

Acute inhalation of benzene vapours has dose-dependent CNS depressant or anaesthetic effects, with clinical signs such as dizziness, headache and vertigo at levels of 250-3000 ppm, leading to drowsiness, tremor, delirium and loss of consciousness at 700-3000 ppm. Benzene vapours have been observed to cause skin, eye and respiratory tract irritation in workers exposed to concentrations >33 ppm. Exposure to 25 ppm benzene for 8 h is not associated with any adverse signs or symptoms.

As discussed in Section 17, occasional short-term exposures to benzene levels ranging from 10-20 ppm cannot be excluded in wharf operators involved in ship to shore transfer of benzene feedstock, laboratory workers who use pure benzene for research or analysis, or vehicle mechanics with tasks that require fuel systems to be broken open. There is also the potential for short-term air levels ranging up to several thousand ppm benzene during maintenance work in confined spaces such as tanks used for storage of benzene or benzene-containing products in the petroleum, coal gas, coal tar and chemical industries. However, these industries have procedures that prescribe the use of suitable controls (including eye, respiratory and skin protection) in all such situations. As such, Australian workers are unlikely to be effectively exposed to benzene vapours at concentrations exceeding 25 ppm.

Therefore, occupational exposure to benzene is not expected to pose any appreciable risk of acute health effects, given the control measures already in place.

18.2.2 Effects from repeated exposure

The most significant adverse effects from chronic exposure to benzene are haematotoxicity, genotoxicity and carcinogenicity. Human health hazards for

which a causative association with benzene exposure is established are bone marrow depression and leukaemia, in particular AML. There is also some evidence of an association between benzene exposure and the risk for lymphoma, particularly NHL and MM, but a dose-time-response relationship cannot be determined from the available data. In experimental animals, benzene has also been found to have reproductive effects and cause mammary gland and skin tumours at high exposure levels. However, the available epidemiological data indicate that these effects are only weakly associated with benzene exposure in humans and there is no evidence of a dose-response relationship. For these reasons, the critical health effects from repeated exposure to benzene are considered to be bone marrow depression and leukaemia. Whereas bone marrow depression is likely to have a threshold mechanism of action, leukaemia is considered a non-threshold effect.

Bone marrow depression

No data are available to determine an inhalation NOAEL based on bone marrow depression, although human studies with various limitations indicate that it is likely to be >0.5 ppm (TWA_8) in healthy workers. As discussed in Sections 11.4.4 and 13.2.3, based on current human data, 7.6 ppm (TWA_8) is considered the best estimate for a LOAEL which may be close to the point of departure for the onset of haematological effects. This LOAEL is derived from a study in 44 workers with long-term exposure to benzene where the only haematological abnormality in the lowest exposure group (n = 11; median exposure (TWA_8) = 7.6 ppm; range 1-20 ppm) was a modest decrease (16%) in ALC.

Long-term occupational exposure levels in Australia are assessed to be ≤0.7 ppm (TWA_8) (Section 17). An appropriate NOAEL is not available. However, since the observed haematological effects at the human LOAEL were minimal and unlikely to give rise to clinical signs in otherwise healthy people, the LOAEL is expected to be close to the NOAEL, justifying a risk characterisation based on the margin of exposure between the LOAEL and the estimated human exposure. This margin of exposure is >10 in all workers, which is likely to imply a low to negligible risk for bone marrow depression.

Leukaemia

Data from the most recent follow-up of the Pliofilm cohort indicate that the risk for leukaemia is significantly elevated at cumulative exposures >50 ppm-years, corresponding to a long-term occupational exposure level >1.25 ppm benzene over a working life of 40 years. This is higher than any of the assessed long-term exposure levels in Australian workers, which range from 7 ppb to 0.7 ppm. However, although exposures from 7 ppb to 0.7 ppm indicate a margin of exposure from 1.8-180, this is difficult to interpret as the human dose-response analysis derives from a single cohort with insufficient statistical power to rule out the possibility of some increase in leukaemia risk in individuals exposed to benzene levels <1.25 ppm over an entire working life.

In the absence of evidence to the contrary, genotoxic carcinogens such as benzene are assumed to have a non-threshold mechanism of action. As a ‘safe’or ‘no effect’ level therefore cannot be identified, quantitative risk estimation is often used to express the cancer risk (probability) in numerical terms. The quantitative estimate is derived from the slope of a modelled dose-response curve fitting the available data points for the carcinogenicity end point and then extrapolated downwards to (x,y) = (0,0) to predict the risk at lower exposure levels.

The available quantitative risk estimates based on the most recent follow-up of the Pliofilm cohort are summarised in Table 18.1.

Table 18.1: Estimates of human leukaemia risk from occupational exposure to a cumulative benzene dose of 45 ppm-years, based on dose-response data from the most recent follow-up of the Pliofilm cohort

Mathematical model	Exposure estimate	Additional lifetime leukaemia deaths per 1000 workers*	Reference
Linear	Crump & Allen (1984, unpublished)	5	Crump (1994)
	Paustenbach et al. (1992)	3	
Nonlinear (AUC-dependent)†	Crump & Allen (1984, unpublished)	5	Crump (1994)
	Paustenbach et al. (1992)	3	
Nonlinear (intensity-dependent)	Crump & Allen (1984, unpublished)	5	Crump (1994)
	Paustenbach et al. (1992)	0.04	
Proportional hazards regression	Crump & Allen (1984, unpublished)	0.3	Paxton et al. (1994b)
	Paustenbach et al. (1992)	0.5	
	Rinsky et al. (1981, 1987)	1	

* Rounded to one significant figure
† AUC = area under the curve = cumulative exposure

The estimated number of additional lifetime deaths from leukaemia assumes a cumulative occupational exposure of 45 ppm-years for which estimates are available from both Crump (1994) and Paxton et al. (1994b). Because 45 ppm-years is mid-range in the cumulative exposure distributions in the Pliofilm cohort for all three sets of exposure estimates, the estimations did not require extrapolation below the range of observation. Furthermore, 45 ppm-years correspond to an average exposure of 1.125 ppm, which is reasonably close to the assessed maximum average long-term exposure level in Australian workers of 0.7 ppm.

The mathematical dose-response models listed in the table are statistical in nature and make no assumptions about the mechanisms of carcinogenesis, other than the absence of a threshold level. Although 3 out of 9 risk estimates are 1-2 orders of magnitude lower than the others, the majority lie in the range from 1-5 additional deaths, irrespective of the choice of model and exposure estimate. It is therefore prudent to base the quantitative characterisation of the risk for leukaemia on an incidence of 5 additional lifetime leukaemia deaths per 1000 workers exposed to a cumulative benzene dose of 45 ppm-years.

To predict the risk at other occupational exposure levels, it can be assumed to be directly proportional to the cumulative exposure, with exposure spread evenly across the entire working life (40 years). The results of this estimation are shown below for the current national exposure standard and a range of assessed occupational exposures:

- At the current national exposure standard of 5 ppm (Section 19.2.1), the estimated additional lifetime risk for leukaemia is 22/1000 workers.
- The assessed maximum long-term benzene exposure level is 0.7 ppm in the downstream petroleum, steel and coal tar distillation industries. At an exposure level averaging 0.7 ppm over 40 years, the estimated additional lifetime risk for leukaemia is 3/1000 workers.
- The assessed maximum benzene exposure level is 0.5 ppm in the chemical industry and in laboratories using benzene for research and analysis. At an exposure level averaging 0.5 ppm over 40 years, the estimated additional lifetime risk for leukaemia is 2/1000 workers.
- The assessed maximum benzene exposure level is 0.2 ppm in vehicle mechanics and professional users of petrol-fuelled implements. At an exposure level averaging 0.2 ppm over 40 years, the estimated additional lifetime risk for leukaemia is 1/1000 workers.
- The assessed maximum benzene exposure level is 0.1 ppm in the upstream petroleum industry. At an exposure level averaging 0.1 ppm over 40 years, the estimated additional lifetime risk for leukaemia is 0.4/1000 workers.
- The assessed maximum benzene exposure level is 48 ppb in people who work in roadside, indoor or in-vehicle environments contaminated with vehicle exhaust fumes or tobacco smoke. At an exposure level averaging 48 ppb over 40 years, the estimated additional lifetime risk for leukaemia is 0.2/1000 workers.

In comparison, the lifetime risk (0-78 years, males and females combined) for leukaemia from any cause is 1 in 118, or 8.5/1000 population, based on 1996 incidence figures for Australia (AIHW, 1999).

18.2.3 Uncertainties involved

The risk characterisation for acute effects and bone marrow depression involves uncertainties due to limitations in the amount and/or quality of relevant animal and human data. In the case of bone marrow depression, further uncertainties arise from the lack of an appropriate NOAEL and the use of data from a single ethnic group. Additional uncertainties are inherent in the assessment of benzene exposure levels among Australian workers.

Large uncertainties are involved in the characterisation of the risk for benzene-induced leukaemia. These arise in part from deficiencies in the critical study itself (the Pliofilm cohort), such as its limited size and the assumptions and approximations made to assess exposure levels in the absence of personal monitoring data. They also arise from the lack of sufficient data to validate the mathematical models used to estimate the risk at different levels of cumulative exposure. Furthermore, in extrapolating the estimated risk at 45 ppm-years to a 40-year occupational exposure at average exposure levels from 48 ppb to 0.7 ppm, risk has been assumed to be directly proportional to cumulative exposure (average exposure level multiplied with the duration of exposure), although it is unknown whether a low continuous exposure over a long period of time is equivalent in terms of cancer risk to a shorter exposure to higher benzene levels. There are also uncertainties associated with the assessment of benzene exposure levels among Australian workers.

18.2.4 Areas of concern

The above risk characterisation does not give cause for concern about acute health effects from occupational exposure to benzene, given the control measures which are already in place in Australia.

With regard to chronic exposure to benzene, the risk characterisation suggests that there is little cause for concern about bone marrow depression in Australian workers. However, given the uncertainties involved in the risk characterisation and the likely intra-individual variation in susceptibility to benzene-induced haematotoxicity, it cannot be excluded that cases may occur at the exposure levels encountered in the downstream petroleum, coal gas by-product, coal tar distillation and chemical industries. However, such cases are expected to be mild and, therefore, reversible upon cessation of exposure.

With regard to leukaemia, there are reasons for concern in all workers with repeated occupational exposure to benzene, as no threshold has been established for the genotoxic and carcinogenic effects of the chemical. Based on the available quantitative risk estimates, the magnitude of the concern can be ranked approximately as follows: downstream petroleum industry, coke oven, coal gas by-product and coal tar distillation workers > workers in the chemical industry and in laboratories using benzene for research or analysis > vehicle mechanics and professional users of petrol-fuelled implements > workers in the upstream petroleum industry > workers in roadside, indoor or in-vehicle environments contaminated with vehicle exhaust fumes or tobacco smoke.

18.3 Public health risks

The public are exposed to benzene through the inhalation of indoor, in-vehicle and outdoor air contaminated with the chemical through releases that predominantly derive from vehicle exhaust, petrol evaporation and tobacco smoke. The 24-h average lifetime exposure in the Australian urban population is estimated at 5.2 ppb. It is one-fifth higher in passive smokers exposed to ETS at home, at work and in their cars (6.1 ppb) and almost three times as high (15.2 ppb) in the average smoker (Section 16). Other significant sources of benzene exposure are extended travel in automobiles and from attached garages with access directly from the garage into the house.

The critical effects for public health risk characterisation are the same as those for repeated occupational exposure, that is, bone marrow depression and leukaemia.

18.3.1 Bone marrow depression

As described in Section 18.2.2, a LOAEL of 7.6 ppm (TWA_8) for haematological effects was identified in workers. An occupational exposure level of 7.6 ppm can be considered equivalent to a 24 h, 7-day-a-week level of 7.6 x 8/24 x 5/7 = 1.8 ppm, or 1800 ppb. This is 320 - 375 times higher than the estimated average exposure in any non-ETS-exposed age group in the population in the Australian urban model used in this assessment (Table 16.2). However, the general population is expected to include subpopulations that are more susceptible to benzene-induced bone marrow depression, for example, those with specific genetic polymorphisms (Section 12.4.2) that are expressed with a greater frequency within certain ethnic groups, or lifestyle factors, such as alcohol consumption, that may act as additional risk factors. Even so, in considering the margins of exposure and the type of effects

seen at the LOAEL, the risk for bone marrow depression from environmental exposure to benzene at the assessed levels is likely to be low.

18.3.2 Leukaemia

As mentioned in Section 18.2.2, data from the most recent follow-up of the Pliofilm cohort indicate that the risk for leukaemia is significantly elevated at cumulative exposures >50 ppm-years, corresponding to a long-term occupational exposure level >1.25 ppm benzene over a working life of 40 years. In terms of cumulative dose, occupational exposure to 1.25 ppm over an entire working life is equivalent to lifelong continuous exposure to a benzene level of approximately 130 ppb[10]. This is 25 times higher than the estimated average lifetime exposure of an individual living in an urban area of an Australian city (5.2 ppb; Section 16). However, this margin of exposure is difficult to interpret as the human dose-response analysis derives from a single occupational cohort study with insufficient statistical power to rule out the possibility of some increase in leukaemia risk at cumulative exposure levels which correspond to continuous exposure levels <130 ppb over a lifetime.

The additional risk for leukaemia attributable to environmental exposure to benzene can be predicted by low-dose extrapolation of the quantitative estimates used above to characterise the excess lifetime leukaemia risk associated with occupational exposure to the chemical (Table 18.2). Crump (1994) and USEPA (1998a) both predict the number of additional leukaemia deaths at two lifetime exposure levels, namely 1 ppm and 1 ppb, however, only the latter is relevant for exposure to benzene in the general environment.

Table 18.2: Predicted human leukaemia risk from continuous lifetime exposure to 1 ppb benzene, based on the occupational risk estimates shown in Table 18.1 (from Crump (1994) and USEPA (1998a))

Mathematical model	Exposure estimate	Additional lifetime leukaemia deaths per 100,000 population*	Data source
Linear	Crump & Allen (1984, unpublished)	2	Crump (1994)
	Paustenbach et al. (1992)	2	
Nonlinear (AUC-dependent) †	Crump & Allen (1984, unpublished)	2	Crump (1994)
	Paustenbach et al. (1992)	1	
Nonlinear (intensity-dependent)	Crump & Allen (1984, unpublished)	2	Crump (1994)
	Paustenbach et al. (1992)	0.00002	
Proportional hazards regression	Crump & Allen (1984, unpublished)	0.2	Paxton et al. (1994b)
	Paustenbach et al. (1992)	0.4	
	Rinsky et al. (1981, 1987)	0.9	

† AUC = area under the curve = cumulative exposure
* Rounded to one significant figure

[10] A working life is assumed to comprise 8 h/day x 225 days/year x 40 years = 72,000 hours. A lifetime is assumed to comprise 24 h/day x 365 days/year x 78 years = 683,280 hours. Therefore, in terms of cumulative dose, an average occupational exposure of 1.25 ppm over 40 years is equivalent to a 24-h average lifetime exposure of 1.25 x (72,000/683,280) = 0.132 ppm, or approximately 130 ppb.

With the exception of one outlier which is 4-5 orders of magnitude lower than the remaining predictions, the risks shown in the table do not differ by more than one order of magnitude, irrespective of the choice of model and exposure estimate. It is therefore reasonable to base the risk characterisation on the most conservative prediction, that is, a lifetime leukaemia risk equivalent to 2 additional deaths per 100,000 population at 1 ppb.

By extrapolation, the lifetime leukaemia risk equivalent for increasing exposure levels can be calculated as follows:

1 ppb ~ 2 additional deaths/ 100,000 population

2 ppb ~ 4 additional deaths/ 100,000 population

5 ppb ~ 10 additional deaths/ 100,000 population

10 ppb ~20 additional deaths/ 100,000 population

20 ppb ~ 40 additional deaths/ 100,000 population

The estimated average lifetime exposure of an individual living in an urban area of an Australian city is 5.2 ppb. The predicted excess lifetime risk of leukaemia is therefore 1/10,000, or 1.2% of the lifetime risk of contracting leukaemia of any cause (1 in 118, or 85/10,000 population, based on 1996 incidence figures for Australia (AIHW, 1999)).

18.3.3 Uncertainties involved

Substantial uncertainties are involved in the above public health risk characterisations. These derive in part from the database limitations and lack of a validated risk estimation model. Moreover, the prediction of leukaemia risk at low environmental exposure levels by extrapolation from high occupational exposures may overestimate the risk, since the efficiency of DNA repair systems at low exposure levels may be increased. In addition, uncertainties are inherent in the assumptions and approximations made in order to estimate the likely exposure to benzene in the Australian urban population. The model assumes, for example, a relatively high population density, with associated high levels of benzene due to car use. At the same time, there is an assumption that each of the households in the model population will have a lawn which they mow on a weekly basis. The indoor levels, which contribute significantly to overall benzene exposure, are derived from the outdoor levels by the application of a standard ratio. The ratio was estimated by using ratios found in a range of overseas cities, and making conservative assumptions to extrapolate these findings to the Australian situation. This may result in an overestimation of indoor levels both from conservatively high outdoor levels, and also from a ratio which may overestimate the indoor levels.

18.3.4 Conclusions

Notwithstanding the considerable uncertainties involved in the public health risk characterisation, the findings set out above can be considered indicative of the risks to the public based on estimates of benzene levels in urban air. However, the general population will include subpopulations with a greater exposure to benzene and hence at greater risk. These subpopulations include smokers, those frequently using petrol powered devices (e.g. private motor vehicles, lawn mowers, outboard engines) and individuals who live or work in areas with a high traffic density or near to industrial sources of benzene emission. As such, adverse health effects

from benzene-induced bone marrow toxicity are not expected to constitute a significant public health risk.

With regard to leukaemia, no safe level of exposure has been established. USEPA (1989) and the Dutch Ministry of Housing, Physical Planning and the Environment (OECD, 1995) have provided guidance which effectively states that an additional lifetime cancer risk of 1/1,000,000 can be considered negligible, while an additional lifetime cancer risk of 1/10,000 is the maximum permissible risk to an individual for any single substance under consideration. At the assessed public exposure level in a model Australian urban environment, that is, at 5.2 ppb, the excess lifetime risk of benzene-induced leukaemia is estimated to be 1/10,000, or 1.2% of the lifetime risk of contracting leukaemia of any cause. This is a conservative estimate, based on the conservative nature of the quantitative risk prediction at low environmental exposure levels, and also based on the conservative exposure assessment. The risk could be estimated more accurately following collection of monitoring data which better represents the Australian benzene levels, including both indoor and outdoor levels.

18.4 Risk assessments by other national or international bodies

Government of Canada

Benzene has been assessed for environmental and public health effects (Government of Canada, 1993). It is considered to be of low risk to the environment, but is characterised as a non-threshold human carcinogen and as such meets the Canadian criteria for being considered a chemical that constitutes or may constitute a danger to human life or health. For AML, the $TD_{0.05}$ (the lower confidence limit of the benchmark dose that corresponds to a 5% increase in mortality) is calculated at 4.6 ppm, based on an early report on the Pliofilm cohort (Rinsky et al, 1987), the exposure estimates by Crump & Allen (1984, unpublished) and a linear-quadratic mathematical model. With an estimated average ambient air concentration of 1.4 ppb, the exposure level is about 3000 times lower than the $TD_{0.05}$. Under the Canadian criteria, the priority for further analysis of options to reduce exposure was therefore considered to be high.

UK Department of the Environment, Transport and the Regions

The Department's Expert Panel on Air Quality Standards took the view that although benzene is genotoxic and as such may be presumed to be a non-threshold carcinogen, the risks become smaller as the cumulative exposure of an individual is reduced and that, for all practical purposes, there is a concentration at which the risks are exceedingly small and unlikely to be detectable by any practicable method (DoE, 1994). Based on the available epidemiological studies, the Panel determined that the risk of leukaemia in workers was not detectable when average exposures over a working lifetime were around 0.5 ppm. Allowing for a 100-fold uncertainty factor to account for the difference between working lifetime and chronological life and for interindividual differences in sensitivity, the Panel concluded that an ambient air level of 5 ppb (as a running annual average) presented an exceedingly small risk to the health of the general public.

The Department subsequently commissioned the UK Medical Research Council's Institute for Environment and Health to prepare a more detailed evaluation of the possible adverse health effects resulting from exposure of the UK general population to benzene. This assessment found that the major health risk associated

with low-level benzene exposure is leukaemia, particularly ANLL, and that there is no evidence to suggest that continuous exposure to environmental levels of benzene manifests as any other adverse health effect. Based on the work by Schnatter et al. (1996b) discussed in Section 11.6.1, the lowest level of exposure at which an increased incidence of ANLL was reliably detected among occupationally exposed workers was estimated to be in the range of 10-25 ppm. The general population exposure levels were estimated to range from 1.19-12.80 ppb, or three orders of magnitude less than the occupational lowest observed effect level. As such, the assessment concluded that any risk of leukaemia to the general population is likely to be exceedingly small and probably not detectable using current methodology (IEH, 1999).

US Environmental Protection Agency

The critical public health effects considered by USEPA are haematotoxicity, immunotoxicity and leukaemia.

The risk for haemato- and immunotoxicity was assessed on the basis of an occupational study that identified a concentration of 7.6 ppm as a LOAEL for a reduction in ALC (Rothman et al, 1996a, 1996b; see Section 11.4.4). This value was multiplied by 10/20 x 5/7 to correct for differences between occupational and non-occupational respiratory volumes and a 5-day work week and divided by an uncertainty factor of 1000 to account for human variability, lack of an appropriate NOAEL, subacute exposure (<10% of a lifetime) and database deficiencies. The final result was a human chronic air concentration, considered to be safe, equal to 3 ppb (USEPA, 1998c).

The estimated additional lifetime risk for leukaemia due to continuous exposure to benzene is 26/1000 at 1 ppm (USEPA, 1985). This estimate was originally developed by Crump & Allen (1984, unpublished) as the geometric mean of a set of risk estimates determined separately for each of three occupational cohorts (the CMA, Dow Chemical and Pliofilm cohorts described in Section 11.6.1) and adjusted for the difference between working lifetime and chronological life. Since the mathematical model is linear, the predicted risk at 1 ppb is equal to the unit risk divided by 1000, that is, 26/1,000,000 population. The public health risk for leukaemia was reassessed in 1998 (USEPA, 1998a). USEPA concluded that the evidence made available since 1985 was insufficient to reject a linear dose-response curve for benzene and that more recent unit risk estimates based on a linear model ranged from 7-25/1000 and thus were close to the 1985 USEPA estimate.

However, in accordance with the proposed 1996 draft USEPA guidelines for carcinogen risk assessment, the USEPA (1998a) update includes an alternative risk characterisation based on a margin of exposure approach, in which exposure levels in the general population are compared to the lowest cumulative dose for which there is evidence of a carcinogenic effect ('the point of departure'). The point of departure is taken to be 40 ppm-years of occupational exposure, equivalent to a lifetime (76 years) environmental exposure of 120 ppb. Using the value of 4.7 ppb reported by Wallace (1996) as an example of a reasonable estimate of long-term average exposures in the general population, the margin of exposure for the general public equals 120/4.7, or about 26, which must then be interpreted in light of the uncertainty about the slope of the dose-response curve below the point of departure, the nature and magnitude of higher short-term exposures, the extent of individual

differences in sensitivity, and the modes of action of benzene and its metabolites (USEPA, 1998a).

World Health Organization (WHO) programs

Benzene risk assessments have been carried out by the International Agency for Research on Cancer (IARC), under the International Programme on Chemical Safety (IPCS), and in the course of the development of WHO drinking water and air quality guidelines.

In general, IARC does not provide risk estimates; however, an exception has been made for two chemicals classified as carcinogenic to man: benzidine and benzene (IARC, 1982b). Based on preliminary data from the Pliofilm cohort (Rinsky et al, 1981) and supported by other published evidence, IARC concluded that a working lifetime exposure to 100 ppm of benzene would be likely to result in 140-170 cases of leukaemia per 1000 exposed workers.

The IPCS (1993) assessment concluded that occupational exposure to benzene may lead to bone marrow depression and myelogenous leukaemia. With regard to the former, IPCS estimated very approximately that exposure to high benzene levels (50-100 ppm) for one year would most likely produce bone marrow toxicity in a large percentage of workers and aplastic anaemia in some cases, whereas little effect would be expected at lower doses. In contrast, exposure to low doses (1-10 ppm) for 10 years was roughly estimated to have the potential to result in a 1-5% incidence of bone marrow depression. With regard to carcinogenicity, IPCS concluded that a TWA of 1 ppm over a 40-year working period has not been statistically associated with any increase in deaths from leukaemia, although it emphasised that the epidemiological evidence was not capable of distinguishing between a small increase in mortality and a no-risk situation. IPCS also cautioned that since benzene is a human carcinogen, exposures should be limited to the lowest technically feasible level.

The drinking water quality guideline for benzene (10 μg/L) is stated to be derived from a rounded estimate of the inhalation exposure level associated with a low level excess risk of leukaemia (1/100,000), as calculated by the application of a linear extrapolation model to unspecified occupational data (WHO, 1984).

According to the most recent air quality guideline document, the predicted excess lifetime risk for leukaemia is 6/1,000,000 at a 24-h environmental exposure level of 1 $\mu g/m^3$ (19/1,000,000 at 1 ppb), based on the geometric mean of four occupational risk estimates selected from Crump (1994). This corresponds to an excess lifetime risk of 1/10,000 at a 24-h benzene exposure level of 5.3 ppb, 1/100,000 at 0.53 ppb and 1/1,000,000 at 0.053 ppb (WHO, 2000).

Organisation for Economic Cooperation and Development

An OECD Screening Information Assessment Report for benzene has been drafted, but is not available in final form at this time (OECD, 2000).

19. Risk Management

This section discusses currently employed measures to reduce the likelihood of adverse human health effects from exposure to benzene. The information reviewed was obtained from applicants, site visits and the open literature.

19.1 Environmental and public health controls

Several countries around the world have introduced regulations that aim to limit the exposure of the general public to benzene. Examples include standards for the maximum annual average concentration of benzene in ambient air in Japan (1 ppb), The Netherlands (3.1 ppb) and UK (5 ppb); maximum acceptable concentrations of benzene in drinking water ranging from 1 μg/L in the European Union to 10 μg/L in Japan and New Zealand; and limits on the concentration of benzene in petrol in Canada, Japan and New Zealand (all at a maximum of 1% v/v).

In Australia, the industrial use and discharge to the environment of benzene are controlled by State and Territory regulations pertaining to dangerous goods and protection of the environment that are enforced by means of a system of conditional permits, licenses and warrants.

Among other conditions, such permits may set limits relating to the emissions of benzene to the environment. As described in Section 7.2, systems employed to reduce industrial emissions of benzene to air include vapour return and recovery systems, carbon bed filters, fume-scrubbing systems and the burning of off-gases. Systems employed to reduce emissions to water include the treatment of effluents by steam stripping, in water/oil separators and/or in biological treatment plants.

Benzene is also one of 36 chemicals included in the National Pollutant Inventory, which was established in 1998 as a joint Commonwealth, State and Territory initiative, and must be reported if the quantity used or handled per site exceeds 10 t per annum (EA, 1999b).

Australian water quality guidelines for fresh and marine waters were established in 1992 and suggested a maximum benzene concentration of 300 μg/L. These guidelines are currently under revision, with the previous benzene limit likely to be replaced by freshwater and marine trigger levels equal to 230 μg/L and 170 μg/L respectively (ANZECC, 2000). These trigger levels are similar to the lowest NOEC of 170 μg/L for chronic exposure in aquatic organisms (Section 8.3.1). The current Australian drinking water guidelines propose a limit of 1 μg/L, based on a consideration of health effects in relation to the limit of determination, to provide guidance in the unlikely event of contamination and because benzene has been detected in drinking water overseas (NHMRC, 1996).

The Australian Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) lists benzene in Schedule 7, except for preparations containing ≤15 mL/L (1.5% v/v) or petrol containing ≤50 mL/L (5% v/v) of benzene (Australian Health Ministers' Advisory Council, 1999). Schedule 7 poisons must not be possessed, sold or supplied for domestic purposes. Furthermore, benzene is listed with a recommended condition in Part 2 of Appendix J that it is 'not to be available except to authorised or licensed persons'. The labelling requirements for benzene include the warning statement 'Vapour is harmful to health on prolonged exposure' and the

safety directions 'Avoid contact with eyes', 'Avoid contact with skin' and 'Use only in well ventilated area'. The recommended first aid instructions are: 'If poisoning occurs, contact a doctor or Poisons Information Centre'; 'If swallowed, do NOT induce vomiting; give a glass of water'; 'If skin contact occurs, remove contaminated clothing and wash skin thoroughly'; and 'Remove from contaminated area; apply artificial respiration if not breathing'. This schedule has been adopted by all jurisdictions and any use of preparations or petrol containing more than 1.5% or 5% benzene respectively requires the permission of the relevant state or territory health authority.

A voluntary Australian Standard limits the benzene content of petrol for motor vehicles to a maximum of 5% v/v (Standards Australia, 1990). In Western Australia, the *Environmental Protection (Diesel and Petrol) Regulations 1999* stipulate a maximum level of benzene in petrol of 2.0% v/v, with a further reduction to 1.0% v/v from 1 January 2001. In Queensland, the *Environmental Protection Amendment Regulation (No. 3) 2000*, which came into effect on 14 July 2000, prohibits the distribution of petrol with a benzene content exceeding 3.5% v/v (as an average over 6 months or over 6 consecutive batches). At the national level, the *Fuel Quality Standards Act 2000* enables the Commonwealth to make mandatory quality standards for fuel supplied in Australia. Among others, these will include a maximum content of benzene in petrol of 1% v/v from January 1 2006 (EA, 2000b).

The Victorian EPA has proposed setting an intervention level of 0.075 mg/m^3 (1 h average; 23.3 ppb) for benzene under their *State Environment Protection Policy (The Air Quality Management* (EPA, 2000). Intervention levels will be used to determine whether air quality within a local area or neighbourhood is acceptable. These are risk-based numbers designed for the protection of human health. The proposed intervention level for benzene is based upon the Effects Screening Level (ESL) set by the Texas Natural Resources Conservation Commission (TNRCC), which was set to protect against the carcinogenic effects of benzene.

In 1999 the Commonwealth Government established the *Living Cities* - Air Toxics Program (http://www.environment.gov.au/epg/airtoxics/). Under this program the Commonwealth is committed to supporting the development of national management strategies to address air toxics, including benzene. In February 2001, the National Environment Protection Council (NEPC) established a working group to scope an air toxics National Environment Protection Measure (NEPM). NEPMs are broad framework-setting statutory instruments outlining agreed national objectives for protecting or managing particular aspects of the environment. NEPC will consider commencing the development of an Air Toxics NEPM in June 2001. Subject to appropriate approvals from NEPC, the Air Toxics NEPM could be finalised by December 2002. The NEPM development process provides for extensive public consultation.

19.2 Occupational health and safety controls

19.2.1 Regulatory controls

Exposure standard

Table 19.1 summarises the current occupational exposure standards in Australia and several overseas countries, including 8-h TWA and short-term exposure limits

and the presence or absence of a skin notation to indicate that absorption through the skin may be a significant source of exposure.

In Australia, the current national exposure standard for benzene is 5 ppm (16 mg/m^3) expressed as an 8-h TWA airborne concentration, Carcinogen Category 1 (NOHSC, 1995a). This standard was established in 1990 and has been adopted by all States and Territories. Category 1 includes substances that are known to cause cancer in humans. There is no short-term exposure limit and no skin notation.

The current exposure standard is close to the level at which there is statistically significant evidence of haematotoxicity in humans (7.6 ppm (TWA_8)) and it is higher than the level at which there is statistically significant evidence of an increased risk for leukaemia (1.25 ppm (TWA_8)). Furthermore, benzene is a genotoxic carcinogen for which no safe level of exposure has been established.

The recommendations made by the NOHSC Exposure Standards Working Group were based on a review of the then available information about exposure levels associated with haematological, carcinogenic and genotoxic effects in animals and humans (NOHSC, 1996a). The Working Group did not agree with the exposure limit of 10 ppm recommended at the time by the American Conference of Governmental Industrial Hygienists (ACGIH), as cases of leukaemia could be identified with exposure of less than 10 ppm in some human studies. Nor did it support the US Occupational Safety and Health Administration (OSHA) limit of 1 ppm, which it considered to be based on inadequate epidemiological studies.

ACGIH first recommended an 8-h TWA threshold limit value for benzene of 35 ppm in 1948. The recommended limit was lowered to 25 ppm in 1952, 10 ppm in 1974 and 0.5 ppm in 1997. The basis for the currently recommended limit was the re-analysis of the Pliofilm cohort by Schnatter et al. (1996b) (Table 11.6 in Section 11.6.1) which was interpreted to suggest that at a TWA of 0.5 ppm, the odds of death from leukaemia due to occupational exposure to benzene would be indistinguishable from the odds of death from leukaemia for a worker who is not exposed to benzene (ACGIH, 2000).

A US federal standard of 10 ppm was established in 1970. Based on the reports by Infante et al. (1977) and Ott et al. (1978) of an excess mortality from leukaemia in rubber and chemical workers exposed to benzene, OSHA lowered the statutory limit to 1 ppm in 1978. This action was challenged by the US petroleum industry, and the US Supreme Court barred OSHA from upholding the lower limit on the grounds that it had not demonstrated that the new limit would achieve a substantial health risk reduction (Nicholson & Landrigan, 1989). OSHA subsequently developed a quantitative risk estimate for benzene-induced leukaemia and reimposed the 1 ppm limit in 1987.

Table 19.1: National occupational exposure standards for benzene (from ACGIH (2000) and EC (2000))

Country*	Exposure limit (ppm)		Skin notation‡
	8-h TWA	STEL†	
Australia	5	-	-
European Union			
• Belgium§	10	-	-
• Denmark§	5	-	+
• Finland§	5	10	+
• France§	5	-	-
• Germany§	1**	4	+
• Ireland§	5	-	-
• The Netherlands	1	-	+
• Sweden	0.5	3	+
• United Kingdom§	5	-	-
European Union as of 26/06/03	1	Optional	Optional
USA			
• ACGIH	0.5	2.5	+
• NIOSH	0.1	1	-
• OSHA	1	5	-

* ACGIH = American Conference of Governmental Industrial Hygienists (recommended limits); NIOSH = National Institute of Occupational Safety and Health (recommended limits); OSHA = Occupational Safety and Health Administration (statutory limits)
† STEL = short-term (15-min) exposure limit
‡ A skin notation indicates that absorption through the skin may be a significant source of exposure.
§ According to EC (2000), Council Directive 97/42/EC (27 June 1997, amending Directive 90/394/EEC) requires these European Union member states to implement a regulation in their national legislation which reduces the exposure limit to 1 ppm as of 26 June 2003
** In Germany, the exposure limit is 2.5 ppm for coking plants, tank farms and work on benzene- or petrol-conducting plant in the chemical and petroleum industries (OECD, 2000)

Atmospheric monitoring

The use of Category 1 carcinogens, such as benzene, should be controlled to the highest practicable standard. According to the NOHSC *Exposure Standards for Atmospheric Contaminants in the Occupational Environment* (NOHSC, 1995a), routine monitoring of the workplace is essential for indication of control performance.

Health surveillance

Following an amendment in 1995, Schedule 3 of the *NOHSC National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994b) lists benzene as a hazardous substance for which health surveillance is required where there is a significant health risk to workers from exposure to the substance. For benzene, the health surveillance must include demography, occupational and medical history and health advice, a baseline blood sample for haematological profile, and records of personal exposure (NOHSC, 1995b). A specific health surveillance guideline for benzene is available (NOHSC, 1996b).

Scheduled carcinogenic substances

The NOHSC *Model Regulations for the Control of Scheduled Substances* (NOHSC, 1995c) lists benzene as a Schedule 2 notifiable carcinogenic substance

when used as a feedstock containing more than 50% v/v of the chemical. Requirements of the regulation include:

- notification to the relevant public authority of any proposed use of benzene and the quantity to be used per annum;
- a work assessment including an assessment of potential exposure, to be carried out prior to its use;
- the keeping of records of employees likely to be exposed;
- the reporting of exposure incidents to the relevant public authority; and
- advising employees of any accidental exposure.

Employers who use any scheduled carcinogenic substance in a laboratory for research or analysis must make a separate notification to the relevant authority.

Control of major hazard facilities

Because of its Australian Dangerous Goods Class and Packaging Group status, benzene must be taken into account when determining whether a site is a major hazard facility under the NOHSC *National Standard for the Control of Major Hazard Facilities* (NOHSC, 1996c). For flammable liquids in Packaging Group II, such as benzene, the threshold quantity is 50,000 t. The purpose of this standard is to prevent, and minimise the effects of, major accidents and near misses by requiring the person in control of the facility to:

- identify and assess all hazards and implement control measures to reduce the likelihood and effects of a major accident;
- provide information to the relevant public authority and the community, including other closely located facilities, regarding the nature of hazards of a major hazard facility and emergency procedures in the event of a major accident;
- report and investigate major accidents and near misses, and take appropriate corrective action; and
- record and discuss the lessons learnt and the analysis of major accidents and near misses with employees and employee representatives.

State and Territory regulations

The States and Territories have included the NOHSC model regulations and standards referred to above in relevant workplace health and safety or dangerous goods legislation. Benzene is a flammable liquid and should be stored and handled in accordance with relevant state and territory dangerous goods legislation. In addition, some jurisdictions have regulations prescribing an upper limit on the concentration of benzene in paint, including New South Wales and the Northern Territory where the limit is 1% in all paints, and Western Australia where it is 1.5% in spray painting materials. However, benzene is no longer used in paints and painting materials.

19.2.2 Current control measures

Workplace control measures

Workplace control measures include isolation by distance or full containment in enclosed systems, engineering controls, safe work practices and personal protective equipment (PPE).

Petroleum industry

The petroleum industry has developed a guideline for the protection of employees from exposure to benzene (AIP, 1994). The guideline emphasises the importance of full containment and engineering controls such as closed sampling systems in reducing exposure to benzene, particularly in locations where streams containing >5% benzene are handled. It also recommends that areas where airborne benzene levels may exceed 1 ppm have restricted access and be clearly marked.

The recommended PPE includes suitable gloves and boots; a full apron and sleeves where contact with any liquids containing benzene is foreseeable; eye protection when handling products or streams containing >5% benzene; and suitable respiratory protection in all situations where benzene levels are expected or known to approach or exceed 1 ppm.

In the distribution sector, engineering controls include floating-roof tanks with electronic gauging systems, vapour return and recovery systems, and the use of bottom-loaded rail and road tankers fitted with dry break couplings, capacitance probes and earthing points. Workers are required to wear gloves during loading and unloading.

Steel and associated industries

At the Port Kembla steelworks, the coal gas by-product plant and BTX road tanker loading bay are fenced off and access restricted to inducted personnel and contractors. An emission control system under completion involves equipping all tank vents in the by-product plant with a sealpot arrangement to minimise releases to air from tank breathing.

At the Whyalla steelworks, personnel must wear gloves, protective clothing, waterproof boots and vapour cartridge masks to access the coke ovens and by-product plant for inspection and maintenance.

At Koppers coal tar distillery, control measures include full enclosure, fume scrubbing and written operating procedures specifying safe work practices and PPE for each task where there is the potential for exposure to hazardous chemicals.

Chemical industry

In the chemical industry, the main control measures are full containment in enclosed systems and engineering controls such as closed sampling systems. In addition, skin and eye protection is used where contact with liquids containing benzene may occur and suitable respiratory protection is worn in situations where airborne levels of benzene are likely to exceed a limit which varies from 1-3 ppm depending on company policy and the limit of detection of 'instantaneous' measuring equipment. Engineering controls applied to minimise emissions during transport and storage of BTX and feedstock benzene include the use of bottom-loaded road tankers fitted with dry break couplings, capacitance probes and

earthing points; closed dipping or electronic gauging of tanks; and vapour return and recovery systems to prevent releases to the atmosphere from vapour displacement and tank breathing.

Industrial and research laboratories

The main control measure in laboratories is the confinement of all handling procedures to a fume cupboard.

Contaminated workplace environments

Ventilation is the predominant control measure in workplaces such as garages and bars contaminated with petrol vapours, engine exhaust fumes or tobacco smoke from indoor sources. Air purification systems may be used in environments contaminated with vehicle exhaust from outdoor sources, such as vehicle cabins, tollbooths and drive-in outlets.

Emergency procedures

All applicants in the petroleum, chemical and steel and associated industries that manufacture, use or handle benzene have comprehensive written emergency response plans setting out how workers and emergency services should deal with on-site leaks, spills, releases, fires and explosions. These sites routinely handle or use a number of hazardous chemicals in large quantities and have on-site emergency squads which can be activated via alarm buttons posted throughout the site. Workers are trained to respond to emergencies by sounding the alarm, informing a manager and then promptly evacuating the incident area.

Separate exposure and first-aid procedures for emergencies involving benzene are in use in the petroleum industry (AIP, 1994). The exposure procedures include the following instructions:

- remove affected person immediately from contaminated area;
- urgently seek medical advice;
- give artificial respiration with oxygen if required;
- in the event of benzene being swallowed advise the hospital that a lavage of the stomach will be required.

Advice for doctors comprises the following:

- aspiration can take place. Aspiration after ingestion may cause chemical pneumonitis;
- acute exposure to high concentrations of benzene by inhalation may kill by depression of the CNS leading to unconsciousness and death or by fatal acardiac arrhythmia;
- keep victim under close observation and treat symptomatically as indicated by the patient's condition.

Hazard communication

Labels

Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers or employers shall ensure that all containers of hazardous

substances used at work are appropriately labelled in accordance with the NOHSC *Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994a).

In accordance with the current version of the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b), labels for containers of benzene should contain the following risk and safety phrases:

R11	**Highly flammable**	**S45**	**In case of accident or if you feel unwell, seek medical advice immediately (show the label whenever possible)**
R45(1)	**May cause cancer (Category 1)**		
R48/23/24/25	**Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed**	**S53**	**Avoid exposure – obtain special instructions before use**

However, Section 14.3 lists additional risk phrases that will apply as a result of this assessment.

Labelling with risk phrase R45(1) is required for all mixtures containing ≥0.1% benzene. Risk phrase R48/23/24/25 applies to liquid mixtures containing ≥10% and gaseous mixtures containing ≥5% benzene. Liquid mixtures containing ≥1% but <10% and gaseous mixtures containing ≥0.5% but <5% benzene must be labelled with risk phrase R48/20/21/22 ('Harmful: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed'). Liquid mixtures containing <1% and gaseous mixtures containing <0.5% benzene are not required to be labelled with risk phrase R48.

Labels for containers of reagent grade benzene for laboratory use were not available for assessment. One applicant provided a label from a cardboard box used to transport individual containers of the chemical. This label was found to meet all relevant requirements in the ADG Code (Section 19.3).

Bulk storage vessels and tanks must be labelled according to the appropriate State or Territory dangerous goods regulation, generally with an affixed hazard sign or placard similar to the one required for road tankers under the ADG Code. As a minimum, dedicated benzene lines and pipes must be labelled with the name of the chemical.

Material Safety Data Sheets

Material safety data sheets (MSDS) are the primary source of information for workers involved in the handling of chemicals. Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers of a hazardous chemical for use at work are obliged to provide a current MSDS to their customers. Employers must ensure that an MSDS is readily accessible to employees with potential for exposure to the chemical.

A total of five MSDS for BTX, feedstock and analytical grade benzene were available for assessment against the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b). No major deficiencies were identified.

A sample MSDS prepared in accordance with the findings of this assessment and the NOHSC *National Code of Practice for the Preparation of Material Safety Data*

Sheets (NOHSC, 1994b) is provided at Appendix 1. Although it refers to analytical grade benzene for laboratory use, some of the information may also be appropriate for other benzene-containing substances. The sample is for guidance purposes only, as manufacturers and importers are responsible for preparing their own MSDS and ensuring that the information is accurate and up-to-date.

Education and training

All applicants in the petroleum, chemical and steel and associated industries that manufacture, use or handle benzene have specific induction and refresher training for employees and contractors in benzene hazards and safety procedures. Workers potentially exposed to benzene are also trained in the proper use and maintenance of respiratory protective equipment.

19.3 National transport regulation (ADG Code)

Under the ADG Code, benzene (UN Number 1114) is classified in Class 3, flammable liquids, and assigned Packaging Group II (FORS, 1998).

According to the Code, road and rail tankers carrying benzene in bulk must be placarded with class 3 ('flammable liquid') and an emergency information panel containing additional information such as the proper shipping name of the chemical ('benzene'), its UN Number, Hazchem Code and the name and telephone number of the consignor of the goods. The Hazchem Code for benzene, 3WE, reflects the initial emergency response recommended in case of fire, leakage or spillage. The number '3' indicates that foam should be used for firefighting. The letter 'W' means that there is a risk of violent reaction or explosion; that emergency personnel should wear full protective clothing (breathing apparatus, protective gloves, appropriate boots and a chemical splash suit); and that any spillage should be contained so as to prevent the chemical from entering drains or water courses. The letter 'E' denotes that evacuation of people from the neighbourhood of an incident should be considered.

The ADG Code also contains provisions for the marking of packages containing benzene with its UN Number, shipping name, class label and the name and address in Australia of the consignor of the goods.

20. Discussion and Conclusions

Benzene is ubiquitous in the environment, with numerous sources of entry including bush fires, crop residue and forest management burning, petrol combustion and evaporation, wood fires, tobacco smoking and emissions and waste streams from various industries. In a modelled Australian urban environment, 85% of benzene in outdoor air is due to petrol engine exhaust fumes, with industry and petrol service station emissions accounting for 13% and solid fuel combustion for 2% of the total.

Based on 1998-99 data, industrial use of benzene in Australia is estimated at 535 kt per year. All of the benzene introduced by the petroleum industry (82% of total consumption) was retained as a component in petrol. Benzene feedstock for the synthesis of other organic chemicals accounted for 18% of total consumption and less than 1% was either burned as fuel or utilised as solvent or reagent. In consequence, future developments in petrol demand and composition will have a major impact on the introduction of benzene. Thus, the annual use of benzene as a component in petrol is predicted to increase from 434 kt in 1998 to 461 kt in 2007 if the average concentration of benzene in petrol is maintained at 2.6-3.3% v/v, whereas a nationwide standard limiting benzene content to a maximum of 1% would reduce the quantity to 176 kt in 2007.

20.1 Environmental exposure and risks

Benzene may be considered biodegradable and in environmental terms is soluble in water. Its removal from aqueous systems occurs significantly as a result of volatilisation and, at equilibrium, over 99% of the chemical would be expected to partition to the atmosphere where it will break down primarily through reaction with hydroxyl radicals. Concentrations likely to occur in aquatic systems are expected to be far lower than of concern, and this expectation is supported by reported international monitoring data. A low aquatic risk is therefore predicted.

Additionally, the short atmospheric lifetime of benzene indicates concentrations will not occur at levels harmful to the atmosphere. While widespread transport within the troposphere is possible, the chemical is not expected to reach the stratosphere and therefore would not have an influence on global warming or ozone depletion.

Due to the low expected exposure to the terrestrial compartment, a low environmental risk is predicted to terrestrial organisms.

As such, the findings in this assessment have not identified any significant risk to the environment resulting from exposure to benzene.

20.2 Health effects

Benzene is well absorbed by the inhalation and oral routes in all animal species tested. It is also absorbed through the skin, although in practice skin contact is unlikely to result in significant absorption because of the rapid evaporation of the chemical. In humans, the absorption of benzene by the inhalation route is maximal within minutes of exposure and subsequently declines to a constant level, with 20-80% of the inhaled dose being retained after short-term exposure to air levels in the

order of 1-100 ppm. In the body, benzene accumulates in lipid-rich tissues such as the brain. It also reaches the liver, where it is first metabolised by CYP2E1-mediated hydroxylation of the aromatic ring. Subsequent oxidations take place in several organs and result in a series of polyphenols and, to a lesser extent, cleavage of the ring, with a variety of metabolites occurring in the urine within 2 h of exposure. Benzene is also eliminated unchanged with exhaled air, particularly at higher exposure levels that saturate the enzymes which convert it to water-soluble metabolites.

Benzene is not highly acutely toxic to experimental animals. By repeated exposure, the main manifestations of benzene toxicity are CNS depression, immunosuppression, bone marrow depression, degenerative lesions of the gonads, and foetal growth retardation. Benzene also causes damage to genetic material (DNA, chromosomes); increases the incidence of lymphoma in mice strains where this is a common spontaneous tumour type; and induces malignant tumours in the mouth, nasal cavities, lung alveoli, Harderian, Zymbal, preputial and mammary glands, and the ovary. However, a valid animal model for benzene-induced leukaemia has not been identified.

The reported lethal dose in humans is 20,000 ppm by inhalation for 5-10 min, or 125 mg/kg by ingestion. The most significant acute effects are irritation of the skin, eyes and respiratory system at benzene vapour concentrations >33 ppm and progressive CNS depression at concentrations ≥250 ppm.

It is well documented through epidemiological studies that the critical human health effects from repeated exposure to benzene are bone marrow depression and leukaemia, specifically AML (ANLL). There are also observations showing an association between long-term benzene exposure and the risk for lymphoma (NHL, MM), although the evidence is not as conclusive as it is for leukaemia. Furthermore, structural and numerical chromosome aberrations have been detected in peripheral blood cells of workers exposed to high benzene levels.

For bone marrow depression, a NOAEL has not been determined, but occupational studies with various limitations indicate that it is likely to be >0.5 ppm. Based on current human data, 7.6 ppm (TWA_8) is considered the best estimate for a LOAEL which may be close to the threshold for blood count changes in otherwise healthy workers. No threshold has been established for the genotoxic and carcinogenic effects of benzene. However, the available epidemiological evidence shows that the risk of leukaemia increases with exposure and is significantly elevated at cumulative exposures >50 ppm-years, corresponding to >1.25 ppm (TWA_8) over a working life of 40 years.

Experimental studies indicate that the toxic effects of benzene on the bone marrow are due to several secondary metabolites that are formed locally in relatively high concentrations. These metabolites act in an additive or synergistic manner to disrupt a range of mechanisms that regulate blood stem cell division and maturation and cause other cell damage through a combination of genetic and non-genetic changes. Damaged cells are usually eliminated, but may on occasion possess activated oncogenes or have lost tumour suppressor genes, which could enable them to proliferate as clonal lines of leukaemic cells.

The kinetics and metabolism of benzene are similar in men and women. There are no data on age-related differences. However, there is likely to be substantial variations in the sensitivity of an individual to the toxic effects of the chemical as both genetic polymorphisms and lifestyle factors may modulate the expression or

activity of several enzymes involved in the biotransformation of benzene to toxic metabolites.

20.3 Public exposure and health risks

The benzene content in consumer products is nil or negligible, except for tobacco smoke and petrol. Mainstream tobacco smoke contains about 50 (range: 3-60) μg benzene per cigarette, corresponding to an intake of 0.89 mg benzene/day in the average smoker (17.8 cigarettes/day). This is equivalent to the intake from continuous inhalation of ambient air containing 12.5 ppb of the chemical. Although the general public may have skin contact with petrol and inhale petrol vapours, for example, during refuelling at self-service stations, such exposures would be infrequent and of short duration and thus have little impact on total intake. Benzene has been detected in human breast milk, however, there are no good data on secretion levels of benzene in breast milk. Benzene has not been detected in Australian drinking water and overseas studies have, in general, found benzene levels in food to be very low. As such, the predominant pathway for public exposure to benzene is the inhalation of ambient air in the microenvironments where people spend most of their time, that is, the home, the school or workplace, outdoors and in vehicles on the road.

For the purposes of this assessment, an estimated benzene level in outdoor urban air was predicted based upon releases to the atmospheric air column above a model city with a population of 300,000 and a population density approaching 2500 people/km^2 (similar to Sydney). This gave a value of 3.4 ppb, which is comparable to individual results measured in various Australian urban centres. Based on a review of the available Australian and overseas data, the concentration of benzene in indoor air in urban homes and non-residential buildings such as schools and offices was estimated at 1.4 times the outdoor air concentration, or 4.8 ppb. Average benzene exposures resulting from urban transport activities, such as the use of cars (15-48 ppb) and buses and trams (7.5 ppb), were also estimated. Contamination with ETS was estimated to augment exposures in indoor/in-vehicle microenvironments by 1.2 ppb. Overall exposure levels were then calculated by factoring in the length of time various age groups within the general population are likely to spend in the relevant microenvironments.

The results of this exercise indicate that the lifetime weighted 24-h exposure to benzene in the general urban population is 5.2 ppb in non-ETS exposed persons, 6.1 ppb in passive smokers exposed to ETS at home, at work and in their cars and 15.2 ppb in the average smoker.

Benzene emissions to the urban atmosphere will tend to reduce over time as older petrol vehicles with higher emissions are removed from the fleet (EA, 2000c). Under the *Fuel Quality Standards Act 2000*, the Commonwealth will establish national standards prescribing a range of characteristics for petrol and diesel. These will include a maximum content of benzene in petrol of 1% (v/v) from January 1 2006 and standards for other relevant quality parameters such as the content of aromatics, which are predicted to result in a further reduction in benzene emissions (EA, 2000c). As 85% of benzene in both outdoor and indoor air in the model used for this assessment is due to petrol engine exhaust fumes, renewal of the car fleet and implementation of the proposed fuel quality standards would clearly lead to a downward revision of the estimated levels of exposure among the general population.

Based upon the occupational LOAEL for bone marrow depression corrected for the difference between working hours and chronological time and on the conservative nature of the assessed exposure, adverse health effects from benzene-induced haematotoxicity are not expected to present a significant public health risk.

Based upon low-dose extrapolation of relevant quantitative risk estimates, the excess lifetime risk of benzene-induced leukaemia is 2/100,000 population per 1 ppb benzene in the air breathed. In the Australian model city mentioned above, the average exposure was estimated at 5.2 ppb corresponding to an excess lifetime risk of benzene-induced leukaemia in the order of 1/10,000, which is at the maximum permissible level for any single carcinogenic substance according to Dutch and US authorities. This estimate, however, is based on substantial uncertainties in the exposure assessment. Personal and ambient exposure monitoring of representative samples of the Australian population would enable validation of this estimate. Further indoor/outdoor air monitoring data, including in rural areas, would also be helpful in refining the assessment of benzene-associated risks to human health.

Nevertheless, as benzene is an established human carcinogen for which no safe level of exposure has been established, any increase in public exposure should be avoided and, where practicable, measures should be taken to reduce exposure. Given the extensive contribution of vehicle exhaust to ambient benzene levels, reductions in total benzene emitted by vehicles would be effective in lowering public exposure to benzene. A reduction in benzene levels in petrol from 3% to 1%, as proposed in the Fuel Quality Standards, will likely result in significantly lowering benzene exposure in the general population. Measures to reduce environmental tobacco smoke in enclosed public areas should also be continued. A range of lifestyle choices can also be made by individuals to reduce their exposure to benzene, including minimising the time spent in a vehicle in heavy traffic, avoidance of ETS and managing air flow in the home to minimise indoor benzene levels. As high indoor levels of benzene have been found in houses with direct access from attached garages, indoor levels may be reduced by ensuring that doorways are adequately sealed and fitted with automatic door closers.

In one study in the UK, mean benzene levels in fatty foods sold at petrol stations and roadside stalls were in the order of 10 to 20 ng/g. Other studies in both Germany and the UK did not detect elevated levels. The possibility of elevated benzene levels in food sold at sites with elevated ambient benzene levels should be referred to ANZFA and to State Health Departments for their consideration.

Australia, unlike a number of other countries, does not have an ambient air standard for benzene. It is important that such a standard be set, so that the results of monitoring studies can be considered and action taken where appropriate.

The development of a National Environment Protection Measure (NEPM) which sets ambient standards for air toxics is to be considered by the National Environment Protection Council (NEPC) in June 2001. Should the development of the NEPM proceed, it is expected that it will be completed in December 2002.

20.4 Occupational exposure and health risks

Inhalation of vapours is the predominant route of occupational exposure to benzene, although significant skin absorption may occur in workers having prolonged skin contact with benzene or benzene-containing liquids such as petrol.

Exposure occurs principally in the petroleum, chemical, coal gas, coal tar and associated industries which use, produce, store, distribute or otherwise handle high volume streams or products containing benzene at concentrations that range from 0.1% in crude oil to 99% in chemical feedstock. In these industries, exposure is generally controlled by full containment in enclosed systems located in naturally ventilated, outdoor facilities. As such, the main sources of exposure are fugitive emissions from pumps and seals, transfers between closed systems resulting in drips, spills and/or vapour displacement, and sampling, dipping, cleaning and maintenance operations that require open access to the closed system. Various engineering controls are also in place, as are safe work practices and the use of PPE in situations where air levels above 1-2 ppm benzene or skin contact with the chemical may occur.

The number of potentially exposed workers in these industries is not known with certainty, but is probably in the order of 25,000-35,000 in the petroleum industry and 700-800 in the chemical, coal gas and coal tar industries. It is estimated that current long-term occupational exposure levels are <0.1 ppm in the upstream petroleum industry; <0.5 ppm in the chemical industry (except < 0.7 ppm for maintenance workers in phenol plants); <0.7 ppm in the down-stream petroleum industry; and ≤0.7 ppm in coke oven, coal gas by-product and coal tar workers in the steel and associated industries. Higher individual full shift exposure levels have been measured in reformer operators (up to 54 ppm), distribution terminal workers (up to 7.9 ppm), workers involved in ship to shore transfer of benzene feedstock (up to 5.6 ppm), chemical plant engineers (up to 1.5 ppm) and coal gas by-product plant operators (up to 11 ppm), but are not expected to be of regular or frequent occurrence. The highest short-term exposure reported is 12 ppm during ship to shore transfer of benzene feedstock.

Furthermore, it is estimated that around 600 workers are potentially exposed to benzene vapour in laboratories where minor quantities of the chemical are used for research or analytical purposes. The predominant control measure in these workplaces is the confinement of all handling procedures to a fume cupboard. Based on an inherently conservative model, the average long-term occupational exposure level in these workers is predicted to range from 0.25-0.5 ppm, although short-term exposures may reach 10-20 ppm.

Finally, workplace environments may contain benzene air concentrations that exceed those of normal ambient or indoor air because of contamination with petrol vapours, engine exhaust or tobacco smoke. There are no control measures in these workplaces that specifically target benzene, however, ventilation and air purification systems in use for other reasons may also reduce the concentration of benzene in the workers' breathing zone.

Occupations potentially exposed to petrol vapours and engine exhaust include in the order of 100,000-400,000 vehicle mechanics, professional users of petrol-fuelled implements such as gardeners and loggers, and people who work in the immediate vicinity of busy roads, such as professional drivers, road labourers, staff at fast-food outlets, toll collectors and traffic wardens. Overseas data indicate that vehicle mechanics and professional users of petrol-fuelled implements have long-term occupational exposure levels <0.2 ppm benzene. Based on a modelled Australian urban environment, exposure levels are estimated at 7-48 ppb in the case of professions whose workplace environment is on or near heavily trafficked roads. In the case of vehicle mechanics, tasks that require the fuel system to be broken

open may entail short-term exposure levels ≤15 ppm benzene, in addition to skin contact with the chemical.

Occupations potentially exposed to environmental tobacco smoke include up to 150,000 workers in the clubs and pubs, taverns and bars industries, whose long-term occupational exposure levels are estimated at 8-21 ppb.

The impact of fuel quality standards on ambient benzene levels has been discussed in Section 20.3 above. A mandatory reduction of the concentration of benzene in petrol from current levels to 1% is likely to result in a substantial reduction in the average occupational exposure levels in workers exposed to petrol fumes, such as petrol distribution workers and vehicle mechanics. The reduction in exposure is likely to be approximately proportional to the reduction in benzene content, that is, 2- to 3-fold. The predicted reduction in vehicle emissions of benzene would also reduce the occupational exposure of professional drivers and similar road or roadside workers to the chemical. As non-benzene aromatics in fuel can cause around 70-80% of the exhaust benzene formed and some also forms from other hydrocarbons, it is difficult to quantify the extent of the reduction in occupational exposure.

The banning of smoking in all enclosed public areas would reduce benzene exposure in the hospitality industry to background levels.

The occupational risk characterisation does not give cause for concern about acute health effects from exposure to benzene.

With regard to chronic exposure to benzene, it cannot be excluded that cases of mild bone marrow depression may occur at the exposure levels encountered in the downstream petroleum, coal gas by-product, coal tar distillation and chemical industries. However, such cases would be picked up by the prescribed health surveillance and are expected to be reversible upon cessation of exposure.

There is concern about leukaemia in all workers with repeated occupational exposure to benzene. Although no threshold has been established for the genotoxic and carcinogenic effects of benzene, the risk for leukaemia is proportional to cumulative exposure. Therefore, exposure should be controlled to the highest practicable standard.

In workplaces where benzene or benzene-containing streams are contained in fully enclosed systems, particular attention should be paid to engineering control techniques and operating procedures aimed at reducing fugitive emissions from pumps and seals as well as drips, spills and vapour displacement during transfers between closed systems, and to improvements which eliminate the need to break open the closed system for the purposes of sampling, dipping and cleaning. In workplaces where benzene or benzene-containing products are not contained in closed systems, such as laboratories and car repair shops, particular attention should be paid to safe work practices and the availability of good local exhaust ventilation. Where skin contact with benzene or petrol may occur, workers should wear appropriate PPE, including benzene-resistant gloves.

As benzene is flammable and classified as a dangerous good, it should be stored, handled, labelled and transported in accordance with state and territory dangerous goods legislation.

The current national occupational exposure standard of 5 ppm (TWA_8) should be revised as 5 ppm is close to the human LOAEL for bone marrow toxicity (7.6 ppm)

and higher than the level at which there is statistically significant evidence of an increased risk for leukaemia (1.25 ppm). Furthermore, the exposure data collected from Australian workplaces for this assessment indicate that it is technically feasible to keep exposures below 0.5 ppm (TWA_8).

The NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) classifies benzene as flammable (R11), a carcinogen in Category 1 (R45) and toxic by prolonged exposure through inhalation, in contact with skin and if swallowed (R48/23/24/25). This classification has been adopted from the European Union where it has remained unchanged since 1967 (although currently under review). In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a), this assessment has reviewed the classification of benzene, and amended the above classification to include the following risk phrases: 'Irritating to eyes, respiratory system and skin' (R36/37/38) and 'Possible risk of irreversible effects' (R40, that is, a mutagenic substance in Category 3). Additional safety phrases are not considered warranted, given the prescribed labelling of all mixtures containing ≥0.1% benzene with S53: 'Avoid exposure – obtain special instructions before use'.

20.5 Data gaps

For the purposes of risk assessment, the most significant data gaps are as follows:

- epidemiological data permitting the establishment of an appropriate human NOAEL for bone marrow depression;
- epidemiological data on the additional risk for leukaemia at benzene exposure levels that fall within the range experienced by the general population;
- data on whether various subpopulations are more susceptible to adverse health effects of benzene exposure; and
- personal and ambient monitoring data on the benzene exposure of a representative cross-section of the Australian population.

In addition, further research is needed to determine if benzene is a germ cell mutagen and could cause reproductive effects and contribute to the risk for breast cancer in humans.

21. Recommendations

Preamble

This section provides the recommendations arising from the assessment of benzene. The critical issues, summarised below, have been taken into consideration in formulating these recommendations:

- benzene is a known human genotoxic carcinogen for which there is no known safe level of exposure;
- occupational exposure to benzene occurs during its manufacture and through the use of benzene-containing products, particularly petroleum products;
- the main sources of public exposure to benzene are the use of petrol and diesel fuelled equipment, smoking and releases from industrial processes;
- the best available LOAEL value for non-carcinogenic effects in humans is 7.6 ppm for haematotoxicity;
- a statistically significant increased risk for leukaemia has been measured at and above 1.25 ppm (TWA_8) in occupational studies;
- the estimated excess lifetime risk of benzene-induced leukaemia is 2/100,000 population per 1 ppb benzene in air;
- the current Australian exposure standard is set at 5 ppm (16 mg/m^3) TWA_8; and
- best practice must be implemented to minimise occupational and public exposure to benzene.

Recommendation 1: NOHSC occupational hazard classification

Benzene is currently listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b) with the following classification:

R11	**Highly flammable**
R45	**May cause cancer, Carcinogen Category 1**
R48/23/24/25	**Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed**

This assessment has amended the above classification to include the following:

R36/37/38	**Irritating to eyes, respiratory system and skin**
R40	**Possible risks of irreversible effects, Mutagen Category 3**

Recommended safety phrases include:

S45 In case of accident or if you feel unwell, seek medical advice immediately (show the label whenever possible).

S53 Avoid exposure – obtain special instructions before use.

It is recommended that suppliers and employers take note of this amendment and that it be taken up in the NOHSC *List of Designated Hazardous Substances* as soon as possible.

Based on the cut-off concentration levels tabulated in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b), risk phrase R36/37/38 applies to liquid mixtures containing ≥20% and gaseous mixtures containing ≥5% benzene, whereas R40 applies to all mixtures containing ≥1% benzene.

MSDS, labels and training materials should be amended accordingly and where appropriate provide relevant information about the irritant and mutagenic effects of benzene.

Recommendation 2: National occupational exposure standard

It is recommended that NOHSC lower the occupational exposure standard for benzene with urgency. Given benzene is a human carcinogen and noting that exposures below 0.5 ppm (TWA_8) for the majority of workers, NICNAS recommends that the standard be lowered to 0.5 ppm (TWA_8).

However, industry has raised concerns that lowering the standard below 1 ppm (TWA_8) is not practicable. The NOHSC exposure standard setting process requires a statutory period of public comment, where practicability data may be submitted. Therefore, it is recommended that NOHSC consult on a proposal to lower the exposure standard to 0.5 ppm (TWA_8), including seeking information on practicability. In the interim, it is recommended that companies immediately adopt 1 ppm (TWA_8) as an internal standard.

Recommendation 3: Workplace control measures

a) ***Engineering controls and safe work practices:*** It is recommended that benzene is eliminated or substituted with less hazardous chemicals in industrial processes wherever practicable. In workplaces where this is not practicable, employers should strive for further improvements in current workplace control measures and utilise best available technology to minimise worker exposure to benzene, wherever this is technically and economically feasible.

- In workplaces where benzene or benzene-containing streams are contained in fully enclosed systems, particular attention should be paid to engineering control techniques and operating procedures aimed at reducing fugitive emissions from pumps and seals as well as drips, spills and vapour displacement during transfers between closed systems;
- Improvements that eliminate the need to break open the closed system for the purposes of sampling, dipping, maintenance and cleaning;
- In workplaces where benzene or benzene-containing products are not contained in closed systems, such as laboratories and car repair shops, particular attention should be paid to safe work practices and the availability of good local exhaust ventilation;
- Where skin contact with benzene or petrol may occur, workers should wear appropriate personal protective equipment, including benzene-resistant gloves; and

- In workplace environments contaminated due to petrol vapour, vehicle exhaust or tobacco smoke, measures should be implemented to reduce exposure levels as low as possible, such as good local exhaust ventilation and air purification system.

b) ***Exposure monitoring:***

- Personal monitoring should be conducted where a workplace assessment indicates that there is a significant risk to health.
- Health surveillance should be conducted in accordance with the 1995 amendment to Schedule 3 of the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994b) listing benzene as a hazardous substance for which health surveillance is required where there is a significant health risk to workers from exposure to the chemical (NOHSC, 1995b). The health surveillance must include a baseline blood sample for haematological profile, as further detailed in the specific health surveillance guideline for benzene (NOHSC, 1996b).
- It is recommended that the State and Territory occupational health and safety authorities review the compliance of larger workplaces in the petroleum, chemical (benzene-related), coal gas by-product and coal tar industries with the requirements for personal exposure monitoring and health surveillance. State and Territory authorities should also review compliance of workplaces with respect to scheduled carcinogenic substances, major hazard facilities and dangerous good legislation.
- Given the very large number of small workplaces with the potential for occupational exposure to benzene contained in petrol, it is recommended that relevant industry organisations such as the Australian Institute of Petroleum and the Institute of Automotive Mechanical Engineers develop programs aimed at improving control measures in petrol stations and car repair shops. NICNAS will prepare a Safety Information Sheet for benzene, aimed primarily at workers, which can be distributed to workplaces. It is recommended that industry and State jurisdictions distribute this information widely.

Recommendation 4: Public health recommendations

a) Public health authorities should update their advice on how to minimise exposure to benzene. For example, indoor air levels of benzene in houses with attached garages may be reduced by ensuring that internal garage doorways are adequately sealed and fitted with automatic door closures.

b) Public health authorities should continue to seek measures to reduce environmental tobacco smoke in enclosed public areas.

c) This assessment report will be forwarded to the Australia New Zealand Food Authority and to State Health Departments for their consideration with respect to levels of benzene in foods sold in areas with high ambient benzene levels, such as roadside shops or stalls or petrol stations.

d) To more accurately estimate the risk to the public, personal and ambient air monitoring data should be collected. The data should focus on those scenarios where the greatest uncertainties exist, such as indoor air levels, urban air levels and air levels near potential industrial point sources. The Department of Environmental

Protection (Western Australia) in association with the University of Western Australia, Murdoch University, CSIRO, EPA Victoria, NSW EPA, SA EPA, Flinders University, Monash University and NSW Health is currently conducting an air monitoring study for the Living Cities – Air Toxics Program, which will provide some of these data.

e) It is recommended that an ambient air standard for benzene be set. The findings of this report will be provided to the National Environment Protection Council so that they may be taken into account when considering benzene in the context of developing a National Environment Protection Measure (NEPM) for air toxics.

f) It is recommended that government authorities improve public health cancer registers to include information on occupation and workplace factors and identification of leukaemia type.

22. Secondary Notification

Under Section 65 of the *Industrial Chemicals (notification and Assessment) Act 1989*, secondary notification of benzene may be required where an introducer of the chemical becomes aware of circumstances that may warrant a reassessment of its hazards and risks. Specific circumstances include:

- the function or use of benzene has increased, or is likely to change, significantly;
- the amount of benzene introduced into Australia has increased, or is likely to increase, significantly;
- the method of manufacture of the chemical in Australia has changed, or is likely to change, in a way that may result in an increased risk of adverse health effects or adverse environmental effects; and
- additional information has become available to the introducers as to the adverse health effects or adverse environmental effects of the chemical.

The Director (Chemicals Notification and Assessment) must be notified within 28 days of the manufacturer/importer becoming aware of any of the above or other circumstances prescribed under Section 65 of the Act.

Appendix 1

Sample Material Safety Data Sheet for Benzene

Date of issue	8 December 2000

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Benzene is classified as Hazardous according to the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)].

Company details

Company name		
Address		
	State	Postcode
Telephone number	Emergency telephone number	
Facsimile number	Telex number	

Identification

Product name	Benzene
Other names	Benzol; cyclohexatriene
Manufacturer's product code	
UN number	1144
Dangerous goods class and subsidiary risk	Class 3
Hazchem code	3WE
Poisons Schedule number	Schedule 7
Use	Laboratory reagent

Physical description and properties

Appearance
Colourless liquid

Boiling point
80.1°C

Melting point
5.5°C

Vapour pressure
12.6 kPa at 25°C

Specific gravity
0.87 at 25°C (water = 1)

Flashpoint
-11°C (closed cup)

Flammability limits
1.4-7.9%

Solubility in water
1.8 g/L at 25°C

Other properties

Odour: Sweet, aromatic
Odour threshold: 0.8-160 ppm (average: 2 ppm)
Vapour density: 2.8 (relative to air = 1)
Autoignition temperature: 560°C

Ingredients

Chemical entity	CAS Number	Proportion
Benzene	71-43-2	

Health hazard information

HEALTH EFFECTS

Acute:

Inhalation: Irritating to respiratory system (including mouth, nose and throat) at 30-60 ppm. Dizziness and headache progressing to drowsiness and unconsciousness at 250-3000 ppm. Inhalation at 20,000 ppm may be fatal within 5-10 minutes.

Skin: Liquid and vapour irritating to skin. Readily absorbed through skin.

Eye: Liquid and vapour cause eye irritation.

Swallowed: The lowest reported fatal dose is 10 mL. Smaller doses can cause dizziness and headache progressing to drowsiness and unconsciousness. Severe lung damage can occur if drawn into the lungs (aspirated) during swallowing or vomiting.

Chronic:

Skin: No evidence of sensitisation in animals or humans.

Inhalation: Prolonged or repeated exposure can cause decreased bone marrow production of blood cells, severe blood disorders and leukaemia (cancer of the white blood cells). Damage to the chromosomes of white blood cells has been observed at high concentrations.

Other information:

Benzene is secreted in breast milk.

Risk phrases:

R11 Highly flammable

R45 May cause cancer (Carcinogen Category 1

R48/23/24/25 Toxic: Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed

R36/37/38 Irritating to eyes, respiratory system and skin

R40 Possible risk of irreversible effects (Mutagen Category 3)

FIRST AID

Inhalation: Remove from exposure to fresh air immediately. If breathing with difficulty, give oxygen. If not breathing, clear airways and apply artificial respiration. Call a doctor.

Skin: Remove contaminated clothing and wash skin thoroughly. Seek medical attention if irritation develops.

Eye: Irrigate immediately with copious quantities of water for at least 15 minutes. Seek medical attention.

Swallowed: Do not give anything by mouth if victim is losing consciousness, unconscious or convulsing. Do not induce vomiting, give a glass of water. If breathing with difficulty, give oxygen. If not breathing, clear airways and apply artificial respiration. Call a doctor.

FIRST AID FACILITIES

An emergency safety shower and eye wash station should be available in the immediate work area.

ADVICE TO DOCTOR

Treatment is symptomatic and supportive. No specific antidote.

Precautions for use

EXPOSURE STANDARD

Australian Exposure Standard: 5 ppm (16 mg/m^3)TWA,
Carcinogen Category 1 (known human carcinogen).

ENGINEERING CONTROLS

Control airborne concentrations well below the exposure standard.

Use only in flameproof fume cupboard or with good local exhaust ventilation.

Cover working surfaces with an absorbent material backed by plastic and replace at regular intervals and immediately a spillage occurs.

Do not decant into plastic containers that may be permeable to benzene, or from large bottles into measuring cylinders or beakers as splashing or spills may occur.

PERSONAL PROTECTION

Wear long-sleeved protective clothing, safety glasses and benzene resistant gloves in accordance with manufacturer's recommendation. A respirator with full-face protection may be required where engineering controls are inadequate, such as in the case of spills.

FLAMMABILITY

Highly flammable. Vapour may form explosive mixtures with air.

Avoid all sources of ignition.

Vapour is heavier than air and may travel along the ground to a source of ignition and flash back.

Safe handling information

STORAGE AND TRANSPORT

Regulated dangerous goods in Class 3, Packaging Group III.

Store in screw-capped, unbreakable, chemically resistant container in locked flammable liquids/poisons cupboard in a ventilated storage room.

SPILLS AND DISPOSAL

Small spills can be cleaned up with absorbent material. Wear appropriate personal protective equipment to prevent skin and eye contamination and, if necessary, a respirator with full-face protection. Collect contaminated material in sealable containers for disposal in accordance with all Local, State and Federal regulations at an approved waste disposal facility.

Do not allow the substance to enter drains and waterways.

In the case of large spills, evacuate the area, shut off all possible sources of ignition and follow institutional emergency procedures.

Prior to disposal, keep contaminated pipette tips in ventilated fume cupboard until completely dry.

Dispose of at an approved waste disposal facility in accordance with all Local, State and Federal regulations.

FIRE/EXPLOSION HAZARD

Highly flammable. Vapour may form explosive mixtures with air.

Carbon monoxide may be released in a fire involving benzene.

Fire fighters should wear self-contained breathing apparatus and complete protective clothing. For fires, foam, carbon dioxide or dry chemical extinguishing media may be used.

Other information

ANIMAL TOXICITY DATA

Acute (inhalation) LD_{50}(4h): 13,700 ppm (rat).
Acute (oral) LD_{50}: 810-9900 mg/kg (rat).
Acute (dermal) LD_{50}: >8200 mg/kg (rabbit).

Repeated dose toxicity: Benzene has been shown to cause central nervous system depression, immunosuppression and bone marrow depression in mice and rats.

Fertility effects: High doses can have toxic effects on the testes and ovaries in mice. Data on reproductive capacity are inconclusive.

Developmental toxicity: In rats and mice exposed to 100-500 ppm during pregnancy, benzene causes foetal growth retardation. There is no evidence of birth defects.

Lactation effects: No data.

Genetic toxicity: Benzene is positive in several test systems.

Carcinogenicity: Benzene has been shown to induce malignant tumours in several organs in rats and mice.

ENVIRONMENTAL DATA

Acute (mg/L):

Selenastrum capricornutum (alga)	72-h EC_{50}	29
Daphnia magna	48-h EC_{50}	>100
Ceriodaphnia dubia (water flea)	24-h EC_{50}	18.4
Scylla serata (crab species)	96-h LC_{50}	3.7-7.7
Pimephales promelas (fathead minnow)	96-h LC_{50}	12.6-24.6
Poecilia reticulata (guppy)	96-h LC_{50}	28.6
Oncorhynchus mykiss (rainbow trout)	96-h LC_{50}	5.3-9.2
Morone saxatilis (striped bass)	96-h LC_{50}	5.8

Chronic:

The lowest recorded no observed effect concentration is 0.17 mg/L in *Cancer magister* (Dungeness crab).

FURTHER INFORMATION

National Health and Medical Research Council: Guidelines for laboratory personnel working with carcinogenic or highly toxic chemicals (Australian Government Publishing Service, 1990).

Guidelines for Health Surveillance: Benzene (NOHSC, 1996).

National Industrial Chemicals Notification and Assessment Scheme: Full Public Report – Priority Existing Chemical No. XX – Benzene (NICNAS, 2001).

Contact point

Contact name	Telephone number
Position title	
Address	
State	Postcode	Country

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