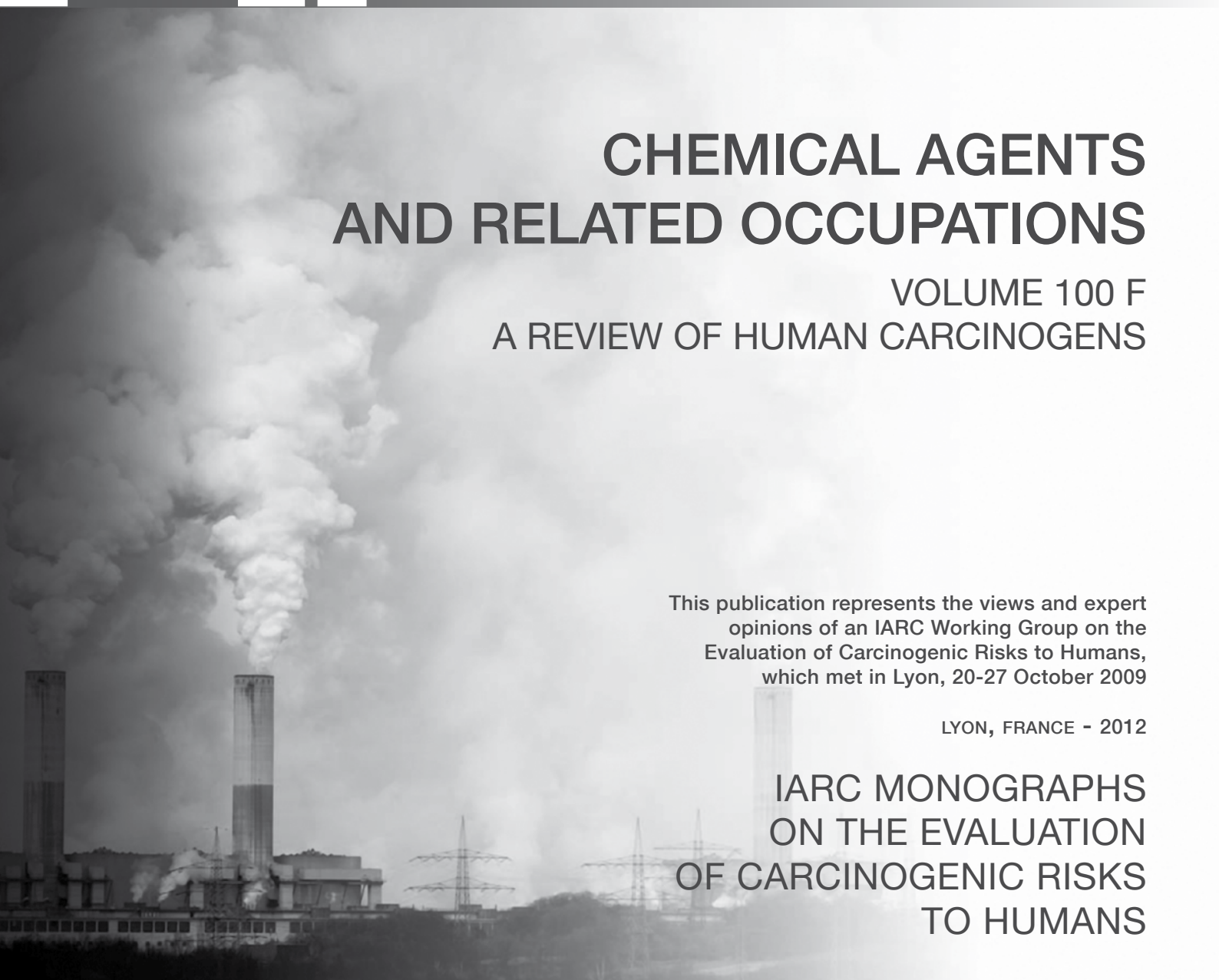
IARC MONOGRAPHS



CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 20-27 October 2009

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
World Health Organization

BENZENE

Benzene was considered by previous IARC Working Groups in 1981 and 1987 (IARC, 1982, 1987). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 71–43–2
Chem. Abstr. Serv. Name: Benzene
IUPAC Systematic Name: Benzene

C6H6
Relative molecular mass: 78.1
From O'Neil (2006) and Lide (2008), unless otherwise stated
Description: Clear, colourless, volatile, highly flammable liquid
Solubility: Slightly soluble in water; miscible with acetone, chloroform, diethyl ether and ethanol; soluble in carbon tetrachloride
Octanol/water partition coefficient: log K_{ow}, 2.13 (Hansch *et al.*, 1995)
Conversion factor: ppm = 0.313 × mg/m^3

1.2 Uses

Historically, benzene has been used as a component of inks in the printing industry, as a solvent for organic materials, as starting material and intermediate in the chemical and drug industries (e.g. to manufacture rubbers, lubricants, dyes, detergents, pesticides), and as an additive to unleaded gasoline (NTP, 2005; ATSDR, 2007; Williams *et al.*, 2008).

The primary use of benzene today is in the manufacture of organic chemicals. In Europe, benzene is mainly used to make styrene, phenol, cyclohexane, aniline, maleic anhydride, alkylbenzenes and chlorobenzenes. It is an intermediate in the production of anthraquinone, hydroquinone, benzene hexachloride, benzene sulfonic acid and other products used in drugs, dyes, insecticides and plastics (Burridge, 2007). In the United States of America, the primary use of benzene is in the production of ethylbenzene, accounting for 52% of the total benzene demand in 2008. Most ethylbenzene is consumed in the manufacture of styrene, which is used in turn in polystyrene and various styrene copolymers, latexes and resins. The second-largest use of benzene in the United States of America (accounting for 22% of demand) is in the manufacture of cumene (isopropylbenzene), nearly

Table 1.1 Estimated numbers of workers exposed to benzene in the European Union (top 10 industries)

Industry, occupational activity	
Personal and household services	942500
Wholesale and retail trade and restaurants and hotels	248300
Land transport	42800
Manufacture of plastic products	17000
Iron and steel basic industries	14900
Manufacture of other chemical products	12700
Manufacture of industrial chemicals	12500
Manufacture of machinery, except electrical	9600
Construction	8300
Education services	7400
TOTAL	1367800

all of which is consumed in phenol production. Benzene is also used to make chemical intermediates: cyclohexane, used in making certain nylon monomers (15%); nitrobenzene, an intermediate for aniline and other products (7%); alkylbenzene, used in detergents (2%); chlorobenzenes, used in engineering polymers (1%); and miscellaneous other uses (1%) (Kirschner, 2009). Benzene occurs naturally in petroleum products (e.g. crude oil and gasoline) and is also added to unleaded gasoline for its octane-enhancing and anti-knock properties. Typically, the concentration of benzene in these fuels is 1–2% by volume (ATSDR, 2007).

1.3 Human exposure

1.3.1 Occupational exposure

Occupational exposure to benzene occurs via inhalation or dermal absorption of solvents in the rubber, paint (including paint applications) and parts-manufacturing industries. It also occurs during crude-oil refining and chemical manufacturing, a large component of which entails exposure to gasoline. Workers involved in the transport of crude oil and gasoline and in the dispensing of gasoline at service stations, as well as street workers, taxi drivers and others employed at workplaces with exposure to exhaust gases from motor vehicles also experience exposure to benzene (Nordlinder & Ramnäs, 1987).

CAREX (CARcinogen EXposure) is an international information system on occupational exposure to known and suspected carcinogens, based on data collected in the European Union (EU) from 1990 to 1993. The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry (Kauppinen *et al.*, 2000). Table 1.1 presents the results for benzene in the EU by industry for the top-10 industries (CAREX, 1999). Exposure to benzene is defined as inhalation or dermal exposure at work to benzene likely to exceed significantly non-occupational exposure due to inhaling urban air or filling in gasoline stations (long-term exposure usually below 0.01 ppm)].

From the US National Occupational Exposure Survey (1981–1983), it was estimated that approximately 272300 workers (including 143000 women) were potentially exposed to benzene in the United States of America. Industries where potential exposure occurred included agricultural services, oil and gas extraction, construction (includes general building and special trades

contractors), food products, tobacco manufacturing, textile mills, lumber and wood, printing and publishing, chemical and allied products, petroleum and coal products, rubber manufacturing, leather manufacturing, transportation, and health services (NIOSH, 1990).

van Wijngaarden & Stewart (2003) conducted a critical review of the literature on occupational exposures to benzene in the 1980s in the USA and Canada. The data indicated that workers in most industries experienced exposure levels below the regulatory limit (1 ppm) of the US Occupational Safety and Health Administration (OSHA), with a weighted arithmetic mean of 0.33 ppm across all industries. It was noted that little information was available on exposure levels and their determinants for many industries with potential exposure.

Williams *et al.* (2008) summarized the values of the benzene content of selected petroleum-derived products based on published literature between 1956 and 2003. A total of 22 studies were identified, which contained 46 individual data sets and evaluated potential occupational exposure to benzene in the USA during the handling or use of these petroleum-derived products. All mean (or median) airborne concentrations were less than 1 ppm, and most were < 0.1 ppm. Table 1.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table1.2.pdf) summarizes airborne benzene concentrations from studies and governmental reports published between 1981 and 2006.

Capleton & Levy (2005) tabulated typical benzene-exposure levels in different occupational groups in various areas in Europe and North America (Table 1.3). The values are similar to those reported by van Wijngaarden & Stewart (2003) and Williams *et al.* (2008) for exposures of 1 hour or more.

Williams *et al.* (2005) reviewed available industrial-hygiene data describing exposure during the marine transport of benzene-containing products. Although there were differences in sampling strategies and in benzene content of the liquids being transported, typical benzene concentrations in air (personal time-weighted average) were in the range of 0.2–2.0 ppm during closed loading and 2–10 ppm during open loading-operations.

Liang *et al.* (2005) reviewed and tabulated benzene exposures by industry in the People's Republic of China, using data published between 1960 and 2003. The five industries with the highest reported exposures were those producing leather products, electronic devices, machinery, shoes, and office supplies and sports equipment. Median ambient concentrations in these industries were, respectively: 124.8 mg/m^3, 98.7 mg/m^3, 75.4 mg/m^3, 50.4 mg/m^3, and 50.3 mg/m^3. [The Working Group noted that all data were collected with sampling methods of very short duration (1–20-minute time-weighted averages). In addition, a considerable part of the surveys were follow-up studies of benzene poisonings. Therefore, these data cannot be considered as representative and cannot be compared with the information reported from the USA.] Levels of short-term exposure to benzene varied considerably between industries (Table 1.4) and showed generally a downward trend over time (Fig. 1.1).

Urinary *trans,trans*-muconic acid (*t,t*-MA) and *S*-phenylmercapturic acid (*S*-PMA) are sensitive markers for recent exposure to benzene at low levels (Qu *et al.*, 2005).

1.3.2 Non-occupational exposure

The major sources of benzene in the atmosphere are anthropogenic and include fixed industrial sources, fuel evaporation from gasoline filling-stations and automobile exhaust. Benzene has been measured in outdoor air at various locations in the USA at concentrations ranging from 0.02 ppb (0.06 µg/m^3) in a rural area, to 112 ppb (356 µg/m^3) in an urban area. Exposure to benzene is highest in areas of heavy motor-vehicle traffic and around gasoline filling-stations. Based on

Table 1.3 Typical benzene exposure levels in different occupational groups/areas in Europe and North America[a]

Occupational group/area	Year	Long-term exposure levels (mg/m^3)					Short-term exposure levels (mg/m^3)					Reference
		N	AM	GM	Min	Max	N	AM	GM	Min	Max	
Upstream petrochemical industry												Verma *et al.* (2000)
Conventional oil/gas	1985–96	198	0.206	0.036	0.003	7.78	23	0.662	0.021	< 0.004	7.954	
Conventional gas	1985–96	608[b]	0.089	0.024	0.006	6.868	40	2.328	0.144	< 0.02	35.2	
Heavy oil processing	1985–96	236	0.112	0.051	< 0.003	1.60	24	0.056	0.027	< 0.017	0.731	
Pipeline	1985–96	8	0.392	0.350	0.160	1.540	-	-	-	-	-	
Downstream petrochemical industry												CONCAWE (2000, 2002), Merlo *et al.* (2001)
Refinery												
On-site operators	1993–98	97	0.22	-	0.008	7.88	-	-	-	-	-	
	1999–2001	-	-	-	-	-	6	1.0	0.9	0.8[c]	1.4[c]	
Off-site operators	1993–98	321	0.32	-	0.008	23.3	49	2.19	-	0.08	11.8	
	1999–2001	-	-	-	-	-	7	0.7	0.7	0.6[c]	0.8[c]	
Maintenance workers	1993–98	373	0.41	-	0.008	18.1	7	2.62	-	0.23	8.6	
Laboratory technicians	1993–98	628	0.30	-	0.0015	5.0	5	1.93	-	0.28	4.6	
Marine and rail car loading												
Deck crew, open loading	1993–98	41	0.56	-	0.08	5.4	4	0.23	-	0.23	0.3	
Deck crew, closed loading	1993–98	2	0.56	-	0.51	0.6	-	-	-	-	-	
Marine loading	1993–98	32	0.51	-	0.023	3.7	2	0.7	-	0.23	1.2	
Jetty staff	1993–98	46	0.37	-	0.023	1.7	24	0.79	-	0.23	5.8	
Rail car terminal operators (toploading with VR)	1999–2001	21	0.5	0.4	0.2[c]	0.7[c]	3	0.5	-	0.5	0.5	
Road tanker distribution												
Terminal supervisors	1993–98	151	0.36	-	0.001	3.1	8	2.20	-	0.23	11.2	
Drivers, bottom loading & VR	1999–2001	33	0.6	0.4	0.2[c]	1.2[c]	15	1.8	1.4	0.5[c]	3.8[c]	
Drivers, delivery	1999–2001	-	-	-	-	-	7	0.7	0.4	0.2[c]	1.6[c]	

Table 1.3 (continued)

Occupational group/area	Year	Long-term exposure levels (mg/m³)					Short-term exposure levels (mg/m³)					Reference
		N	AM	GM	Min	Max	N	AM	GM	Min	Max	
Service station												CONCAWE (2000, 2002), Merlo *et al.* (2001) Contd.
Attendants	1999–2000	78	0.102	-	0.0115	0.478	-	-	-	-	-	
Cashiers	1993–98	268	0.05	-	0.001	1.92	-	-	-	-	-	
Miscellaneous workers	1999–2001	6	0.2	0.1	0.1[c]	0.2[c]	-	-	-	-	-	
Gasoline pump maintenance	1993–98	2	0.55	-	0.16	0.93	6	3.8	-	0.19	11.8[d]	
Coke oven industry												Hotz *et al.* (1997)
Coke plant	1994–95	19	0.13[e]	-	ND[f]	1.76[f]	-	-	-	-	-	
Coke plant	1994–95	17	1.79[e]	-	0.52[f]	23.82[f]	-	-	-	-	-	
By-product plant	1994–95	21	1.17[e]	-	0.20[f]	5.30[f]	-	-	-	-	-	
Motor mechanics	1994–98	243	0.362	-	< 0.005	13.0	8	10.15[g]	-	1.2	46	CONCAWE (1986), Nordlinder & Ramnäs (1987), Popp *et al.* (1994), Hotz *et al.* (1997), Javelaud *et al.* (1998)
	1981	-	-	-	-	-	-	0.52	-	0.33	1.50	
Aviation												CONCAWE (2000), Egeghy *et al.* (2003)
Civilian airport operators	1993–98	10	0.10	-	0.008	0.60	-	-	-	-	-	
Military fuel maintenance workers	2003	114	0.252[e]	-	0.006	6.63	-	-	-	-	-	
Military fuel handling, distribution, recovery & testing workers	2003	38	0.007[e]	-	0.001	1.85	-	-	-	-	-	
Firefighters	1991–2002	43	-	-	< 0.37[h]	6.14[h]	22[i]	-	-	< LOD	68.25	Jankovic *et al.* (1991), Bolstad-Johnson *et al.* (2000), Caux *et al.* (2002)
							96[j]	1.24	-	0.228	6.468	

Table 1.3 (continued)

Occupational group/area	Year	Long-term exposure levels (mg/m³)					Short-term exposure levels (mg/m³)					Reference
		N	AM	GM	Min	Max	N	AM	GM	Min	Max	
Urban workers												Fustinoni *et al.* (1995), Carrer *et al.* (2000), Crebelli *et al.* (2001), Merlo *et al.* (2001)
Traffic police/wardens	1994–2000	236	0.020	-	0.009	0.316	-	-	-	-	-	
Bus drivers	1998–2000	152	0.0238	-	0.003	0.092	-	-	-	-	-	
Office workers	1994–2000	289	0.016	-	0.002	0.115	-	-	-	-	-	

[a] When selecting typical benzene exposure values, preference has been given to studies published within the previous 10 years and for which greater than 10 subjects were sampled. Where appropriate, data sets have been combined to give an overall mean exposure.
[b] Data for which an arithmetic mean was available
[c] 10th and 90th percentile values.
[d] The mean was strongly influenced by one high exposure level of 46 mg/m3, if this is excluded the mean exposure is 5.03 mg/m3 (range:1.2–14.0 mg/m3).
[e] Median value.
[f] 5th and 95th percentile values.
[g] Small spillage associated with the highest result.
[h] Exposure estimated from biological monitoring.
[I] Exposure during the knockdown phase of fire fighting.
[j] Exposure during the overhaul phase of fire fighting.
AM, arithmetic mean; GM, geometric mean; Max, maximum; Min, minimum; N, number of samples; VR, vapour recovery
From Capleton & Levy (2005)

Table 1.4 Comparison of the average benzene concentrations (mg/m³) by industry

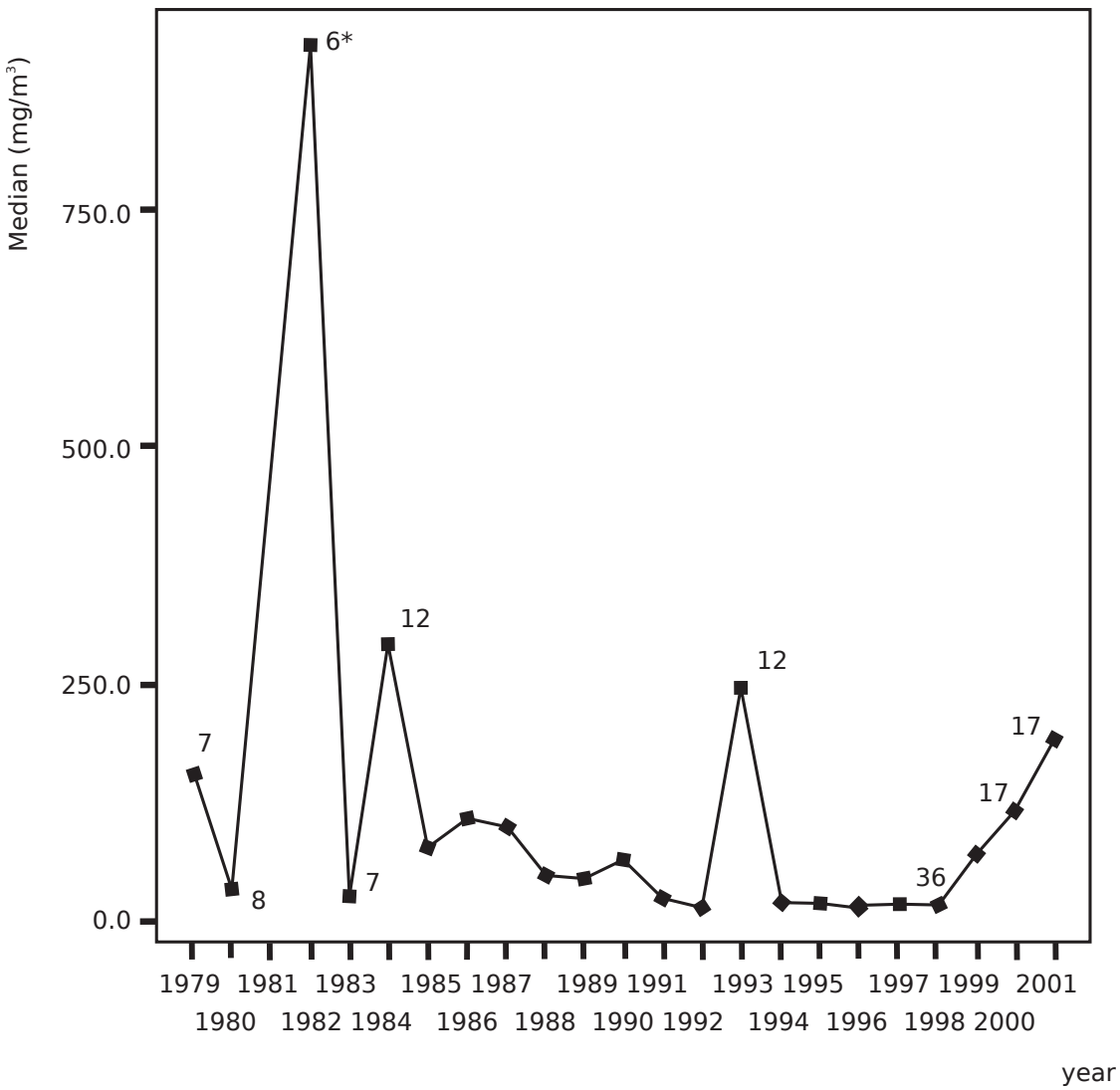
Type of industry	No. of sets	No of samples	Median	Average (range)
Leather products[a]	18	1487	124.8	124.1 (3.7–267.8)
Electronic devices manufacturing[a]	6	1930	98.7	120.2 (4.5–254.9)
Machinery manufacturing[a]	6	6815	75.4	75.6 (4.2–152.7)
Shoes manufacturing, leather[a]	70	12 197	50.4	149.9 (1.3–1488.6)
Office supplies and sports equipment[a]	6	106	50.3	79.4 (10.7–256.0)
Spray painting	29	1186	39.8	53.4 (0–226.8)
Furniture manufacturing	8	618	39.3	36.6 (2.0–72.0)
Misc. electronic parts manufacturing	7	197	33.6	50.5 (3.0–105.6)
Automobile manufacturing	6	3478	32.8	56.8 (0–196.1)
Organic chemical industry	19	650	23.8	39.3 (12.8–130.5)
Rubber products manufacturing	15	182	22.9	114.6 (0.1–633.6)
Other industries	10	6799	18.5	23.8 (2.2–85.5)
Paint manufacturing	37	525	13.2	23.9 (1.0–127.5)
Chemical industry	18	859	7.6	19.3 (0–123.9)
Printing industry	8	6416	6.5	7.2 (0–23.6)
Metal-based products processing	10	77	1.4	7.5 (0–38.0)
Toy manufacturing	2	2531	132.9	132.9 (1.5–264.3)
Coal products manufacturing	3	23	96.0	79.8 (12.8–130.5)
Crude oil processing	3	992	62.6	54.4 (7.4–93.2)
Petroleum & geological prospecting	3	22	57.2	41.9 (5.8–62.6)
Other textile industries/printing & dyeing	1	178	26.2	26.2
Civil engineering & construction	3	137	20.3	122.2 (1.2–345.2)
Pottery & porcelain products manufacturing	3	26	20.2	22.4 (7.1–40.0)
Electronic circuit manufacturing	3	26	20.2	22.4 (7.1–40.0)
Plastic products manufacturing	2	1216	15.2	15.2 (2.3–28.2)
Other precision instruments manufacturing	2	44	14.3	14.3 (8.7–19.9)
Household metal hardware manufacturing	1	1139	2.3	2.3

[a] The top five industries with more than six measurement sets in an individual industry. Industries following the blank space (after Metal-based processing) are those for which fewer than six data sets were available.
From Liang *et al.* (2005)

an average benzene concentration of 12.5 ppb (40 μg/m³) in the air and an exposure of 1 hour per day, the daily intake of benzene from driving or riding in a motor vehicle is estimated to be 40 μg. Exposure is higher for people who spend significant time in motor vehicles in areas of congested traffic (NTP, 2005; ATSDR, 2007).

The primary sources of exposure to benzene for the general population are ambient air containing tobacco smoke, air contaminated with benzene (for example, in areas with heavy traffic, around gasoline filling-stations), drinking contaminated water, or eating contaminated food. The median level of benzene was 2.2 ppb (7 μg/m³) in 185 homes without smokers and 3.3 ppb (10.5 μg/m³) in 343 homes with one or more smokers. Amounts of benzene measured per cigarette ranged from 5.9 to 75 μg in mainstream smoke and from 345 to 653 μg in sidestream smoke. Benzene intake from ingestion of water and foods is very low, compared with intake from ambient air (ATSDR, 1997; NTP, 2005). Residential exposure to benzene can also occur from leaking underground gasoline-storage tanks. Benzene concentrations in homes from such exposures have been estimated to

Fig. 1.1 Overall trend in median benzene exposure in Chinese industry, 1979–2001. The star indicates the number of measurement sets in the database



From Liang *et al.* (2005)

Table 1.5 Benzene in breath, blood and urine samples in the general population without occupational or known exposure to benzene[a]

Country	Analyte	Median/Mean	Reference
People's Republic of China	Urine	120 ng/L	Kim *et al.* (2006a)
People's Republic of China	Urine	69 ng/L	Waidyanatha *et al.* (2001)
People's Republic of China and Malaysia	Urine	1.49 ng/L	Ong *et al.* (1995)
Estonia	Blood Breath Urine	12 nmol/L 7 nmol/L 0.1 nmol/L	Kivistö *et al.* (1997)
Italy	Blood	110 ng/L (NS) 219 ng/L (S)	Brugnone *et al.* (1998)
Italy	Urine	1155 ng/L	Gobba *et al.* (1997)
Mexico	Blood	0.63 µg/L (service attendants) 0.30 µg/L (street vendors) 0.17 µg/L (office workers)	Romieu *et al.* (1999)
Singapore	Blood Urine	1.27 nmol/L 1.29 nmol/L	Ong *et al.* (1996)
Thailand	Blood	65.6 ppt	Navasumrit *et al.* (2005)

[a] Including control workers
NS, non-smoker; S, smoker
From Johnson *et al.* (2007)

range from 0–42 ppm (1–136 mg/m^3) (Patel *et al.*, 2004).

Duarte-Davidson *et al.* (2001) assessed human exposure to benzene in the general population of the United Kingdom. It was estimated that infants (< 1 year old), the average child (11 years old), and non-occupationally exposed adults receive average daily doses of benzene in the range of 15–26 µg, 29–50 µg, and 75–522 µg, respectively. These values correspond to average airborne benzene concentrations in the range of 3.40–5.76 µg/m^3, 3.37–5.67 µg/m^3, and 3.7–41 µg/m^3 for these three groups, respectively.

Benzene concentrations in breath, blood and urine samples collected among the general populations (without occupational or known exposure to benzene) in Asia, Europe and North America are presented in Table 1.5 (Johnson *et al.*, 2007).

2. Cancer in Humans

In *IARC Monographs* Volume 29 (IARC, 1982) the Working Group concluded there was *sufficient evidence* in humans for the carcinogenicity of benzene, noting that a series of cohort and case–control studies showed statistically significant associations between occupational exposure to benzene and benzene-containing solvents and leukaemia (predominantly myelogenous leukaemia). In *IARC Monographs* Supplement 7 (IARC, 1987) benzene was classified as a Group-1 carcinogen, citing additional evidence of an increased incidence of acute nonlymphocytic leukaemia (ANLL) in workers exposed to benzene in three cohort studies, including an update of a cohort cited in Volume 29 (IARC, 1982). Since 1987, there have been numerous reports from cohort studies in populations exposed to benzene, including updates of earlier reports, and new case–control studies of leukaemia or its subtypes, non-Hodgkin lymphoma (NHL), multiple myeloma, and to a

lesser extent other tumours in adults. There have also been several case–control studies of childhood leukaemia with data on benzene, solvents, gasoline, and other related exposures. In addition, several meta-analyses have been published of one or more tumour sites.

[The Working Group decided to restrict its review to those case–control studies of paediatric cancers that included estimates of environmental benzene exposure, rather than surrogate exposures such as proximity to petrol stations or traffic. Also, the Working Group weighed more heavily the findings from studies with estimates of occupational exposure to benzene rather than broader measures (e.g. to solvents) in case–control studies. It was also decided not to rely in general on case–control studies where exposure assessment was limited to asking study subjects directly if they had been exposed to particular chemicals. Furthermore, the Working Group did not consider cohort studies of workers in synthetic rubber-manufacturing due to the difficulty of separating out effects from benzene *vs* those of other chemicals that may cause haematological malignancies. The Working Group decided not to take into consideration a series of meta-analyses of studies of petroleum workers (Wong & Raabe, 1995, 1997, 2000a, b). There were methodological concerns about the expansion from paper to paper of additional studies, cohorts, and countries, and the overall approach may dilute out the risks associated with relatively highly exposed subgroups of these populations that in general were not identified. In addition, an increased risk of ANLL – or the alternative classification, Acute Myelogenous Leukaemia (AML), which is more restrictive but still constitutes most of ANLL – was not detected in the initial meta-analysis by Wong & Raabe (1995), this body of work was not considered relevant for assessing what additional cancers may be associated with exposure to benzene beyond ANLL/AML. Abd finally, the Working Group noted that some meta-analyses of the same tumour came to opposite conclusions, which could be due to different inclusion/exclusion criteria, focusing on different subgroups of the study populations, or to different approaches to selecting risk estimates for inclusion (e.g. Lamm *et al.*, 2005; Steinmaus *et al.*, 2008), thus complicating the overall assessment of the literature. The Working Group therefore decided not to rely in general on results of meta-analyses in its evaluations.]

2.1 Leukemias and lymphomas

2.1.1 Acute non-lymphocytic leukaemia/ acute myelogenous leukaemia

Since 1987, additional analyses of previously published cohort studies (e.g. results in Crump (1994) and Wong (1995), based on the cohort study described in Infante *et al.* (1977) and Rinsky *et al.* (1981, 1987), which reported an excess risk for combined (mostly acute) myelogenous and monocytic leukaemia) and new cohort studies with quantitative data on benzene exposure have shown evidence of a dose–response relationship between exposure to benzene and risk for ANLL/AML in various industries and in several countries (Hayes *et al.*, 1997; Rushton & Romaniuk, 1997; Divine *et al.*, 1999b; Guénel *et al.*, 2002; Collins *et al.*, 2003; Glass *et al.*, 2003; Bloemen *et al.*, 2004; Gun *et al.*, 2006; Kirkeleit *et al.*, 2008; see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.1.pdf). It was also noted that the NCI-CAPM cohort study found evidence of an increased risk for the combined category of ANLL and myelodysplastic syndromes (Hayes *et al.*, 1997). Case–control studies do not add substantively to these conclusions (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.2.pdf). In one case–control study an increased risk for childhood ANLL was found for maternal self-reported occupational exposure to benzene (Shu *et al.*, 1988; see Table 2.1 online). One case–control

study of childhood cancer in Denmark did not find an association of estimates of environmental benzene exposure from air pollution with an increased risk for ANLL (Raaschou-Nielsen *et al.*, 2001).

2.1.2 Acute lymphocytic leukaemia

Acute Lymphocytic Leukaemia (ALL) is now considered one subtype of NHL in the WHO-classification of lymphomas. In multiple cohorts there was a non-significantly increased risk for ALL, but the numbers of cases were small (Rushton, 1993; Wong *et al.*, 1993; Satin *et al.*, 1996; Divine *et al.*, 1999b; Lewis *et al.*, 2003; Kirkeleit *et al.*, 2008; Yin *et al.*, 1996; Guénel *et al.*, 2002; Gun *et al.*, 2006; see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.3.pdf). [The Working Group noted that the magnitude of the risk-estimate in the NCI-CAPM cohort (Yin *et al.*, 1996) was similar to the risk observed for ANLL in the same study, which was statistically significant. This approach has been suggested when attempting to interpret the association between occupational exposure to benzene and hematological subtypes that are less common than AML (Savitz & Andrews, 1997).]

In one case–control study in adults in Shanghai, a significant increased risk for ALL was found for the group with 15 or more years of self-reported occupational exposure to benzene (Adegoke *et al.*, 2003); another study in the USA had only three exposed cases (Blair *et al.*, 2001; Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.4.pdf). In a case–control study of childhood ALL no association was found with maternal self-reported occupational exposure to benzene, but a borderline significant association was noted with exposure to gasoline (Shu *et al.*, 1988; see Table 2.4 online). No association with self-reported maternal exposure to benzene was found in a large study of childhood ALL in the USA (Shu *et al.*, 1999; see Table 2.4 online). A case-control study of childhood cancer in Denmark did not find an association of estimated environmental exposure to benzene from air pollution with ALL (Raaschou-Nielsen *et al.*, 2001).

2.1.3 Chronic myelogenous leukaemia

Several studies in the petroleum industry and in other settings show non-significantly increased risks for CML, whereas other studies show no evidence of an association, including two that had quantitative estimates of exposure to benzene but no dose–response relationship (Rushton & Romaniuk, 1997; Guénel *et al.*, 2002; see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.5.pdf). Case–control studies have shown inconsistent results, with both increased risks (exposure for > 15 years was associated with an OR of 5.0 (1.8–13.9; Adegoke *et al.*, 2003) and no increase in risk (Björk *et al.*, 2001) reported (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.6.pdf).

2.1.4 Chronic lymphocytic leukaemia

Chronic Lymphocytic Leukaemia (CLL) – also referred to as small lymphocytic lymphoma (SLL) – is now considered as a subtype of NHL in the WHO-classification of lymphomas. CLL can be an indolent disease of the elderly, which raises questions about cohorts that are not followed up until the study population is relatively old and about studies that use mortality instead of incident data. In addition, the diagnosis of CLL was less frequently made in the past, until complete blood counts were routinely obtained in recent decades.

Several cohort studies in the petroleum industry showed mixed results, with some non-significantly increased risks reported and other studies showing no association (see Table 2.7 available at http://monographs.iarc.fr/ENG/

Monographs/vol100F/100F-19-Table2.7.pdf). In a nested case–control study in the Australian petroleum industry an increasing risk for CLL was detected with increasing exposure to benzene over a relatively small range of ppm–years, but the increase was not significant (Glass *et al.*, 2003). Similarly, in a nested case–control study within a cohort of French gas and electrical utility workers, a non-significant increase in risk with increasing years of benzene exposure was detected (Guénel *et al.*, 2002). Some evidence of risk with increasing benzene exposure was also found in a cohort study among petroleum workers in the United Kingdom, but the trends were not clear and interpretation is difficult as white- and blue-collar workers were mixed in the analysis and interactions may have been present (Rushton & Romaniuk, 1997). Updates of two cohort studies in the Southern US found an increased risk for CLL, which was significant in one cohort for workers hired before 1950, but not in the other (Huebner *et al.*, 2004).

A case–control study in Italy showed evidence of a dose–response relationship between the extent of benzene exposure with the number of years worked with benzene (Costantini *et al.*, 2008) and in a large multicentre international study in Europe a significant excess in risk for CLL was found with increasing exposure to benzene, but the dose–response was not significant (Cocco *et al.*, 2010; see Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.8.pdf). Blair *et al.* (2001) conducted a study in the Midwestern USA and found no association with benzene exposure although there were only three cases in the high-exposure category. In a study of women in Connecticut, a non-significantly increased risk for CLL was found with increasing exposure to benzene (Wang *et al.*, 2009; see Table 2.8 online).

2.1.5 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of histological subtypes, and the definition of both NHL and its subtypes has evolved over the last several decades with the application and discontinuation of several classification schemes, which complicates the assessment of exposure to benzene and risk for NHL. For example, CLL – now classified by the WHO as a subtype of NHL – has generally not been combined with other types of NHL in reports from cohort studies of benzene-exposed workers or in earlier case–control studies of NHL. Further, given the indolent nature of some NHL subtypes, cohorts with only mortality data may underestimate associations with NHL. In most cohort studies an increased risk for NHL was not detected, one particular exception being the NCI-CAPM cohort study in China (Hayes *et al.*, 1997; Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.9.pdf). An excess of NHL was not detected in the Pilofilm cohort (Rinsky *et al.*, 2002) or in the Australian Health Watch study in an analysis of NHL combined with multiple myeloma (two-thirds of which were NHL cases) (Glass *et al.*, 2003).

Of 14 independent case–control studies that were considered informative, five showed evidence of increased risk with benzene exposure, two (Fabbro-Peray *et al.*, 2001; Dryver *et al.*, 2004) for NHL as a whole (Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.10.pdf). Data on histological subtypes of NHL have generally not been reported in publications of occupational cohort studies of benzene-exposed workers, but they have been mentioned in some case–control studies. For various benzene-exposure metrics, slightly increased, but non-significant risks for NHL were found in a case–control study among women in Connecticut, as well as higher risks – also non-significant – for follicular lymphoma

and diffuse large B-cell lymphoma (DLBCL), two common NHL subtypes (Wang *et al.*, 2009). Cocco *et al.* (2010) conducted an analysis of a large multicentre case–control study of NHL in Europe and found no significant increase in risk for B-cell NHL or DLBCL, but an elevated risk, albeit not statistically significant, for follicular lymphoma associated with exposure to benzene (see Table 2.10 online), and a significant association between combined exposure to benzene/toluene/xylene and follicular lymphoma. Other case–control studies showed increased, non-significant risks for one or both of these histological subtypes, and in one study in Italy a significant association was found between medium/high exposure to benzene and the risk for diffuse lymphoma (Miligi *et al.*, 2006; OR = 2.4, 95%CI: 1.3–1.5).

2.1.6 Multiple myeloma

Most cohort studies showed no association with multiple myeloma (MM) (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.11.pdf). However, there was a statistically significant excess of MM reported for the Pliofilm cohort (SMR 4.1; 95%CI: 1.1–10.5, based upon four deaths) (Rinsky *et al.*, 1987), which did not persist in the most recent update (Rinsky *et al.*, 2002; see Table 2.11 online). In a cohort study among chemical workers at the Monsanto chemical company suggestive evidence was found of a dose–response relationship (Collins *et al.*, 2003), while in a cohort study of Norwegian workers in the upstream petroleum industry (i.e. the phases of oil extraction and initial transportion, which entail extensive exposure to crude oil) a significant increased risk for MM was found (Kirkeleit *et al.*, 2008).

Case–control studies of MM with estimates of exposure to benzene largely show no association (Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.12.pdf). An exception was an early study in which a significant association was found between risk for MM and the proportion of cases and controls with "solvent/benzene" exposure (La Vecchia *et al.*, 1989). In another study, borderline significant effects were detected (Costantini *et al.*, 2008). In a large multicentre case–control study of NHL in Europe there was no association of benzene exposure with MM (Cocco *et al.*, 2010).

A meta-analysis by Infante (2006) analysed data from seven well defined "benzene cohorts" outside of petroleum refining and found a statistically significant increase in risk for MM (RR 2.1; 95%CI: 1.3–3.5).

2.1.7 Hodgkin disease

There are sparse data on Hodgkin disease in studies of benzene-exposed cohorts, with most studies having very small numbers of cases and showing no association (see Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.13.pdf). Overall, there is no evidence of an increased risk. The relatively few case–control studies in adults also show no association (see Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.14.pdf). In a case–control study of childhood cancer in Denmark, an increased risk for Hodgkin disease was detected in association with estimated environmental exposures to benzene (Raaschou-Nielsen *et al.* (2001) (see Table 2.14 online).

2.2 Cancer of the lung

Cohort studies with information on potential or estimated benzene exposure and lung cancer are shown in Table 2.15 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.15.pdf). Although most studies show no association, in two cohorts with quantitative exposure-assessment evidence of a dose–response relationship was found (Hayes *et al.*, 1996; Collins

et al., 2003) and in two others statistically significant increases in risk were observed (Lynge *et al.*, 1997; Sorahan *et al.*, 2005). A case–control study from Canada showed no association of exposure to benzene with lung cancer overall or with the major histological subtypes (Gérin *et al.*, 1998; see Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.16.pdf).

2.3 Cancer of the kidney

Cohort studies with results on kidney cancer are shown in Table 2.17 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.17.pdf). Results generally do not show any association. In a case–control study among males in Germany an association was found between exposure to benzene and an increased risk for kidney cancer (Pesch *et al.*, 2000), but in a study in Montreal, Canada, there was little evidence of an association (Gérin *et al.*, 1998) (see Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.18.pdf).

2.4 Other cancers

In the evaluation of the cohort studies that provided data on the cancer sites considered above, it was apparent that associations have occasionally been found with other cancer sites including malignant melanoma (Schnatter *et al.*, 1996; Consonni *et al.*, 1999; Lewis *et al.*, 2003), nose and stomach cancer (Fu *et al.*, 1996) and prostate cancer (Collingwood *et al.*, 1996), but overall there was no consistency across the cohorts.

3. Cancer in Experimental Animals

Studies on the carcinogenesis of benzene in rats and mice after exposure by inhalation, intragastric gavage, skin application, and by intraperitoneal or subcutaneous injection have been reviewed in *IARC Monographs* Volume 29 and in Supplement 7 (IARC, 1982, 1987). In Supplement 7 it was concluded that there is *sufficient evidence* in experimental animals for the carcinogenicity of benzene. Results of adequately conducted carcinogenicity studies reported before and after 1987 are summarized in Tables 3.1, 3.2, 3.3, 3.4.

Exposure to benzene by inhalation increased the incidence of Zymbal gland carcinomas, liver adenomas, and forestomach and oral cavity carcinomas in female rats (Maltoni *et al.*, 1982a, c, 1983, 1985, 1989). It also increased the incidence of lymphohaematopoietic (lymphoma, myelogenous) neoplasms in male and female mice (Snyder *et al.*, 1980; Cronkite *et al.*, 1984, 1989; Farris *et al.*, 1993), and Zymbal gland carcinomas, squamous cell carcinomas of the preputial gland, and lung adenomas in male mice (Snyder *et al.*, 1988; Farris *et al.*, 1993).

Oral administration of benzene increased the incidence of Zymbal gland carcinomas and oral-cavity papillomas and carcinomas in rats of both sexes, of carcinomas of the tongue, papillomas and carcinomas of the skin and of the lip and papillomas of the palate in male rats, of forestomach acanthomas in both sexes of the rat, and of forestomach carcinomas in female rats (Maltoni & Scarnato, 1979; Maltoni *et al.*,1982b, 1983, 1988, 1989; NTP, 1986; Maronpot, 1987; Huff *et al.*, 1989; Mehlman, 2002). Given by the oral route, benzene also increased the incidence of Zymbal gland carcinomas, forestomach papillomas, lymphomas, and lung adenomas and carcinomas in mice of both sexes, of liver carcinomas, adrenal gland pheochromocytomas, harderian gland adenomas and preputial gland squamous cell carcinomas in male mice,

Table 3.1 Carcinogenicity studies in experimental animals exposed to benzene by inhalation

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley, (M, F) 150 wk Maltoni *et al.* (1982a, c, 1983, 1985, 1989)	Three different treatment groups (n = 54–75) and 2 controls (breeder controls, n = 60; embryo controls, n = 149–158). Pregnant breeders (Group 1) and embryos exposed transplacentally (Group 2) were exposed 4 h/d, 5 d/wk for 7 wk at 200 ppm; then postpartum breeders and offspring were exposed 7 h/d, 5 d/wk for 12 wk during weaning at 200 ppm; after weaning, breeders and offspring were exposed 7 h/d, 5 d/wk for 85 wk at 300 ppm. Group 3 were embryos exposed 4 h/d, 5 d/wk for 7 wk at 200 ppm transplacentally then 7 h/d, 5 d/wk for 8 wk at 200 ppm. Therefore, the embryos were exposed transplacentally during pregnancy and the offspring were exposed by inhalation and possibly by ingestion via milk.	Zymbal's gland carcinomas Group 1 (breeders 104 wk): F–1/60 (controls), 3/54 Group 2 (embryos 104 wk): M–2/158 (controls), 6/75 F–0/149 (controls), 8/65 Group 3 (embryos 15 wk); M–2/158 (controls), 4/70 F–0/149 (controls), 1/59 Liver adenomas Group 1: F–0/60, 1/54 Group 2: M–1/158, 2/75 F–0/149, 5/65 Group 3: M–1/158, 2/70 F–0/149, 5/59 Oral cavity carcinomas Group 1: F–0/60, 2/54 Group 2: M–0/158, 1/75 F–0/149, 10/65 Group 3: M–0/158, 2/70 F–0/149, 6/59	[NS] [NS] [significant] [NS] [NS] [NS] [NS] [significant] [NS] [significant] [NS] [NS] [significant] [NS] [significant]	Breeders were 13 wk old at the start of exposure; embryos were 12 days old at the start of the exposures

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley, (M, F) 150 wk Maltoni *et al.* (1982a, c, 1983, 1985, 1989) Contd.		Forestomach carcinomas (in situ) Group 1: F–0/60, 0/54 Group 2: M–0/158, 0/75 F–0/149, 3/65 Group 3: M–0/158, 0/70 F–0/149, 0/59	 [NS] [NS] [significant] [NS] [NS]	
Mouse, C57BL/6J (M) Lifetime Snyder *et al.* (1980)	0 (filtered air) or 300 ppm benzene, 6 h/d, 5 d/wk 40/group	Total lymphohaematopoietic: 2/40, 8/40 - Lymphocytic lymphoma: 2/40, 6/40 - Plasmocytoma 0/40, 1/40 - Leukaemia 0/40, 1/40	$P < 0.005$, X^2-test $P < 0.001$, X^2-test NS NS	Purity unspecified Exposed mice had body weight gain depression relative to the controls throughout the study. Exposed mice had a median survival of 41 wk vs 75 wk for the controls.
Mouse, CD-1 Lifetime Goldstein *et al.* (1982)	0 or 300 ppm benzene 6 h/d, 5 d/wk 40/group	Myelogenous leukaemia: 0/40, 3/40	NS	Purity unspecified. Sex unspecified Although the incidence of 3/40 is not significantly higher than the 0% incidence observed in control animals ($P = 0.147$), these preliminary findings do give credence to the myeloleukaemogenic effect of benzene due to the lack of observation of spontaneous myeloproliferative disorders in the animal strain under study.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C57Bl/6 BNL (F) Lifetime Cronkite *et al.* (1984)	0 or 300 ppm for 16 wk, 6 h/d, 5 d/wk 88–90/group	Total lymphohaematopoietic malignancies: 0/88, 8/90	[$P < 0.01$]	Purity unspecified
		- Thymic lymphoma: 0/88, 6/90	[$P < 0.05$]	
		- Lymphoma (unspecified): 0/88, 2/90	[NS]	
Mouse, CD-1 (M) Lifetime Snyder *et al.* (1988)	0 (filtered air) or 1200 ppm benzene, 6 h/d, 5 d/wk for 10 wk 50 exposures total 80/group	Lung adenomas: 17/71, 33/71	$P < 0.001$	Purity unspecified
		Zymbal's gland carcinomas: 0/71, 4/71	$P < 0.05$	
Mouse, CD-1 (M) Lifetime Snyder *et al.* (1988)	0 (filtered air) or 300 ppm benzene, 6 h/d, 5 d/wk for 1 wk followed by 2 wk of non exposure for life 60/group	Lung adenomas: 3/46, 14/54	$P < 0.005$	Purity unspecified
		Leukaemia/lymphomas: 1/46, 7/54	NS	
		Zymbal's gland carcinomas: 0/46, 2/54	NS	
Mouse, C57Bl (M) Lifetime Snyder *et al.* (1988)	0 (filtered air) or 1200 ppm benzene, 6 h/d, 5 d/wk for 10 wk 80/group	Zymbal's gland carcinomas: 0/67, 4/68	NS	Purity unspecified
Mouse, C57Bl (M) Lifetime Snyder *et al.* (1988)	0 (filtered air) or 300 ppm benzene, 6 h/d, 5 d/wk for 1 wk followed by 2 wk of non exposure for life 60/group	Zymbal's gland carcinomas: 0/46, 19/54	$P < 0.001$	Purity unspecified

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CBA/Ca BNL (M, F) Lifetime Cronkite *et al.* (1989)	0, 100 (M), 300 (M, F) ppm benzene for 16 wk 6 h/d, 5 d/wk. 60 – 85/group	100 ppm Myelogenous neoplasms: 0/70, 2/85 Other neoplasms, other than hepatoma and haematopoietic: 14/70, 38/85 300 ppm Myelogenous neoplasms: M–0/60, 11/57 F–1/60, 6/54 Other neoplasms, other than hepatoma and haematopoietic: M–13/60, 30/57 F–21/60, 43/54	 NS $P < 0.001$ $P < 0.001$ $P = 0.040$ $P < 0.001$ $P < 0.001$	Purity unspecified Medium lifespan in male (510 days) and female (580 days) mice exposed to 300 ppm was significantly reduced versus sham –exposed males (1 030 days) and females (1 100 days). Myelogenous neoplasms included acute myeloblastic and chronic granulocytic leukaemia. Other neoplasms included Zymbal's and Harderian gland tumours, squamous cell carcinoma, mammary gland adenocarcinoma, and papillary adenocarcinoma of the lung.
Mouse, CBA/Ca (M) 22 months Farris *et al.* (1993)	0, 300 ppm benzene 6 h/d, 5 d/wk for 16 wk 125/group	Malignant lymphomas: 2/119, 14/118 Preputial gland (squamous cell carcinomas): 0/118, 71/118 Lung (alveolar/bronchiolar adenomas): 17/119, 42/119 Zymbal's gland (carcinomas): 1/125, 14/125 Forestomach (squamous cell carcinomas): 0/125, 9/125 Harderian gland: 6/125, 7/125	$P < 0.002$ $P < 0.01$ $P < 0.01$ See comments See comments See comments	100% pure Exposure to benzene caused a significant decrease ($P < 0.01$) in survival and was a significant cause ($P < 0.01$) of early mortality during the first 9 mo post exposure. Most (12) of the lymphomas were of the lymphoblastic or lymphocytic type; two (2) were of the mixed type. Zymbal's gland, forestomach and Harderian gland were examined microscopically only when gross lesions were evident.

d, day or days; h, hour or hours; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; ppm, parts per million; wk, week or weeks; yr, year or years

Table 3.2 Carcinogenicity studies in experimental animals exposed to benzene by gavage

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 103 wks NTP (1986), Maronpot (1987), Huff *et al.* (1989)	0, 50, 100, 200 mg/kg bw benzene in corn oil (M); 0, 25, 50, or 100 mg/kg bw in corn oil (F) 5 d/wk 60/group	***Zymbal's Gland:***		> 99.7% pure Groups of 10 rats/sex/group were removed at 51 wks for blood sampling and killed at 52 wks. Survival decreased with increasing dose in both sexes; survival of the high-dose females was significantly less than that of the controls; control females had a greater than average survival normally observed for female F344 rats. Final mean body weight of the high dose males was significantly less than that of the vehicle controls. Most of the dosed rats that died before 103 wks had neoplasms.
		Carcinoma: M–2/32, 6/46, 10/42, 17/42 F–0/45, 5/40, 5/44, 14/46	$P < 0.001$, $P = 0.193$, $P = 0.017$, $P < 0.001$ (M); $P < 0.001$, $P < 0.022$, $P < 0.018$, $P < 0.001$ (F)	
		Adenoma/Carcinoma: M–2/32, 7/46, 10/42, 18/42 F–0/45, 5/40, 6/44, 15/46	$P < 0.001$, $P = 0.131$, $P = 0.017$, $P < 0.001$ (M); $P < 0.001$, $P = 0.022$, $P = 0.010$, $P < 0.001$ (F)	
		Palate:		
		Papilloma: M–0/50, 4/50, 4/50, 9/50 F–1/50, 3/50, 5/50, 3/50	$P < 0.001$, $P = 0.064$, $P = 0.057$, $P < 0.001$ (M); $P = 0.103$, $P = 0.240$, $P = 0.053$, $P = 0.183$ (F)	
		Lip:		
		Papilloma: M–0/50, 2/50, 5/50, 5/50 F–0/50, 0/50, 2/50, 2/50	$P < 0.001$, $P = 0.216$, $P = 0.015$, $P = 0.008$ (M)	
		Carcinoma: M–0/50, 0/50, 0/50, 3/50 F–0/50, 0/50, 0/50, 0/50	$P = 0.002$, -,-, $P = 0.035$ (M)	
		Papilloma/Carcinoma: M–0/50, 2/50, 5/50, 8/50 F–0/50, 0/50, 2/50, 2/50	$P < 0.001$, $P = 0.216$, $P = 0.015$, $P = 0.008$ (M)	
		Tongue:		
		Papilloma: M–1/50, 0/50, 2/50, 2/50 F–0/50, 1/50, 1/50, 0/50		
		Carcinoma: M–0/50, 3/50, 4/50, 4/50 F–0/50, 0/50, 4/50, 4/50	$P = 0.039$, $P = 0.133$, $P = 0.051$, $P = 0.028$ (M)	
		Papilloma/Carcinoma: M–1/50, 3/50, 6/50, 6/50 F–0/50, 1/50, 5/50, 4/50	$P = 0.013$, $P = 0.328$, $P = 0.044$, $P = 0.028$ (M)	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 103 wks NTP (1986), Maronpot (1987), Huff *et al.* (1989) Contd.		***Oral Cavity*** (overall rates): Papilloma: M–1/50, 6/50, 11/50, 13/50 F–1/50, 4/50, 8/50, 5/50	$P < 0.001$, $P = 0.058$, $P = 0.001$, $P < 0.001$ (M); $P = 0.017$, $P = 0.127$, $P = 0.006$, $P = 0.032$ (F)	
		Carcinoma: M–0/50, 3/50, 5/50, 7/50 F–0/50, 1/50, 4/50, 5/50	$P = 0.001$, $P = 0.133$, $P = 0.030$, $P = 0.001$ (M); $P = 0.003$, $P = 0.468$, $P = 0.047$, $P = 0.010$ (F)	
		Papilloma/Carcinoma: M–1/50, 9/50, 16/50, 19/50 F–1/50, 5/50, 12/50, 9/50	$P < 0.001$, $P = 0.012$, $P < 0.001$, $P < 0.001$ (M); $P < 0.001$, $P = 0.068$, $P < 0.001$, $P = 0.001$ (F)	
		Skin: Papilloma: M–0/50, 2/50, 1/50, 5/50	$P < 0.001$, $P = 0.216$, $P = 0.451$, $P < 0.005$ (M)	
		Carcinoma: M–0/50, 5/50, 3/50, 8/50 =	$P < 0.001$, $P = 0.032$, $P = 0.098$, $P < 0.001$ (M)	
		Papilloma/Carcinoma: M–1/50, 7/50, 5/50, 12/50	$P < 0.001$, $P = 0.031$, $P = 0.076$, $P < 0.001$ (M)	
		Uterus: Endometrial stromal polyp: F–7/50, 7/50, 7/49, 14/50	$P = 0.001$, $P = 0.468$, $P = 0.420$, $P = 0.003$ (F)	
Rat, Wistar (M, F) Lifetime Maltoni *et al.* (1983, 1988, 1989), Mehlman (2002)	0, (control), 500 mg/kg bw benzene in olive oil once/d, 5 d/wk, 104 wk 40/group/sex	**Zymbal's gland:** Carcinoma: M–0/40, 7/40 F–0/40, 6/40	[$P < 0.01$]; [$P < 0.05$]	99.93% pure Mortality was higher in benzene-treated male and female rats. Benzene treated rats had lower body weights.
		Oral cavity: Carcinoma: M–1/40, 2/40 F–0/40, 4/40	[NS]	
		Nasal cavity: Carcinoma: M–0/40, 2/40 F–1/40, 1/40	[NS]	
		Malignant tumours: M–8/40, 19/40 F–10/40, 21/40	-	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) Lifetime Maltoni *et al.* (1983, 1989), Maltoni & Scarnato (1979), Mehlman (2002)	Benzene in olive oil 0 (control), 50 or 250 mg/kg bw once/d, 4–5 d/wk for 52 wk 30 or 35/group	**Leukaemia:** M–0/28, 0/28, 4/33 F–1/30, 2/30, 1/32	[NS]	99.93% pure
		Zymbal's gland (carcinomas): M–0/28, 0/28, 0/33 F–0/30, 2/30, 8/32*	*[$P < 0.005$] (F)	
Rat, Sprague-Dawley (M, F) Lifetime Maltoni *et al.* (1989) Maltoni *et al.* (1983), Mehlman (2002), Maltoni *et al.* (1982b)	Benzene in olive oil 0 (control), 500 mg/kg bw once/d, 4–5 d/wk for 104 wk Controls, 50/group Treated, 40/group	**Leukaemia:** M–3/50, 1/40 F–1/50, 3/40	[NS]	99.93% pure
		Zymbal's gland: Carcinoma: M–1/50, 18/40 F–0/50, 16/40	[$P < 0.0001$] (M, F)	
		Nasal cavity: Carcinoma: M–0/50, 3/40 F–0/50, 1/40	[NS]	
		Oral cavity: Carcinoma: M–0/50, 21/40 F–0/50, 20/40	[$P < 0.0001$] (M, F)	
		Skin: Carcinoma: M–0/50, 9/40 F–1/50, 0/40	[$P < 0.001$] (M)	
		Liver: Hepatomas: M–3/50, 3/40 F–0/50, 1/40	[NS]	
		Angiosarcoma: M–0/50, 2/40 F–0/50, 3/40		
		Forestomach: Acanthoma/dysplasia: M–0/50, 10/40 F–0/50, 7/40	[$P < 0.005$] (M, F)	
		Carcinoma M–0/50, 1/40 F–0/50, 6/40	[$P < 0.01$] (F)	
		Total Malignant tumours: M–12/50, 68/40 F–11/50, 59/40	-	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 103 wks NTP (1986), Maronpot (1987), Huff *et al.* (1989)	0, 25, 50, or 100 mg/kg bw benzene in corn oil (M, F) 5 d/wk 60/group	***Zymbal's Gland:*** Carcinoma: M–0/43, 1/34, 4/40, 21/39 F–0/43, 0/32, 1/37, 3/31	$P < 0.001$, $P = 0.489$, $P = 0.012$, $P < 0.001$ (M); $P = 0.007$,–, $P = 0.450$, $P = 0.045$ (F)	> 99.7% pure Groups of 10 mice/sex/group were removed at 51 wks for blood sampling and killed at 52 wks. Survival decreased with increasing dose in both sexes; survival of the high dose males and high dose females was significantly less than those of the controls ($P < 0.001$ and $P = 0.004$, respectively). Final mean body weights of the high dose males and females were less than that of the vehicle controls. Increased incidence of neoplasms were observed at multiple sites for male and female mice.
		Preputial Gland: Squamous cell carcinoma: 0/21, 3/28, 18/29, 28/35	$P < 0.001$, $P = 0.225$, $P < 0.001$, $P < 0.001$ (M)	
		Carcinoma NOS: 0/21, 2/28, 1/29, 3/35	$P < 0.019$, $P = 0.359$, $P = 0.445$, $P = 0.043$ (M)	
		Carcinoma (all types): 0/21, 5/28, 19/29, 31/35	$P < 0.001$, $P = 0.091$, $P < 0.001$, $P < 0.001$ (M)	
		Ovary Tubular adenoma: 0/47, 0/44, 3/49, 3/48	$P = 0.008$, -, $P = 0.090$, $P = 0.047$	
		Granulosa cell tumour or carcinoma: 1/47, 1/44, 6/49, 8/48	$P < 0.001$, $P = 0.730$, $P < 0.040$, $P < 0.004$ (F)	
		Benign mixed cell tumour: 0/47, 1/44, 12/49, 7/48	$P < 0.001$, $P = 0.471$, $P < 0.001$, $P < 0.001$ (F)	
		Mammary gland: Carcinoma: F–0/49, 2/45, 5/50, 10/49	$P < 0.001$, $P = 0.202$, $P < 0.026$, $P < 0.001$ (F)	
		Carcinosarcoma: F–0/49, 0/45, 1/50, 4/49	$P < 0.001$, –, $P < 0.495$, $P < 0.017$ (F)	
		Harderian gland: Adenoma: M–0/49, 9/46, 13/49, 11/48 F–5/48, 6/44, 10/50, 6/47	$P < 0.001$, $P = 0.001$, $P < 0.001$, $P < 0.001$ (M); $P = 0.133$, $P = 0.369$, $P = 0.090$, $P = 0.204$ (F)	
		Carcinoma: M–1/49, 2/46, 0/49, 3/48 F–0/48, 0/44, 0/50, 4/47	$P < 0.001$, –, –, $P = 0.020$ (F	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 103 wks NTP (1986), Maronpot (1987), Huff *et al.* (1989) Contd.		Adenoma/Carcinoma: M–1/49, 10/46, 13/49, 14/48 F–5/48, 6/44, 10/50, 10/47	$P < 0.001$, $P = 0.002$, $P < 0.001$, $P < 0.001$ (M); $P = 0.009$, $P = 0.369$, $P = 0.090$, $P = 0.017$ (F)	
		Lung (alveolar/bronchiolar): Adenoma: M–6/49, 6/48, 8/50, 12/49 F–4/49, 2/42, 5/50, 9/49	$P < 0.001$, $P = 0.499$, $P = 0.188$, $P = 0.005$ (M); $P = 0.003$, $P = 0.437$N, $P = 0.398$, $P = 0.011$ (F)	
		Carcinoma: M–5/49, 11/48, 12/50, 14/49 F–0/49, 3/42, 6/50, 6/49	$P < 0.001$, $P = 0.052$, $P = 0.017$, $P < 0.001$ (M); $P = 0.002$, $P = 0.084$, $P = 0.010$, $P = 0.004$ (F)	
		Adenoma/Carcinoma: M–10/49, 16/48, 19/50, 21/49 F–4/49, 5/42, 10/50, 13/49	$P < 0.001$, $P = 0.069$, $P = 0.007$, $P < 0.001$ (M); $P = < 0.001$, $P = 0.0.366$, $P = 0.039$, $P < 0.001$ (F)	
		Lymphohaematopoietic: Lymphoma: M–4/49, 9/48, 9/50, 15/49 F–15/49, 24/45, 24/50, 20/49	$P < 0.001$, $P = 0.075$, $P < 0.030$, $P < 0.001$ (M); $P = 0.031$, $P = 0.021$, $P = 0.025$, $P = 0.037$ (F)	
		Leukaemia: M–0/49, 1/48, 1/50, 0/49 F–0/49, 1/45, 2/50, 2/49	NR	
		Lymphoma/leukaemia: M–4/49, 10/48, 10/50, 15/49 F–15/49, 25/45, 26/50, 22/49	$P < 0.001$, $P = 0.048$, $P < 0.018$, $P < 0.001$ (M); $P = 0.014$, $P = 0.014$, $P = 0.012$, $P = 0.017$ (F)	
		Forestomach: Papilloma: M–2/45, 1/42, 2/44, 5/38 F–1/42, 3/40, 6/45, 5/42	$P = 0.003$, $P = 0.567$N, $P < 0.556$, $P < 0.014$ (M); $P = 0.022$, $P = 0.288$, $P = 0.038$, $P = 0.040$ (F)	
		Carcinoma: M–2/45, 1/42, 2/44, 5/38	NR	
		Papilloma/carcinoma: M–2/45, 2/42, 3/44, 5/38	$P = 0.004$, $P = 0.623$, $P = 0.335$, $P = 0.014$ (M)	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 103 wks NTP (1986), Maronpot (1987), Huff *et al.* (1989) Contd.		***Liver:*** Adenoma: M–7/49, 11/48, 6/50, 3/47 F–1/49, 8/44, 5/50, 4/49	$P = 0.156$, $P = 0.008$, $P = 0.079$, $P = 0.077$ (F)	
		Carcinoma: M–9/49, 8/48, 17/50, 8/47 F–3/49, 4/44, 8/50, 4/49	$P = 0.072$, $P = 0.589$, $P = 0.028$, $P = 0.293$ (M)	
		Adenoma/Carcinoma: M–15/49, 17/48, 22/50, 11/47 F–4/49, 12/44, 13/50, 7/49	$P = 0.076$, $P = 0.256$, $P = 0.029$, $P = 0.225$ (M); $P = 0.103$, $P = 0.014$, $P = 0.008$, $P = 0.086$ (F)	
		Adrenal Gland: Pheochromocytoma: M–1/47, 1/48, 7/49, 1/46 F–6/49, 1/44, 1/50, 1/48	$P = 0.096$, $P = 0.725$, $P = 0.010$, $P = 0.632$ (M)	
Mouse, A/J (M, F) 24 wk Stoner *et al.* (1986)	0 (control), 24 g/kg bw in tricaprylin vehicle 3x/wk for 8 wk 16/group	**Lung** (adenomas): M–3/15, 8/16 F–2/14, 5/15	NR	Purity NR
		tumours/ mouse: M–0.27 ± 0.59, 0.63 ± 0.72 F–0.14 ± 0.36, 0.53 ± 0.92	$P < 0.05$ NS	
Mouse, Swiss (M, F) Lifetime Maltoni *et al.* (1988)	0 (control), 500 mg/kg bw benzene in olive oil once/d, 5d/wk 40/group	**Mammary gland** (carcinomas): M–1/40, 0/40 F–2/40, 19/40	[$P < 0.0001$] (F)	99.93% pure
		Lung (adenomas): M–3/40, 16/40 F–4/40, 15/40	[$P < 0.01$] (M, F)	
		Zymbal's gland (carcinomas): M–0/40, 4/40 F–0/40, 1/40	[NS]	
		Malignant tumours: M–9/40, 14/40 F–11/40, 28/40	-	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, RF/J (M, F) Lifetime Maltoni *et al.* (1989), Mehlman (2002)	0 (control), 500 mg/kg bw benzene in olive oil once/d, 4–5 d/wk for 52 wk Male, 45/group Female, 40/group	**Mammary Gland** (carcinomas): M–0/45, 0/45 F–1/40, 9/40	[$P < 0.05$] (F)	99.93% pure
		Lung: All tumours: M–5/45, 23/45 F–3/40, 15/40	[$P < 0.005$] (M, F)	
		Adenocarcinomas: M–0/45, 0/45 F–0/40, 1/40	[NS]	
		Leukaemia: M–17/45, 26/45 F–14/40, 24/40	[NS]	
Mouse, C57Bl/6-Trp53 (F) 26 wk French & Saulnier (2000)	0 (control), 200 mg/kg bw benzene 5d/wk Controls – 20/group Dosed – 40/group	**Subcutis** (sarcomas): 0/20, 16/39	[$P < 0.001$]	> 99.9% pure vehicle unspecified
		Thymus (lymphomas): 0/20, 3/39	[NS]	
Mouse, haploinsufficient $p16^{Ink4a}/p19^{Arf}$ (M, F) 27 wk NTP (2007)	0 (control), 25, 50, 100, 200 mg/kg bw benzene in corn oil 5 d/wk 15/group	**Malignant lymphomas:** M–0/15, 0/15, 0/15, 0/15, 5/15	$P = 0.021$ (high dose) $P < 0.001$ (trend)	

d, day or days; F, female; i.p., intraperitoneal; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks; yr, year or years; bw, body weight

Table 3.3 Carcinogenicity studies in experimental animals exposed to benzene by intraperitoneal injection

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M, F) 24 wk Stoner *et al.* (1986)	0 (control), 480, 1 200, 2 400 mg/kg bw in tricaprylin vehicle 3x/wk for 8 wk 16/group	**Lung adenomas:** M–3/16, 5/15, 8/16, 10/16 F–4/16, 4/15, 4/16, 6/15	NR	Purity NR
		Tumours/ mouse: M–0.25 ± 0.58, 0.53 ± 0.92, 0.63 ± 0.72, 0.69 ± 0.60 F–0.31 ± 0.60, 0.44 ± 0.89, 0.25 ± 0.45, 0.47 ± 0.64	$P < 0.05$ (1 200 and 2 400 mg/kg) (M)	

F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks; bw, body weight

Table 3.4 Carcinogenicity studies in experimental animals exposed to benzene via skin application

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, hemizygous and homozygous Tg.AC (v-Ha-*ras*) (M, F) 20 wk Blanchard *et al.* (1998)	200 µl of acetone: vehicle control 200 µl benzene, neat 2–7x/wk 10 mice/treated group	Skin papillomas: Hemizygous Tg.AC M–6/65, 3/10 F–2/65, 4/10 Homozygous Tg.AC M–NR, 10/10 F–NR, 9/10	 [NS] [$P < 0.01$] - -	Purity NR
Mouse, hemizygous Tg.AC (v-Ha-*ras*) (M, F) 26 wk Holden *et al.* (1998)	G1: Untreated (shaved) G2: acetone 200 µl, 7d/wk, 20 wk G3: 100 µl benzene, 3x/wk, 20 wk G4: 150 µl benzene, 3x/wk, 20 wk 10 mice/group	Skin (papillomas): M–0/10, 0/10, 0/10, 3/10 F–0/10, 0/10, 1/10, 1/10	$P \leq 0.05$, G4 vs negative controls	Purity NR
Mouse, homozygous, FVB/N-Tg.AC (v-Ha-*ras*) (F) 32 wk French & Saulnier (2000)	0 µl/wk: 200 µl acetone 1/d 3x/wk for 20 wk (control) 450 µl/wk: 150 µl in 50 µl acetone 1/d, 3x/wk for 20 wk 800 µl/wk: 200µl neat, 2/d, 2/wk for 20 wk 20 mice/group	Granulocytic leukaemia: 0/19, 4/14*, 11/15*	*$P \leq 0.05$	> 99.9% pure

d, day or days; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks; yr, year or years

and of benign and malignant ovarian tumours, mammary gland carcinomas and carcinosarcomas, and Harderian gland carcinomas in female mice (NTP, 1986; Stoner *et al.*, 1986; Maronpot, 1987; Maltoni *et al.*, 1988, 1989; Huff *et al.*, 1989; Mehlman, 2002).

Increased multiplicity of lung adenomas was observed in male mice after intraperitoneal injection of benzene (Stoner *et al.*, 1986).

Exposure of genetically altered, tumour-prone mice to benzene by oral administration, skin application, or inhalation resulted in increased incidences of skin tumours (Blanchard *et al.* 1998; Holden *et al.*, 1998; French & Saulnier, 2000) and lymphohaematopoietic malignancies (French & Saulnier, 2000; NTP, 2007; Kawasaki *et al.*, 2009).

4. Other Relevant Data

4.1 Genetic and related effects

Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchange in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* but did not induce sister chromatid exchange in cultured human lymphocytes, except in one study in which high concentrations of an exogenous metabolic system were used. In some test systems, benzene induced cell transformation. It did not induce sister chromatid exchange in rodent cells *in vitro*, but it did induce aneuploidy and, in some studies, chromosomal aberrations in cultured Chinese hamster ovary cells. Benzene induced mutation and DNA damage in some studies in rodent cells *in vitro*. In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation and gene conversion in fungi. Benzene was not mutagenic to bacteria (IARC, 1982, 1987). Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene for decades (Forni, 1979; IARC, 1982; Eastmond, 1993; Zhang *et al.*, 2002; Holecková *et al.*, 2004).

4.2 Leukaemogenic potential of benzene

Benzene is carcinogenic to the bone marrow causing leukaemia and myelodysplastic syndromes (MDS) and probably also to the lymphatic system causing non-Hodgkin lymphoma. Its carcinogenic mechanism of action is likely to be different for these two target tissues and probably multifactorial in nature. The metabolism of benzene will be summarized below and a review is presented of the current state of knowledge on the mechanisms of leukaemia and lymphoma induction by benzene. With regard to leukaemia, probable mechanisms of leukaemogenesis in the myeloid series, mainly acute myeloid leukaemia (AML) and MDS are discussed. Then, potential mechanisms by which benzene could cause acute lymphocytic leukaemia (ALL) in both adults and children are reviewed. Finally, mechanisms for the benzene-induced development of non-Hodgkin lymphoma are summarized, including that of chronic lymphocytic leukaemia (CLL), as it is now classified as a form of lymphoma.

4.2.1 Metabolism of benzene and its relevance to carcinogenicity

Benzene must be metabolized to become carcinogenic (Ross, 2000; Snyder, 2004). Its metabolism is summarized in Fig. 4.1. The initial metabolic step involves cytochrome P450 (CYP)-dependent oxidation to benzene oxide,

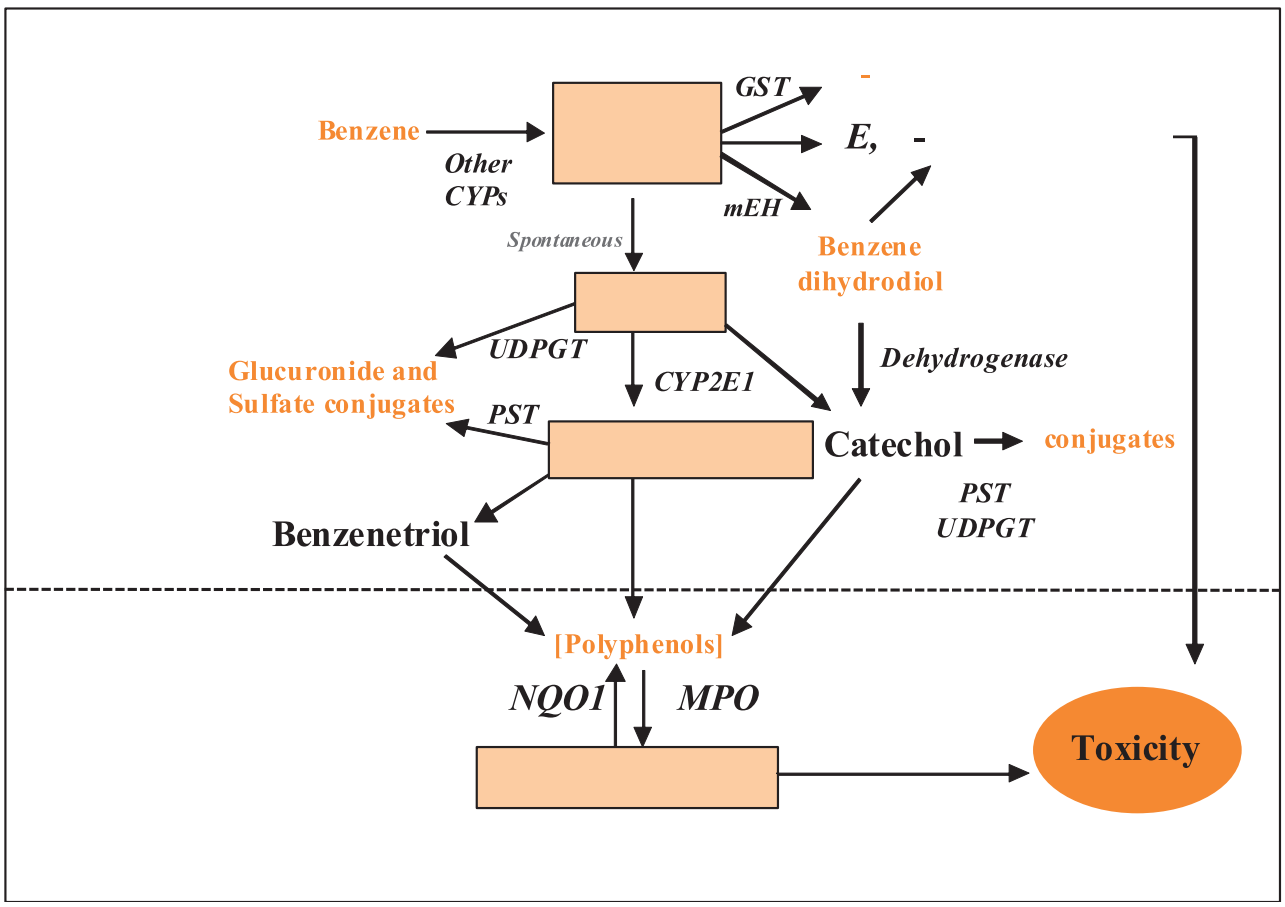
which exists in equilibrium with its tautomer oxepin. Most benzene oxide spontaneously rearranges to phenol, which is either excreted or further metabolized to hydroquinone and 1,4-benzoquinone. The remaining benzene oxide is either hydrolysed to produce benzene 1,2-dihydrodiol (catechol), which is further oxidized to 1,2-benzoquinone, or it reacts with glutathione to produce *S*-phenylmercapturic acid. Metabolism of oxepin is thought to open the aromatic ring, to yield the reactive muconaldehydes and *E,E*-muconic acid. Human exposure to benzene at concentrations in air between 0.1 and 10 ppm, results in urinary metabolite profiles with 70–85% phenol, 5–10% each of hydroquinone, *E,E*-muconic acid and catechol, and less than 1% of *S*-phenylmercapturic acid (Kim *et al.*, 2006b). Benzene oxide, the benzoquinones, muconaldehydes, and benzene dihydrodiol epoxides (formed from CYP-mediated oxidation of benzene dihydrodiol) are electrophiles that readily react with peptides, proteins and DNA (Bechtold *et al.*, 1992; McDonald *et al.*, 1993; Bodell *et al.*, 1996; Gaskell *et al.*, 2005; Henderson *et al.*, 2005; Waidyanatha & Rappaport, 2005) and can thereby interfere with cellular function (Smith, 1996). It remains unclear what role these different metabolites play in the carcinogenicity of benzene, but benzoquinone formation from hydroquinone via myeloperoxidase in the bone marrow has been suggested as being a key step (Smith, 1996). There is considerable evidence for an important role of this metabolic pathway that leads to benzoquinone formation, as the benzoquinone-detoxifying enzyme NAD(P)H:quinone oxidoreductase1 (NQO1) protects mice against benzene-induced myelodysplasia (Long *et al.*, 2002; Iskander & Jaiswal, 2005) and humans against the hematotoxicity of benzene (Rothman *et al.*, 1997). However, this does not rule out adverse effects from other metabolites.

Increased susceptibility to the toxic effects of benzene has been linked to genetic polymorphisms that increase the rate of metabolism of benzene to active intermediates, or decrease the rate of detoxification of these active intermediates (Rothman *et al.*, 1997; Xu *et al.*, 1998; Kim *et al.*, 2004).

Recently it has been shown that benzene is most likely metabolized initially to phenol and *E,E*-muconic acid via two enzymes rather than just one CYP enzyme, and that the putative, high-affinity enzyme is active primarily at benzene concentrations below 1 ppm (Rappaport *et al.*, 2009). CYP2E1 is the primary enzyme responsible for mammalian metabolism of benzene at higher levels of exposure (Valentine *et al.*, 1996; Nedelcheva *et al.*, 1999). CYP2F1 and CYP2A13 are reasonable candidate enzymes that are active at environmental levels of exposure below 1 ppm (Powley & Carlson, 2000; Sheets *et al.*, 2004; Rappaport *et al.*, 2009). These CYPs are highly expressed in the human lung. Despite much research, more work is needed to elucidate the different roles of multiple metabolites in the toxicity of benzene and the pathways that lead to their formation.

A role for the aryl-hydrocarbon receptor (AhR) is also emerging in the haematotoxicity of benzene. AhR is known mainly as the mediator for the toxicity of certain xenobiotics (Hirabayashi & Inoue, 2009). However, this transcription factor has many important biological functions and evidence is emerging that it has a significant role in the regulation of haematopoietic stem cells (Hirabayashi & Inoue, 2009; Singh *et al.*, 2009). It has been hypothesized that AhR expression is necessary for the proper maintenance of quiescence in these cells, and that AhR downregulation is essential for their "escape" from quiescence and subsequent proliferation (Singh *et al.*, 2009). It has been demonstrated that AhR-knockout (KO) ($AhR^{-/-}$) mice do not show any haematotoxicity after exposure to benzene (Yoon *et al.*, 2002). Follow-up studies have shown that mice that had been lethally irradiated and repopulated with marrow cells from AhR-KO mice did not display any sign of benzene-induced

Fig. 4.1 Simplified metabolic scheme for benzene showing major pathways and metabolizing enzymes leading to toxicity. CYP2E1, cytochrome P450 2E1; GST, glutathione-*S*-transferase; NQO1, NAD(P)H:quinone oxidoreductase 1; MPO, myeloperoxidase; UDPGT, Uridine diphosphate glucoronosyl transferase; PST, phenol sulphotransferase; mEH, microsomal epoxide hydrolase



haematotoxicity (Hirabayashi *et al.*, 2008). The most likely explanation for these findings is that the absence of AhR removes haematopoietic stem cells from their quiescent state and makes them susceptible to DNA damage from benzene exposure and subsequent cell death through apoptosis. Further research is needed to examine the effects of benzene and its metabolites on cycling and quiescent haematopoietic stem cells.

4.2.2 Mechanisms of myeloid leukaemia development

(a) General

AML and MDS are closely-related diseases of the bone marrow that arise de novo (without an obvious cause) in the general population or following therapy with alkylating agents, topoisomerase II inhibitors, or ionizing radiation (therapy-related AML and MDS, i.e. t-AML and t-MDS) (Pedersen-Bjergaard *et al.*, 2006, 2008). Occupational exposure to benzene is widely thought to cause leukaemias that are similar to various forms of t-AML and t-MDS (Irons

& Stillman, 1996; Larson & Le Beau, 2005; Zhang *et al.*, 2007). AML and MDS both arise from genetically altered CD34+ stem cells or progenitor cells in the bone marrow (Morgan & Alvares, 2005; Passegué & Weisman, 2005) and are characterized by many different types of recurrent chromosome aberrations (Pedersen-Bjergaard *et al.*, 2006; Mrózek & Bloomfield, 2008). These aberrations have been shown to often develop into the genetic mutations that produce leukaemia. Cytogenetic analysis of chromosome number and structure has therefore become important in diagnosis and treatment of MDS and AML (Pedersen-Bjergaard *et al.*, 2006; Mrózek & Bloomfield, 2008). Recent research has shown that the chromosome aberrations and gene mutations detected in therapy-related and de novo MDS and AML are identical, although the frequencies with which they are observed in different subtypes may differ (Pedersen-Bjergaard *et al.*, 2008). Hence, therapy-related and de novo MDS and AML are considered identical diseases (Pedersen-Bjergaard *et al.*, 2008).

At least three cytogenetic categories of AML and MDS are commonly observed: those with unbalanced aberrations, with balanced rearrangements, and with normal karyotype:

Unbalanced chromosome aberrations comprise primarily the loss of various parts of the long arm or loss of the whole chromosome 5 or 7 (5q–/–5 or 7q–/–7) and gain of a whole chromosome 8 (+8) (Pedersen-Bjergaard *et al.*, 2006, 2007, 2008). These cases often have a complex karyotype and carry point mutations of *TP53* or *AML1*. Unbalanced chromosome aberrations are common after therapy with alkylating agents.

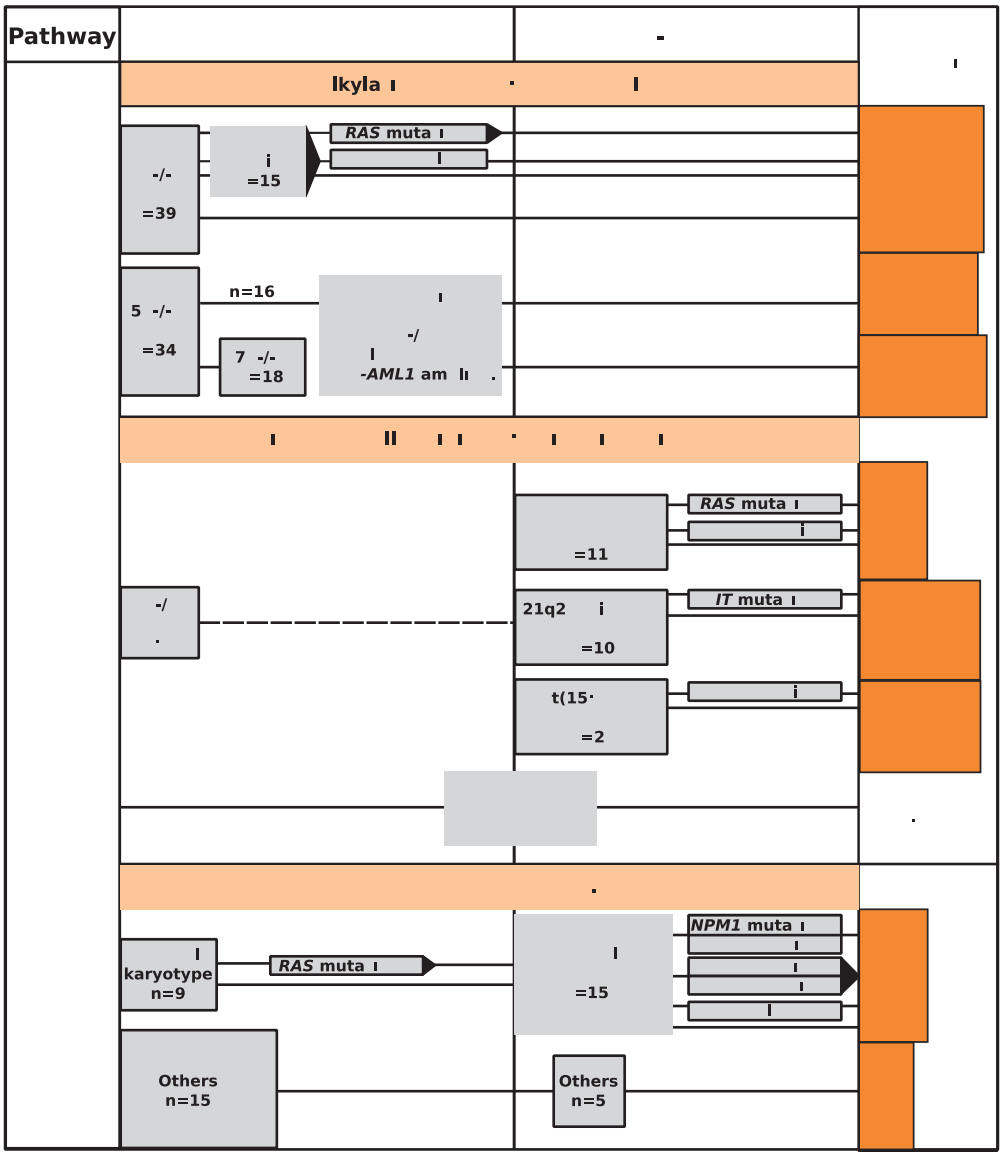
Balanced rearrangements are recurrent balanced translocations [e.g. t(11q23), t(8;21) and t(15;17)] or inversions [e.g. inv(16)], which arise, at least in the therapy-related subset of cases, as illegitimate gene recombinations related to functional inhibition of topoisomerase II (Pedersen-Bjergaard *et al.*, 2006, 2008). Among the most important rearranged transcription-factor genes are the mixed-lineage leukaemia (*MLL*) at 11q23, the *AML1* at 21q22, the retinoic-acid receptor-α *RARA* at 17q21 and the core-binding factor subunit-β (*CBFB*) at 16q22 (Pedersen-Bjergaard *et al.*, 2007).

Cases with a normal karyotype often harbour mutations of the *NPM1* gene (which encodes nucleophosmin), internal tandem duplications of the *FLT3* gene (which encodes fms-related tyrosine kinase), and/or point mutations or an altered methylation status of the *C/EBPα* gene (which encodes CCAAT/enhancer binding protein α) (Cuneo *et al.*, 2002; Pedersen-Bjergaard *et al.*, 2006, 2007, 2008; Hackanson *et al.*, 2008).

Within these three cytogenetic categories there are at least eight different genetic pathways that lead to MDS and AML, as defined by the specific chromosome aberrations present in each (Pathways I –VIII in Fig. 4.2). As more becomes clear about the molecular cytogenetics of leukaemia, it seems likely that many other pathways to AML and MDS will be discovered. For example, recent unbiased high-resolution genomic screens have identified many genes not previously implicated in AML that may be relevant for pathogenesis, along with many known oncogenes and tumour-suppressor genes (Ley *et al.*, 2008; Mardis *et al.*, 2009; Walter *et al.*, 2009).

Another classical pathway to AML is through the transformation of a myeloproliferative disorder (MPD) (Abdulkarim *et al.*, 2009), although there is less evidence for this pathway as a relevant mechanism to benzene-induced AML. MPDs include Philadelphia chromosome (Ph)-positive chronic myelogenous leukaemia (CML) and the Ph-negative conditions *polycythemia vera*, essential trombocythemia and idiopathic myelofibrosis. It is well established that AML may occur as a late complication in all these disorders. Over the first ten years after diagnosis, the incidence of leukaemic transformation is reported to be higher in patients with idiopathic myelofibrosis (8–23%) compared with

Fig. 4.2 Genetic Pathways to Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukaemia



From Pedersen-Bjergaard *et al.* (2006)

patients with essential trombocythemia (0.5–1%) and *polycythemia vera* (1–4%) (Abdulkarim *et al.*, 2009). Thus, benzene may first produce an MPD, which later transforms into AML.

An important role for epigenetic changes is also emerging in association with the development of leukaemia. Functional loss of the CCAAT/enhancer binding protein α (*C/EBPα*) (also known as CEBPA), a central regulatory transcription factor in the haematopoietic system, can result in a differentiation block in granulopoiesis and thus contribute to leukaemic transformation (Fröhling & Döhner, 2004). Recent work has shown that epigenetic alterations of *C/EBPα* occur frequently in AML and that *C/EBPα* mRNA is a target for miRNA-124a (Hackanson *et al.*, 2008). This miRNA is frequently silenced by epigenetic mechanisms in leukaemia cell lines. *C/EBPα* is also capable of controlling *miRNA-223* expression, which is vital in granulocytic differentiation (Fazi *et al.*, 2005). Altered expression of several miRNAs is also observed in some forms of AML (Dixon-McIver *et al.*, 2008; Marcucci *et al.*, 2008).

(b) *Mechanisms of benzene-induced myeloid leukaemia development*

There is strong evidence that benzene can induce AML via pathways I, II and IV, considerable supporting evidence for pathway V, some evidence for pathway III, but little information regarding pathways VI–VIII (see Fig. 4.2). Exposure to benzene has been associated with higher levels of the chromosomal changes commonly observed in AML, including 5q–/–5 or 7q–/–7, +8, and t(8;21) in the blood cells of highly exposed workers (Smith *et al.*, 1998; Zhang *et al.*, 1999, 2002). The benzene metabolite hydroquinone produces these same changes in cultured human cells, including cultures of CD34+ progenitor cells (Smith *et al.*, 2000; Stillman *et al.*, 2000). This provides strong evidence for the induction by benzene of AML via pathways I, II and IV (see Fig. 4.2).

Pathways III, IV and V are related to the inhibition of the DNA-related enzyme topoisomerase II, which is essential for the maintenance of proper chromosome structure and segregation; it removes knots and tangles from the genetic material by passing an intact double helix through a transient double-stranded break that it creates in a separate segment of DNA (McClendon & Osheroff, 2007; Bandele & Osheroff, 2009). To maintain genomic integrity during its catalytic cycle, topoisomerase II forms covalent bonds between active-site tyrosyl residues and the 5′-DNA termini created by cleavage of the double helix (Bandele & Osheroff, 2009). Normally, these covalent topoisomerase II-cleaved DNA complexes (known as cleavable complexes) are fleeting intermediates and are tolerated by the cell. However, when the concentration or longevity of cleavage complexes increases significantly, DNA double-strand breaks occur (Lindsey *et al.*, 2004). If topoisomerase II–induced double-strand breaks are incorrectly repaired, two unrelated (nonhomologous) chromosomes are fused together to produce translocations or inversions (Deweese & Osheroff, 2009).

There are different types of topoisomerase-II inhibitors. Epidophyllotoxins, such as etoposide, cause chromosome damage and kill cells by increasing physiological levels of topoisomerase II-DNA cleavage complexes (Baker *et al.*, 2001; Felix, 2001; Deweese & Osheroff, 2009). These drugs are referred to as topoisomerase-II poisons to distinguish them from catalytic inhibitors of the enzyme because they convert this essential enzyme to a potent cellular toxin. Other drugs, such as merbarone, act as inhibitors of topo-II activity but, in contrast to etoposide they do not stabilize topoisomerase II-DNA cleavable complexes. Nevertheless, they are potent clastogens both in vitro and in vivo (Wang *et al.*, 2007).

Several studies have shown that benzene in vivo, and its reactive metabolites hydroquinone

and 1,4-benzoquinone in vitro, inhibit the functionality of topoisomerase II and enhance DNA cleavage (Chen & Eastmond, 1995; Frantz *et al.*, 1996; Hutt & Kalf, 1996; Eastmond *et al.*, 2001; Fung *et al.*, 2004; Lindsey *et al.*, 2004, 2005; Whysner *et al.*, 2004). Bioactivation of hydroquinone by myeloperoxydase to 1,4-benzoquinone enhances topoisomerase-II inhibition (Eastmond *et al.*, 2005). Indeed, 1,4-benzoquinone was shown to be a more potent topoisomerase-II inhibitor than hydroquinone in a cell-free assay system (Hutt & Kalf, 1996; Baker *et al.*, 2001). These findings demonstrate that benzene through its reactive quinone metabolites can inhibit topoisomerase II and probably cause leukaemias with chromosome translocations and inversions known to be generated by topoisomerase-II inhibitors, including AMLs harbouring t(21q22), t(15;17) and inv(16) in a manner consistent with pathways IV and V (Andersen *et al.*, 2002; Voltz *et al.* 2004; Mistry *et al.*, 2005; Pedersen-Bjergaard *et al.*, 2007, 2008). The evidence for rearrangements of the mixed lineage leukaemia (*MLL*) gene through t(11q23) via pathway III in benzene-induced leukaemia is less convincing but may occur through an apoptotic pathway (Vaughan *et al.*, 2005).

AML can arise de novo via pathways VII and VIII without apparent chromosome abnormalities, but molecular analysis has revealed many genetic changes in these apparently normal leukemias, including mutations of *NPM1, AML1, FLT3, RAS* and *C/EBPα*. (Fig. 4.2; Cuneo *et al.*, 2002; Falini *et al.*, 2007; Mardis *et al.*, 2009). More work is needed to clarify the ability of benzene and its metabolites to produce mutations of the type found in these leukaemias, along with those found in Ph-negative MPDs such as Janus kinase 2 (*JAK2*), and somatic mutations in the ten-eleven translocation 2 (*TET2*) oncogene, which are found in about 15% of patients with various myeloid cancers (Delhommeau *et al.*, 2009). One potential mechanism for the induction of such mutations is through the generation of reactive oxygen species.

The ability of benzene and/or its metabolites to induce epigenetic changes related to the development of leukaemia, such as altered methylation status of *C/EBPα,* is unclear at this time. Bollati *et al.* (2007) reported that hypermethylation in *p15* (+0.35%; $P = 0.018$) and hypomethylation in the *MAGE-1* gene (encoding the human melanoma antigen) (–0.49%; $P = 0.049$) were associated with very low exposures to benzene (~22 ppb) in healthy subjects including gas-station attendants and traffic-police officers, although the corresponding effects on methylation were very low. Further study of the role epigenetics in the haematotoxicity and carcinogenicity of benzene is warranted, including studies of aberrant DNA methylation and altered microRNA expression.

While benzene and its metabolites are clearly capable of producing multiple forms of chromosomal mutation, including various translocations, deletions and aneuploidies, these are usually insufficient as a single event to explain the induction of leukaemia (Guo *et al.*, 2008; Lobato *et al.*, 2008). Other secondary events, such as specific gene mutations and/or other chromosome changes, are usually required (Guo *et al.*, 2008; Lobato *et al.*, 2008). Thus, benzene-induced leukaemia probably begins as a mutagenic event in the stem cell or progenitor cell and subsequent genomic instability allows for sufficient mutations to be acquired in a relatively short time. Studies have shown that the benzene metabolite hydroquinone is similar to ionizing radiation in that it induces genomic instability in the bone marrow of susceptible mice (Gowans *et al.*, 2005). Recent findings showing the importance of genes involved in DNA repair and maintenance – such as the *WRN* gene encoding the Werner syndrome protein – in determining genetic susceptibility to the toxicity of benzene also support this mechanism (Shen *et al.*, 2006; Lan *et al.*, 2009; Ren *et al.*, 2009).

Haematotoxic effects may also contribute to leukaemogenesis from benzene. Haematopoietic stem cells occupy an ordered environment in the bone marrow and interact with supportive stromal cells and mature lymphocytes. Haematotoxic damage to this ordered stem-cell microenvironment most likely allows for the clonal expansion of the leukaemic stem cells. This dual mode of action for benzene fits with the known ability of benzene metabolites to induce chromosomal mutations and genomic instability in blood stem cells and progenitor cells, and with the fact that haematotoxicity is associated with an increased risk for benzene-induced haematopoietic malignancies (Rothman *et al.*, 1997).

Thus, exposure to benzene can lead to multiple alterations that contribute to the leukaemogenic process. Benzene may act by causing chromosomal damage (aneuploidy, deletions and translocations) through inhibition of topoisomerase II, disruption of microtubules and other mechanisms; by generating oxygen radicals that lead to point mutations, strand breaks and oxidative stress; by causing immune system dysfunction that leads to decreased immunosurveillance (Cho, 2008; Li *et al.*, 2009); by altering stem-cell pool sizes through haematotoxic effects (Irons *et al.*, 1992); by inhibiting gap-junction intercellular communication (Rivedal & Witz, 2005); and by altering DNA methylation and perhaps specific microRNAs. This multimodal mechanism of action for benzene suggests that the effects of benzene on the leukaemogenic process are not singular and can occur throughout the process.

4.2.3 Potential mechanisms of benzene-induced acute lymphocytic leukaemia (ALL) development

Evidence of an association between exposure to benzene from air pollution and childhood leukaemia is growing. The most common form of childhood leukaemia is ALL, with AML being less common at around 15% of the incidence of ALL. The opposite is true for adults where the ratio is reversed, with AML being predominant. Reasons for this difference were suggested to be age-related defects in lymphopoiesis (Signer *et al.*, 2007). Studies with a murine model of chronic myeloid leukaemia – an adult-onset malignancy that arises from transformation of haematopoietic stem cells by the breakpoint cluster region-Ableson (*BCR-ABL*^{P210}) oncogene – demonstrated that young bone-marrow cells transformed with *BCR-ABL*^{P210} initiated both MPD and B-lymphoid leukaemia, whereas *BCR-ABL*^{P210}-transformed old bone-marrow cells recapitulated the human disease by inducing MPD with rare lymphoid involvement (Signer *et al.*, 2007). Thus, if benzene were to induce a leukaemia-related oncogenic mutation in young bone-marrow cells, it could produce either an MPD that transformed to AML, or a B-cell ALL, whereas exposure in an adult would have only a very limited chance of producing ALL.

The long-standing distinction between AML and ALL also has become somewhat blurred in recent years. Both forms of leukaemia arise in pluripotential stem cells or early progenitor cells in the bone marrow. Either disease can occur under conditions that formerly seemed restricted to AML. These include ALL occurring in the acute leukaemia seen in Down Syndrome (Kearney *et al.*, 2009); in secondary leukaemias related to chemotherapy (Lee *et al.*, 2009); and in the blast crisis of chronic myelogenous leukaemia (Calabretta & Perrotti, 2004). Similarly, the Philadelphia chromosome, long considered to be specific to chronic myelogenous leukaemia, is also the most common chromosome rearrangement in adult ALL (Ravandi & Kebriaei, 2009).

Since the genotoxic action of benzene metabolites on pluripotent precursor cells in the bone marrow appears promiscuous, producing multiple genetic abnormalities, it seems probable that exposure to benzene can initiate both AML and ALL by causing the chromosomal rearrangements

and mutations that are on the causal pathway to these malignancies. For childhood ALL and AML it has been shown that the disease is usually initiated *in utero*, since leukaemic translocations and other genetic changes have been detected in blood spots collected at birth (Wiemels *et al.*, 1999; Wiemels *et al.*, 2002; Greaves & Wiemels, 2003; McHale *et al.*, 2003). Thus, exposure of the mother, and perhaps even the father, to benzene could be just as important as exposure of the child in producing childhood AML and ALL, as has been suggested in several epidemiological studies (van Steensel-Moll *et al.*, 1985; McKinney *et al.*, 1991; Shu *et al.*, 1999; Scélo *et al.*, 2009). Supporting this hypothesis is an animal study demonstrating that *in utero* exposure to benzene increases the frequency of micronuclei and DNA recombination events in haematopoietic tissue of fetal and post-natal mice (Lau *et al.*, 2009). Another study showed that oxygen radicals play a key role in the development of *in utero*-initiated benzene toxicity through disruption of haematopoietic cell-signalling pathways (Badham & Winn, 2010). These studies support the idea that genotoxic and non-genotoxic events following exposure to benzene may be initiators of childhood leukaemia *in utero*.

4.2.4 Mechanisms of lymphoma development

(a) General

Lymphoma is a cancer of the immune system that includes over 40 malignant diseases originating from B- and T-lymphocytes and natural killer (NK) cells (Swerdlow *et al.*, 2008). It is therefore not surprising that functional disorders of immune-system cells are associated with a risk for malignant transformation. Immune deficiency is one of the strongest known risk factors for non-Hodgkin lymphoma (NHL) (Hartge & Smith, 2007). The risk for NHL increases with the degree of immune deficiency, and there is no evidence of a threshold (Grulich *et al.*, 2007). Thus, even modest immunosuppression, especially at the local level, may increase the risk for lymphoma.

It is well recognized that lymphomas, like other tumours, develop according to a multistep pathogenic process (Smith *et al.*, 2004). Clonal progression of an initiated cell to a clone of highly malignant cells is well documented. Natural selection of clones already present within oligoclonal expansions gives rise to true monoclonal lymphomas. Thus, it is possible to make generalizations about the type of molecular mechanism responsible for each of the stages involved in lymphomagenesis. For example, a cell may become initiated and genetically unstable through errors in recombination and DNA repair, which could be spontaneous or induced by an exogenous chemical agent. Other early molecular events often inhibit apoptosis and lead to the expansion of an intrinsically genetically unstable population of cells, which is at risk for additional genetic events and tumour progression. An example is the t(14;18) chromosome translocation associated with B-cell lymphoma 2 gene *BCL2* dysregulation, which inhibits apoptosis (Cimmino *et al.*, 2005; Thomadaki & Scorilas, 2006). Normally, one of the key protectors against the selection and progression of malignant clones of cells into full-blown lymphoma is local immunosurveillance in which activated T-cells kill the mutated clones. It is generally accepted that if this immunosurveillance is no longer intact, e.g. in immuno-suppressed individuals, then the malignant cells divide and grow rapidly, collecting more mutations to become aggressive, rapidly growing tumours.

(b) Mechanisms of benzene-induced lymphoma development

From the discussion above, there are at least two probable mechanisms by which exposure to benzene could enhance the incidence of lymphoma, i.e. by inducing chromosome rearrangements associated with NHL, and through

immunosuppression leading to decreased immunosurveillance.

Benzene is well known to produce multiple cytogenetic abnormalities in lymphocytes (Tough & Brown, 1965; Forni, 1971, 1979; Picciano, 1979; Smith & Zhang, 1998; Zhang *et al.*, 2002). Further, benzene induces specific chromosomal changes associated with NHL in human lymphocytes (Zhang *et al.*, 2007). Fluorescence in situ hybridization (FISH) analysis showed increased levels of t(14;18) and del(6q) in benzene-exposed workers, but the higher levels of t(14;18) could not be confirmed in a follow-up study by use of real time-PCR (polymerase chain reaction) (McHale *et al.*, 2008). This may be because the PCR method only detected 50% of t(14;18) translocations or that the FISH method detects non-functional as well as functional translocations. Reduced immunosurveillance is another potential mechanism of NHL induction by benzene. The importance of T-cell immunosurveillance in preventing B-cell neoplasia is well established and is carried out by activated cytotoxic T lymphocytes. The toxic effects of benzene on T-cells is well documented and there appears to be a selective effect on $CD4^+$ T-lymphocytes resulting in a lowering of the $CD4^+/CD8^+$ ratio (Lan *et al.*, 2004). This immunosuppressive pattern is similar to the early onset of acquired immuno-deficiency syndrome (AIDS), and although it is not as severe it may be associated with an increased risk for NHL (Grulich *et al.*, 2007). Thus, benzene, like other leukaemogens including alkylating agents, topoisomerase inhibitors, and ionizing radiation, may cause NHL through a combination of immunosuppression and DNA double-strand break induction that leads to illegitimate recombination and chromosome rearrangements in lymphoid cells.

Thus, the biological plausibility of benzene as a cause of lymphoproliferative disorders has been strengthened in recent years. There are additional studies demonstrating that benzene produces lymphomas in laboratory animals, and a recent study showing that it does so simultaneously with AML in *Tp53*-deficient mice (Kawasaki *et al.*, 2009). Multiple studies show that it produces genotoxicity in the lymphocytes of exposed humans. Accordingly, there is considerable support for the notion that it is biologically plausible for benzene to cause human lymphatic tumours.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia.

Also, a positive association has been observed between exposure to benzene and acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma.

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

There is strong evidence that benzene metabolites, acting alone or in concert, produce multiple genotoxic effects at the level of the pluripotent haematopoietic stem cell resulting in chromosomal changes in humans consistent with those seen in haematopoietic cancer. In multiple studies in different occupational populations in many countries over more than three decades a variety of genotoxic changes, including chromosomal abnormalities, have been found in the lymphocytes of workers exposed to benzene.

Benzene is *carcinogenic to humans (Group 1).*

References

Abdulkarim K, Girodon F, Johansson P *et al.* (2009). AML transformation in 56 patients with Ph- MPD in two well defined populations. *Eur J Haematol*, 82: 106–111. doi:10.1111/j.1600-0609.2008.01163.x PMID:19134023

Adegoke OJ, Blair A, Shu XO *et al.* (2003). Occupational history and exposure and the risk of adult leukemia in

Shanghai. *Ann Epidemiol*, 13: 485–494. doi:10.1016/S1047-2797(03)00037-1 PMID:12932623

Andersen MK, Larson RA, Mauritzson N *et al.* (2002). Balanced chromosome abnormalities inv(16) and t(15;17) in therapy-related myelodysplastic syndromes and acute leukemia: report from an international workshop. *Genes Chromosomes Cancer*, 33: 395–400. doi:10.1002/gcc.10043 PMID:11921273

ATSDR (1997). *Toxicological Profile for Benzene*. Update (Final Report), (NTIS Accession No. PB98–101157). Atlanta, GA: Agency for Toxic Substances and Disease Registry, pp. 459

ATSDR (2007). *Toxicological Profile for Benzene*. Atlanta, GA: Agency for Toxic Substances and Disease Registry, pp. 438

Badham HJ & Winn LM (2010). In utero exposure to benzene disrupts fetal hematopoietic progenitor cell growth via reactive oxygen species. *Toxicol Sci*, 113: 207–215. doi:10.1093/toxsci/kfp242 PMID:19812361

Baker RK, Kurz EU, Pyatt DW *et al.* (2001). Benzene metabolites antagonize etoposide-stabilized cleavable complexes of DNA topoisomerase IIalpha. *Blood*, 98: 830–833. doi:10.1182/blood.V98.3.830 PMID:11468185

Bandele OJ & Osheroff N (2009). Cleavage of plasmid DNA by eukaryotic topoisomerase II. *Methods Mol Biol*, 582: 39–47. doi:10.1007/978-1-60761-340-4_4 PMID:19763940

Bechtold WE, Willis JK, Sun JD *et al.* (1992). Biological markers of exposure to benzene: S-phenylcysteine in albumin. *Carcinogenesis*, 13: 1217–1220. doi:10.1093/carcin/13.7.1217 PMID:1638689

Björk J, Albin M, Welinder H *et al.* (2001). Are occupational, hobby, or lifestyle exposures associated with Philadelphia chromosome positive chronic myeloid leukaemia? *Occup Environ Med*, 58: 722–727. doi:10.1136/oem.58.11.722 PMID:11600728

Blair A, Zheng T, Linos A *et al.* (2001). Occupation and leukemia: a population-based case-control study in Iowa and Minnesota. *Am J Ind Med*, 40: 3–14. doi:10.1002/ajim.1066 PMID:11439392

Blanchard KT, Ball DJ, Holden HE *et al.* (1998). Dermal carcinogenicity in transgenic mice: relative responsiveness of male and female hemizygous and homozygous Tg.AC mice to 12-O-tetradecanoylphorbol 13-acetate (TPA) and benzene. *Toxicol Pathol*, 26: 541–547. doi:10.1177/019262339802600410 PMID:9715513

Bloemen LJ, Youk A, Bradley TD *et al.* (2004). Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. *Occup Environ Med*, 61: 270–274. doi:10.1136/oem.2003.007013 PMID:14985523

Bodell WJ, Pathak DN, Lévay G *et al.* (1996). Investigation of the DNA adducts formed in B6C3F1 mice treated with benzene: implications for molecular dosimetry. *Environ Health Perspect*, 104: Suppl 61189–1193. PMID:9118892

Bollati V, Baccarelli A, Hou L *et al.* (2007). Changes in DNA methylation patterns in subjects exposed to low-dose benzene. *Cancer Res*, 67: 876–880. doi:10.1158/0008-5472.CAN-06-2995 PMID:17283117

Bolstad-Johnson DM, Burgess JL, Crutchfield CD *et al.* (2000). Characterization of firefighter exposures during fire overhaul. *AIHAJ*, 61: 636–641. doi:10.1202/0002-8894(2000)061<0636:COFEDF>2.0.CO;2 PMID:11071414

Brugnone F, Perbellini L, Romeo L *et al.* (1998). Benzene in environmental air and human blood. *Int Arch Occup Environ Health*, 71: 554–559. doi:10.1007/s004200050323 PMID:9860165

Burridge E (2007). Chemical Profile: Benzene. *ICIS Chemical Business (Europe/Middle East/Asia)*, **2**(57): 36

Calabretta B & Perrotti D (2004). The biology of CML blast crisis. *Blood*, 103: 4010–4022. doi:10.1182/blood-2003-12-4111 PMID:14982876

Capleton AC & Levy LS (2005). An overview of occupational benzene exposures and occupational exposure limits in Europe and North America. *Chem Biol Interact*, 153-154: 43–53. doi:10.1016/j.cbi.2005.03.007 PMID:15935799

CAREX (1999). Carex: industry specific estimates – Summary. Available at http://www.ttl.fi/en/chemical_safety/carex/Documents/5_exposures_by_agent_and_industry.pdf

Carrer P, Maroni M, Alcini D *et al.* (2000). Assessment through environmental and biological measurements of total daily exposure to volatile organic compounds of office workers in Milan, Italy. *Indoor Air*, 10: 258–268. doi:10.1034/j.1600-0668.2000.010004258.x PMID:11089330

Caux C, O'Brien C, Viau C (2002). Determination of firefighter exposure to polycyclic aromatic hydrocarbons and benzene during fire fighting using measurement of biological indicators. *Appl Occup Environ Hyg*, 17: 379–386. doi:10.1080/10473220252864987 PMID:12018402

Chen H & Eastmond DA (1995). Topoisomerase inhibition by phenolic metabolites: a potential mechanism for benzene's clastogenic effects. *Carcinogenesis*, 16: 2301–2307. doi:10.1093/carcin/16.10.2301 PMID:7586126

Cho JY (2008). Suppressive effect of hydroquinone, a benzene metabolite, on in vitro inflammatory responses mediated by macrophages, monocytes, and lymphocytes. *Mediators Inflamm*, 2008: 298010 doi:10.1155/2008/298010 PMID:19148301

Cimmino A, Calin GA, Fabbri M *et al.* (2005). miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci USA*, 102: 13944–13949. doi:10.1073/pnas.0506654102 PMID:16166262

Cocco P, t'Mannetje A, Fadda D *et al.* (2010). Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. *Occup*

Environ Med, 67: 341–347. doi:10.1136/oem.2009.046839 PMID:20447988

Collingwood KW, Raabe GK, Wong O (1996). An updated cohort mortality study of workers at a northeastern United States petroleum refinery. *Int Arch Occup Environ Health*, 68: 277–288. doi:10.1007/BF00409412 PMID:8832292

Collins JJ, Ireland B, Buckley CF, Shepperly D (2003). Lymphohaematopoeitic cancer mortality among workers with benzene exposure. *Occup Environ Med*, 60: 676–679. doi:10.1136/oem.60.9.676 PMID:12937190

CONCAWE (1986). Review of the European Oil Industry Benzene Exposure Data, Report 3/86. Den Haag, The Netherlands: CONCAWE

CONCAWE (2000). A Review of European Gasoline Exposure Data for the Period 1993–1998, Report 2/00. Brussels, Belgium: CONCAWE

CONCAWE (2002). A Survey of European Gasoline Exposures for the Period 1999–2001, Report 9/02. Brussels, Belgium: CONCAWE

Consonni D, Pesatori AC, Tironi A *et al.* (1999). Mortality study in an Italian oil refinery: extension of the follow-up. *Am J Ind Med*, 35: 287–294. doi:10.1002/(SICI)1097-0274(199903)35:3<287::AID-AJIM9>3.0.CO;2-F PMID:9987562

Costantini AS, Benvenuti A, Vineis P *et al.* (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: evidence from the Italian Multicenter Case-control study. *Am J Ind Med*, 51: 803–811. doi:10.1002/ajim.20592 PMID:18651579

Crebelli R, Tomei F, Zijno A *et al.* (2001). Exposure to benzene in urban workers: environmental and biological monitoring of traffic police in Rome. *Occup Environ Med*, 58: 165–171. doi:10.1136/oem.58.3.165 PMID:11171929

Cronkite EP, Bullis JE, Inoue T, Drew RT (1984). Benzene inhalation produces leukemia in mice. *Toxicol Appl Pharmacol*, 75: 358–361. doi:10.1016/0041-008X(84)90219-9 PMID:6474468

Cronkite EP, Drew RT, Inoue T *et al.* (1989). Hematotoxicity and carcinogenicity of inhaled benzene. *Environ Health Perspect*, 82: 97–108.

Crump KS (1994). Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. *J Toxicol Environ Health*, 42: 219–242. doi:10.1080/15287399409531875 PMID:8207757

Cuneo A, Bigoni R, Cavazzini F *et al.* (2002). Incidence and significance of cryptic chromosome aberrations detected by fluorescence in situ hybridization in acute myeloid leukemia with normal karyotype. *Leukemia*, 16: 1745–1751. doi:10.1038/sj.leu.2402605 PMID:12200689

Delhommeau F, Dupont S, Della Valle V *et al.* (2009). Mutation in TET2 in myeloid cancers. *N Engl J Med*, 360: 2289–2301. doi:10.1056/NEJMoa0810069 PMID:19474426

Deweese JE & Osheroff N (2009). The DNA cleavage reaction of topoisomerase II: wolf in sheep's clothing. *Nucleic Acids Res*, 37: 738–748. doi:10.1093/nar/gkn937 PMID:19042970

Divine BJ, Hartman CM, Wendt JK (1999b). Update of the Texaco mortality study 1947–93: part II. Analysis of specific causes of death for white men employed in refining, research and petrochemicals. *Occup Environ Med*, 56: 174–180. doi:10.1136/oem.56.3.174 PMID:10448326

Dixon-McIver A, East P, Mein CA *et al.* (2008). Distinctive patterns of microRNA expression associated with karyotype in acute myeloid leukaemia. *PLoS ONE*, 3: e2141 doi:10.1371/journal.pone.0002141 PMID:18478077

Dryver E, Brandt L, Kauppinen T, Olsson H (2004). Occupational exposures and non-Hodgkin's lymphoma in Southern Sweden. *Int J Occup Environ Health*, 10: 13–21. PMID:15070021

Duarte-Davidson R, Courage C, Rushton L, Levy L (2001). Benzene in the environment: an assessment of the potential risks to the health of the population. *Occup Environ Med*, 58: 2–13. doi:10.1136/oem.58.1.2 PMID:11119628

Eastmond DA (1993). Induction of micronuclei and aneuploidy by the quinone-forming agents benzene and o-phenylphenol. *Toxicol Lett*, 67: 105–118. doi:10.1016/0378-4274(93)90049-4 PMID:8451753

Eastmond DA, Mondrala ST, Hasegawa L (2005). Topoisomerase II inhibition by myeloperoxidase-activated hydroquinone: a potential mechanism underlying the genotoxic and carcinogenic effects of benzene. *Chem Biol Interact*, 153-154: 207–216. doi:10.1016/j.cbi.2005.03.024 PMID:15935818

Eastmond DA, Schuler M, Frantz C *et al.* (2001). Characterization and mechanisms of chromosomal alterations induced by benzene in mice and humans. *Res Rep Health Eff Inst*, 103: 1–68, discussion 69–80. PMID:11504146

Egeghy PP, Hauf-Cabalo L, Gibson R, Rappaport SM (2003). Benzene and naphthalene in air and breath as indicators of exposure to jet fuel. *Occup Environ Med*, 60: 969–976. doi:10.1136/oem.60.12.969 PMID:14634191

Fabbro-Peray P, Daures JP, Rossi JF (2001). Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes Control*, 12: 201–212. doi:10.1023/A:1011274922701 PMID:11405325

Falini B, Nicoletti I, Martelli MF, Mecucci C (2007). Acute myeloid leukemia carrying cytoplasmic/mutated nucleophosmin (NPMc+ AML): biologic and clinical features. *Blood*, 109: 874–885. doi:10.1182/blood-2006-07-012252 PMID:17008539

Farris GM, Everitt JI, Irons RD, Popp JA (1993). Carcinogenicity of inhaled benzene in CBA mice.

Fundam Appl Toxicol, 20: 503–507. doi:10.1006/faat.1993.1061 PMID:8314465

Fazi F, Rosa A, Fatica A *et al.* (2005). A minicircuitry comprised of microRNA-223 and transcription factors NFI-A and C/EBPalpha regulates human granulopoiesis. *Cell*, 123: 819–831. doi:10.1016/j.cell.2005.09.023 PMID:16325577

Felix CA (2001). Leukemias related to treatment with DNA topoisomerase II inhibitors. *Med Pediatr Oncol*, 36: 525–535. doi:10.1002/mpo.1125 PMID:11340607

Forni A (1971). Chromosome studies in workers exposed to benzene or toluene or both. *Arch Environ Health*, 22: 373–378. PMID:5162138

Forni A (1979). Chromosome changes and benzene exposure. A review. *Rev Environ Health*, 3: 5–17. PMID:395589

Frantz CE, Chen H, Eastmond DA (1996). Inhibition of human topoisomerase II in vitro by bioactive benzene metabolites. *Environ Health Perspect*, 104: Suppl 61319–1323. PMID:9118913

French JE & Saulnier M (2000). Benzene leukemogenesis: an environmental carcinogen-induced tissue-specific model of neoplasia using genetically altered mouse models. *J Toxicol Environ Health A*, 61: 377–379. doi:10.1080/00984100050166389 PMID:11086942

Fröhling S & Döhner H (2004). Disruption of C/EBPalpha function in acute myeloid leukemia. *N Engl J Med*, 351: 2370–2372. doi:10.1056/NEJMp048241 PMID:15575052

Fu H, Demers PA, Costantini AS *et al.* (1996). Cancer mortality among shoe manufacturing workers: an analysis of two cohorts. *Occup Environ Med*, 53: 394–398. doi:10.1136/oem.53.6.394 PMID:8758034

Fung J, Hoffmann MJ, Kim DD, Snyder R (2004). Inhibition of topoisomerase II in 32D.3(G) cells by hydroquinone is associated with cell death. *J Appl Toxicol*, 24: 183–188. doi:10.1002/jat.960 PMID:15211611

Fustinoni S, Buratti M, Giampiccolo R, Colombi A (1995). Biological and environmental monitoring of exposure to airborne benzene and other aromatic hydrocarbons in Milan traffic wardens. *Toxicol Lett*, 77: 387–392. doi:10.1016/0378-4274(95)03322-X PMID:7618166

Gaskell M, McLuckie KI, Farmer PB (2005). Genotoxicity of the benzene metabolites para-benzoquinone and hydroquinone. *Chem Biol Interact*, 153-154: 267–270. doi:10.1016/j.cbi.2005.03.034 PMID:15935826

Gérin M, Siemiatycki J, Désy M, Krewski D (1998). Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal. *Am J Ind Med*, 34: 144–156. doi:10.1002/(SICI)1097-0274(199808)34:2<144::AID-AJIM7>3.0.CO;2-X PMID:9651624

Glass DC, Gray CN, Jolley DJ *et al.* (2003). Leukemia risk associated with low-level benzene exposure. *Epidemiology*, 14: 569–577. doi:10.1097/01.ede.0000082001.05563.e0 PMID:14501272

Gobba F, Rovesti S, Borella P *et al.* (1997). Inter-individual variability of benzene metabolism to *trans,trans*-muconic acid and its implications in the biological monitoring of occupational exposure. *Sci Total Environ*, 199: 41–48. doi:10.1016/S0048-9697(97)05480-6 PMID:9200846

Goldstein BD, Snyder CA, Laskin S *et al.* (1982). Myelogenous leukemia in rodents inhaling benzene. *Toxicol Lett*, 13: 169–173. doi:10.1016/0378-4274(82)90206-5 PMID:6959383

Gowans ID, Lorimore SA, McIlrath JM, Wright EG (2005). Genotype-dependent induction of transmissible chromosomal instability by gamma-radiation and the benzene metabolite hydroquinone. *Cancer Res*, 65: 3527–3530. doi:10.1158/0008-5472.CAN-04-4242 PMID:15867342

Greaves MF & Wiemels J (2003). Origins of chromosome translocations in childhood leukaemia. *Natl Rev*, 3: 639–649.

Grulich AE, Vajdic CM, Cozen W (2007). Altered immunity as a risk factor for non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*, 16: 405–408. doi:10.1158/1055-9965.EPI-06-1070 PMID:17337643

Guénel P, Imbernon E, Chevalier A *et al.* (2002). Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. *Am J Ind Med*, 42: 87–97. doi:10.1002/ajim.10090 PMID:12125084

Gun RT, Pratt N, Ryan P, Roder D (2006). Update of mortality and cancer incidence in the Australian petroleum industry cohort. *Occup Environ Med*, 63: 476–481. doi:10.1136/oem.2005.023796 PMID:16698808

Guo W, Lasky JL, Chang CJ *et al.* (2008). Multi-genetic events collaboratively contribute to Pten-null leukaemia stem-cell formation. *Nature*, 453: 529–533. doi:10.1038/nature06933 PMID:18463637

Hackanson B, Bennett KL, Brena RM *et al.* (2008). Epigenetic modification of CCAAT/enhancer binding protein alpha expression in acute myeloid leukemia. *Cancer Res*, 68: 3142–3151. doi:10.1158/0008-5472.CAN-08-0483 PMID:18451139

Hansch C, Leo A, Hoekman D (1995). *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*. Washington, DC: American Chemical Society, p. 18.

Hartge P & Smith MT (2007). Environmental and behavioral factors and the risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*, 16: 367–368. doi:10.1158/1055-9965.EPI-07-0031 PMID:17344463

Hayes RB, Yin SN, Dosemeci M *et al.* (1996). Mortality among benzene-exposed workers in China. *Environ Health Perspect*, 104: Suppl 61349–1352. PMID:9118919

Hayes RB, Yin SN, Dosemeci M *et al.* Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group (1997). Benzene and the

dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst*, 89: 1065–1071. doi:10.1093/jnci/89.14.1065 PMID:9230889

Henderson AP, Bleasdale C, Delaney K *et al.* (2005). Evidence for the formation of Michael adducts from reactions of (E,E)-muconaldehyde with glutathione and other thiols. *Bioorg Chem*, 33: 363–373. doi:10.1016/j.bioorg.2005.05.004 PMID:16005934

Hirabayashi Y & Inoue T (2009). Aryl hydrocarbon receptor biology and xenobiotic responses in hematopoietic progenitor cells. *Biochem Pharmacol*, 77: 521–535. doi:10.1016/j.bcp.2008.09.030 PMID:18940184

Hirabayashi Y, Yoon BI, Li GX *et al.* (2008). Benzene-induced hematopoietic toxicity transmitted by AhR in wild-type mouse and nullified by repopulation with AhR-deficient bone marrow cells: time after benzene treatment and recovery. *Chemosphere*, 73: SupplS290–S294. doi:10.1016/j.chemosphere.2007.12.033 PMID:18514254

Holden HE, Stoll RE, Spalding JW, Tennant RW (1998). Hemizygous Tg.AC transgenic mouse as a potential alternative to the two-year mouse carcinogenicity bioassay: evaluation of husbandry and housing factors. *J Appl Toxicol*, 18: 19–24. doi:10.1002/(SICI)1099-1263(199801/02)18:1<19::AID-JAT464>3.0.CO;2-Q PMID:9526830

Holecková B, Piesová E, Sivikova K (2004). Dianovskỳ J. Chromosomal aberrations in humans induced by benzene. *Ann Agric Environ Med*, 11: 175–179. PMID:15627321

Hotz P, Carbonnelle P, Haufroid V *et al.* (1997). Biological monitoring of vehicle mechanics and other workers exposed to low concentrations of benzene. *Int Arch Occup Environ Health*, 70: 29–40. doi:10.1007/s004200050183 PMID:9258705

Huebner WW, Wojcik NC, Rosamilia K *et al.* (2004). Mortality updates (1970–1997) of two refinery/petrochemical plant cohorts at Baton Rouge, Louisiana, and Baytown, Texas. *J Occup Environ Med*, 46: 1229–1245. PMID:15591975

Huff JE, Haseman JK, DeMarini DM *et al.* (1989). Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice. *Environ Health Perspect*, 82: 125–163. PMID:2676495

Hutt AM & Kalf GF (1996). Inhibition of human DNA topoisomerase II by hydroquinone and p-benzoquinone, reactive metabolites of benzene. *Environ Health Perspect*, 104: Suppl 61265–1269. PMID:9118903

IARC (1982). Some industrial chemicals and dyestuffs. *IARC Monogr Eval Carcinog Risk Chem Hum*, 29: 1–398. PMID:6957379

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

Infante PF (2006). Benzene exposure and multiple myeloma: a detailed meta-analysis of benzene cohort studies. *Ann N Y Acad Sci*, 1076: 90–109. doi:10.1196/annals.1371.081 PMID:17119195

Infante PF, Rinsky RA, Wagoner JK, Young RJ (1977). Leukaemia in benzene workers. *Lancet*, 2: 76–78. doi:10.1016/S0140-6736(77)90074-5 PMID:69157

Irons RD & Stillman WS (1996). The process of leukemogenesis. *Environ Health Perspect*, 104: Suppl 61239–1246. PMID:9118899

Irons RD, Stillman WS, Colagiovanni DB, Henry VA (1992). Synergistic action of the benzene metabolite hydroquinone on myelopoietic stimulating activity of granulocyte/macrophage colony-stimulating factor in vitro. *Proc Natl Acad Sci USA*, 89: 3691–3695. doi:10.1073/pnas.89.9.3691 PMID:1570288

Iskander K & Jaiswal AK (2005). Quinone oxidoreductases in protection against myelogenous hyperplasia and benzene toxicity. *Chem Biol Interact*, 153-154: 147–157. doi:10.1016/j.cbi.2005.03.019 PMID:15935811

Jankovic J, Jones W, Burkhart J, Noonan G (1991). Environmental study of firefighters. *Ann Occup Hyg*, 35: 581–602. doi:10.1093/annhyg/35.6.581 PMID:1768008

Javelaud B, Vian L, Molle R *et al.* (1998). Benzene exposure in car mechanics and road tanker drivers. *Int Arch Occup Environ Health*, 71: 277–283. doi:10.1007/s004200050281 PMID:9638485

Johnson ES, Langård S, Lin Y-S (2007). A critique of benzene exposure in the general population. *Sci Total Environ*, 374: 183–198. doi:10.1016/j.scitotenv.2006.11.045 PMID:17261327

Kauppinen T, Toikkanen J, Pedersen D *et al.* (2000). Occupational exposure to carcinogens in the European Union. *Occup Environ Med*, 57: 10–18. doi:10.1136/oem.57.1.10 PMID:10711264

Kawasaki Y, Hirabayashi Y, Kaneko T *et al.* (2009). Benzene-induced hematopoietic neoplasms including myeloid leukemia in Trp53-deficient C57BL/6 and C3H/He mice. *Toxicol Sci*, 110: 293–306. doi:10.1093/toxsci/kfp107 PMID:19478238

Kearney L, Gonzalez De Castro D, Yeung J *et al.* (2009). Specific JAK2 mutation (JAK2R683) and multiple gene deletions in Down syndrome acute lymphoblastic leukemia. *Blood*, 113: 646–648. doi:10.1182/blood-2008-08-170928 PMID:18927438

Kim S, Vermeulen R, Waidyanatha S *et al.* (2006a). Using urinary biomarkers to elucidate dose-related patterns of human benzene metabolism. *Carcinogenesis*, 27: 772–781. doi:10.1093/carcin/bgi297 PMID:16339183

Kim S, Vermeulen R, Waidyanatha S *et al.* (2006b). Modeling human metabolism of benzene following occupational and environmental exposures. *Cancer Epidemiol Biomarkers Prev*, 15: 2246–2252. doi:10.1158/1055-9965.EPI-06-0262 PMID:17119053

Kim SY, Choi JK, Cho YH *et al.* (2004). Chromosomal aberrations in workers exposed to low levels of

benzene: association with genetic polymorphisms. *Pharmacogenetics*, 14: 453–463. doi:10.1097/01.fpc.0000114751.08559.7b PMID:15226677

Kirkeleit J, Riise T, Bråtveit M, Moen BE (2008). Increased risk of acute myelogenous leukemia and multiple myeloma in a historical cohort of upstream petroleum workers exposed to crude oil. *Cancer Causes Control*, 19: 13–23. doi:10.1007/s10552-007-9065-x PMID:17906934

Kirschner M (2009). Chemical Profile: Benzene. *ICIS Chemical Business*, available at http://www.icis.com/Articles/2009/02/16/9192064/Chemical-profile-Benzene.html.

Kivistö H, Pekari K, Peltonen K *et al.* (1997). Biological monitoring of exposure to benzene in the production of benzene and in a cokery. *Sci Total Environ*, 199: 49–63. doi:10.1016/S0048-9697(97)05481-8 PMID:9200847

La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1989). Occupation and lymphoid neoplasms. *Br J Cancer*, 60: 385–388. doi:10.1038/bjc.1989.290 PMID:2789947

Lamm SH, Engel A, Byrd DM (2005). Non-Hodgkin lymphoma and benzene exposure: a systematic literature review. *Chem Biol Interact*, 153-154: 231–237. doi:10.1016/j.cbi.2005.03.027 PMID:15885679

Lan Q, Zhang L, Li G *et al.* (2004). Hematotoxicity in workers exposed to low levels of benzene. *Science*, 306: 1774–1776. doi:10.1126/science.1102443 PMID:15576619

Lan Q, Zhang L, Shen M *et al.* (2009). Large-scale evaluation of candidate genes identifies associations between DNA repair and genomic maintenance and development of benzene hematotoxicity. *Carcinogenesis*, 30: 50–58. doi:10.1093/carcin/bgn249 PMID:18978339

Larson RA & Le Beau MM (2005). Therapy-related myeloid leukaemia: a model for leukemogenesis in humans. *Chem Biol Interact*, 153-154: 187–195. doi:10.1016/j.cbi.2005.03.023 PMID:15935816

Lau A, Belanger CL, Winn LM (2009). In utero and acute exposure to benzene: investigation of DNA double-strand breaks and DNA recombination in mice. *Mutat Res*, 676: 74–82. PMID:19486867

Lee SG, Choi JR, Kim JS *et al.* (2009). Therapy-related acute lymphoblastic leukemia with t(9;22)(q34;q11.2):a case study and review of the literature. *Cancer Genet Cytogenet*, 191: 51–54. doi:10.1016/j.cancergencyto.2009.02.002 PMID:19389510

Lewis RJ, Schnatter AR, Drummond I *et al.* (2003). Mortality and cancer morbidity in a cohort of Canadian petroleum workers. *Occup Environ Med*, 60: 918–928. doi:10.1136/oem.60.12.918 PMID:14634182

Ley TJ, Mardis ER, Ding L *et al.* (2008). DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature*, 456: 66–72. doi:10.1038/nature07485 PMID:18987736

Li B, Li YQ, Yang LJ *et al.* (2009). Decreased T-cell receptor excision DNA circles in peripheral blood mononuclear cells among benzene-exposed workers. *Int J Immunogenet*, 36: 107–111. doi:10.1111/j.1744-313X.2009.00832.x PMID:19228219

Liang Y-X, Wong O, Armstrong T *et al.* (2005). An overview of published benzene exposure data by industry in China, 1960–2003. *Chem Biol Interact*, 153-154: 55–64. doi:10.1016/j.cbi.2005.03.009 PMID:15935800

Lide DR, editor (2008). *CRC Handbook of Chemistry and Physics*, 89th ed. Boca Raton, FL: CRC Press, pp. 3–32.

Lindsey RH Jr, Bender RP, Osheroff N (2005). Effects of benzene metabolites on DNA cleavage mediated by human topoisomerase II alpha: 1,4-hydroquinone is a topoisomerase II poison. *Chem Res Toxicol*, 18: 761–770. doi:10.1021/tx049659z PMID:15833037

Lindsey RH Jr, Bromberg KD, Felix CA, Osheroff N (2004). 1,4-Benzoquinone is a topoisomerase II poison. *Biochemistry*, 43: 7563–7574. doi:10.1021/bi049756r PMID:15182198

Lobato MN, Metzler M, Drynan L *et al.* (2008). Modeling chromosomal translocations using conditional alleles to recapitulate initiating events in human leukemias. *J Natl Cancer Inst Monogr*, 39: 58–63. doi:10.1093/jncimonographs/lgn022 PMID:18648005

Long DJ 2nd, Gaikwad A, Multani A *et al.* (2002). Disruption of the NAD(P)H:quinone oxidoreductase 1 (NQO1) gene in mice causes myelogenous hyperplasia. *Cancer Res*, 62: 3030–3036. PMID:12036909

Lynge E, Andersen A, Nilsson R *et al.* (1997). Risk of cancer and exposure to gasoline vapors. *Am J Epidemiol*, 145: 449–458. PMID:9048519

Maltoni C, Ciliberti A, Cotti G *et al.* (1989). Benzene, an experimental multipotential carcinogen: results of the long-term bioassays performed at the Bologna Institute of Oncology. *Environ Health Perspect*, 82: 109–124. doi:10.1289/ehp.8982109 PMID:2792037

Maltoni C, Conti B, Cotti G (1983). Benzene: a multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. *Am J Ind Med*, 4: 589–630. doi:10.1002/ajim.4700040503 PMID:6353911

Maltoni C, Conti B, Cotti G, Belpoggi F (1985). Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: current results and ongoing research. *Am J Ind Med*, 7: 415–446. doi:10.1002/ajim.4700070508 PMID:4003403

Maltoni C, Conti B, Perino G, Di Maio V (1988). Further evidence of benzene carcinogenicity. Results on Wistar rats and Swiss mice treated by ingestion. *Ann N Y Acad Sci*, 534: 1 Living in a C412–426. doi:10.1111/j.1749-6632.1988.tb30131.x PMID:3389671

Maltoni C, Conti B, Scarnato C (1982b). Squamous cell carcinomas of the oral cavity in Sprague-Dawley rats, following exposure to benzene by ingestion. First experimental demonstration. *Med Lav*, 73: 441–445. PMID:7177031

Maltoni C, Cotti G, Valgimigli L, Mandrioli A (1982a). Zymbal gland carcinomas in rats following exposure

to benzene by inhalation. *Am J Ind Med*, 3: 11–16. doi:10.1002/ajim.4700030104 PMID:7124739

Maltoni C, Cotti G, Valgimigli L, Mandrioli A (1982c). Hepatocarcinomas in Sprague-Dawley rats, following exposure to benzene by inhalation. First experimental demonstration. *Med Lav*, 73: 446–450. PMID:7177032

Maltoni C & Scarnato C (1979). First experimental demonstration of the carcinogenic effects of benzene; long-term bioassays on Sprague-Dawley rats by oral administration. *Med Lav*, 70: 352–357. PMID:554913

Marcucci G, Radmacher MD, Maharry K *et al.* (2008). MicroRNA expression in cytogenetically normal acute myeloid leukemia. *N Engl J Med*, 358: 1919–1928. doi:10.1056/NEJMoa074256 PMID:18450603

Mardis ER, Ding L, Dooling DJ *et al.* (2009). Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*, 361: 1058–1066. doi:10.1056/NEJMoa0903840 PMID:19657110

Maronpot RR (1987). Ovarian toxicity and carcinogenicity in eight recent National Toxicology Program studies. *Environ Health Perspect*, 73: 125–130. doi:10.1289/ehp.8773125 PMID:3665857

McClendon AK & Osheroff N (2007). DNA topoisomerase II, genotoxicity, and cancer. *Mutat Res*, 623: 83–97. PMID:17681352

McDonald TA, Waidyanatha S, Rappaport SM (1993). Production of benzoquinone adducts with hemoglobin and bone-marrow proteins following administration of [13C6]benzene to rats. *Carcinogenesis*, 14: 1921–1925. doi:10.1093/carcin/14.9.1921 PMID:8403219

McHale CM, Lan Q, Corso C *et al.* (2008). Chromosome translocations in workers exposed to benzene. *J Natl Cancer Inst Monogr*, 39: 74–77. doi:10.1093/jncimonographs/lgn010 PMID:18648008

McHale CM, Wiemels JL, Zhang L *et al.* (2003). Prenatal origin of childhood acute myeloid leukemias harboring chromosomal rearrangements t(15;17) and inv(16). *Blood*, 101: 4640–4641. doi:10.1182/blood-2003-01-0313 PMID:12756163

McKinney PA, Alexander FE, Cartwright RA, Parker L (1991). Parental occupations of children with leukaemia in west Cumbria, north Humberside, and Gateshead. *BMJ*, 302: 681–687.

Mehlman MA (2002). Carcinogenic effects of benzene: Cesare Maltoni's contributions. *Ann N Y Acad Sci*, 982: 137–148. doi:10.1111/j.1749-6632.2002.tb04929.x PMID:12562633

Merlo DF, Bertazzi PA, Bolognesi C *et al.* (2001). *Exposure to Low Levels of Benzene, Interindividual Biological Variability and Cancer Risk: A Multicentre European Study*. Milan, Italy: Istituto Nazionale per la Ricerca sul Cancro

Miligi L, Costantini AS, Benvenuti A *et al.* (2006). Occupational exposure to solvents and the risk of lymphomas. *Epidemiology*, 17: 552–561. doi:10.1097/01.ede.0000231279.30988.4d PMID:16878041

Mistry AR, Felix CA, Whitmarsh RJ *et al.* (2005). DNA topoisomerase II in therapy-related acute promyelocytic leukemia. *N Engl J Med*, 352: 1529–1538. doi:10.1056/NEJMoa042715 PMID:15829534

Morgan GJ & Alvares CL (2005). Benzene and the hemopoietic stem cell. *Chem Biol Interact*, 153-154: 217–222. doi:10.1016/j.cbi.2005.03.025 PMID:15935819

Mrózek K & Bloomfield CD (2008). Clinical significance of the most common chromosome translocations in adult acute myeloid leukemia. *J Natl Cancer Inst Monogr*, 39: 52–57. doi:10.1093/jncimonographs/lgn003 PMID:18648004

Navasumrit P, Chanvaivit S, Intarasunanont P *et al.* (2005). Environmental and occupational exposure to benzene in Thailand. *Chem Biol Interact*, 153-154: 75–83. doi:10.1016/j.cbi.2005.03.010 PMID:15935802

Nedelcheva V, Gut I, Soucek P *et al.* (1999). Metabolism of benzene in human liver microsomes: individual variations in relation to CYP2E1 expression. *Arch Toxicol*, 73: 33–40. doi:10.1007/s002040050583 PMID:10207612

NIOSH (1990). *National Occupational Exposure Survey (1981–83)*. Cincinnati, OH: US Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health [http://www.cdc.gov/noes/noes2/09070occ.html]

Nordlinder R & Ramnäs O (1987). Exposure to benzene at different work places in Sweden. *Ann Occup Hyg*, 31: 345–355. doi:10.1093/annhyg/31.3.345 PMID:3426034

NTP (1986). NTP toxicology and carcinogenesis studies of benzene (CAS NO. 71–43–2) in F344/N rats and B6C3F1 mice (Gavage studies). *Natl Toxicol Program Tech Rep Ser*, 289: 1–277. PMID:12748714

NTP (2005). BenzeneNTP 11th Report on Carcinogens. *Rep Carcinog*, 11: 1–A32. PMID:19826456

NTP (2007). NTP report on the toxicology and carcinogenesis study of benzene (CAS No. 71–43–2) in genetically modified haploinsufficient p16 Ink4a/p19 Arf mice (gavage study). *Natl Toxicol Program Genet Modif Model Rep*, 8: 1–81. PMID:18784769

O'Neil MJ, editor (2006). *The Merck Index*, 14th ed. Whitehouse Station, NJ: Merck & Co., p. 177.

Ong CN, Kok PW, Lee BL *et al.* (1995). Evaluation of biomarkers for occupational exposure to benzene. *Occup Environ Med*, 52: 528–533. doi:10.1136/oem.52.8.528 PMID:7663638

Ong CN, Kok PW, Ong HY *et al.* (1996). Biomarkers of exposure to low concentrations of benzene: a field assessment. *Occup Environ Med*, 53: 328–333. doi:10.1136/oem.53.5.328 PMID:8673180

Passegué E & Weisman IL (2005). Leukemic stem cells: where do they come from? *Stem Cell Rev*, 1: 181–188. doi:10.1385/SCR:1:3:181 PMID:17142854

Patel AS, Talbott EO, Zborowski JV *et al.* (2004). Risk of cancer as a result of community exposure to gasoline vapors. *Arch Environ Health*, 59: 497–503. doi:10.1080/00039890409605165 PMID:16425659

Pedersen-Bjergaard J, Andersen MK, Andersen MT, Christiansen DH (2008). Genetics of therapy-related myelodysplasia and acute myeloid leukemia. *Leukemia*, 22: 240–248. doi:10.1038/sj.leu.2405078 PMID:18200041

Pedersen-Bjergaard J, Andersen MT, Andersen MK (2007). Genetic pathways in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program*, 392–397. PMID:18024656

Pedersen-Bjergaard J, Christiansen DH, Desta F, Andersen MK (2006). Alternative genetic pathways and cooperating genetic abnormalities in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. *Leukemia*, 20: 1943–1949. doi:10.1038/sj.leu.2404381 PMID:16990778

Pesch B, Haerting J, Ranft U *et al.* (2000). Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. *Int J Epidemiol*, 29: 1014–1024. doi:10.1093/ije/29.6.1014 PMID:11101542

Picciano D (1979). Cytogenetic study of workers exposed to benzene. *Environ Res*, 19: 33–38. doi:10.1016/0013-9351(79)90031-8 PMID:510268

Popp W, Rauscher D, Müller G *et al.* (1994). Concentrations of benzene in blood and *S*-phenylmercapturic and *t,t*-muconic acid in urine in car mechanics. *Int Arch Occup Environ Health*, 66: 1–6. doi:10.1007/BF00386572 PMID:7523309

Powley MW & Carlson GP (2000). Cytochromes P450 involved with benzene metabolism in hepatic and pulmonary microsomes. *J Biochem Mol Toxicol*, 14: 303–309. doi:10.1002/1099-0461(2000)14:6<303::AID-JBT2>3.0.CO;2-8 PMID:11083083

Qu Q, Shore R, Li G *et al.* (2005). Biomarkers of benzene: urinary metabolites in relation to individual genotype and personal exposure. *Chem Biol Interact*, 153-154: 85–95. doi:10.1016/j.cbi.2005.03.012 PMID:15935803

Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH (2001). Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol*, 153: 433–443. doi:10.1093/aje/153.5.433 PMID:11226975

Rappaport SM, Kim S, Lan Q *et al.* (2009). Evidence that humans metabolize benzene via two pathways. *Environ Health Perspect*, 117: 946–952. PMID:19590688

Ravandi F & Kebriaei P (2009). Philadelphia chromosome-positive acute lymphoblastic leukemia. [vi.]*Hematol Oncol Clin North Am*, 23: 1043–1063, vi. doi:10.1016/j.hoc.2009.07.007 PMID:19825452

Ren X, Lim S, Smith MT, Zhang L (2009). Werner syndrome protein, WRN, protects cells from DNA damage induced by the benzene metabolite hydroquinone. *Toxicol Sci*, 107: 367–375.

Rinsky RA, Hornung RW, Silver SR, Tseng CY (2002). Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. *Am J Ind Med*, 42: 474–480. doi:10.1002/ajim.10138 PMID:12439870

Rinsky RA, Smith AB, Hornung R *et al.* (1987). Benzene and leukemia. An epidemiologic risk assessment. *N Engl J Med*, 316: 1044–1050. doi:10.1056/NEJM198704233161702 PMID:3561457

Rinsky RA, Young RJ, Smith AB (1981). Leukemia in benzene workers. *Am J Ind Med*, 2: 217–245. doi:10.1002/ajim.4700020305 PMID:7345926

Rivedal E & Witz G (2005). Metabolites of benzene are potent inhibitors of gap-junction intercellular communication. *Arch Toxicol*, 79: 303–311. doi:10.1007/s00204-004-0638-0 PMID:15690152

Romieu I, Ramirez M, Meneses F *et al.* (1999). Environmental exposure to volatile organic compounds among workers in Mexico City as assessed by personal monitors and blood concentrations. *Environ Health Perspect*, 107: 511–515. doi:10.1289/ehp.99107511 PMID:10378996

Ross D (2000). The role of metabolism and specific metabolites in benzene-induced toxicity: evidence and issues. *J Toxicol Environ Health A*, 61: 357–372. doi:10.1080/00984100050166361 PMID:11086940

Rothman N, Smith MT, Hayes RB *et al.* (1997). Benzene poisoning, a risk factor for hematological malignancy, is associated with the NQO1 609C–>T mutation and rapid fractional excretion of chlorzoxazone. *Cancer Res*, 57: 2839–2842. PMID:9230185

Rushton L (1993). A 39-year follow-up of the U.K. oil refinery and distribution center studies: results for kidney cancer and leukemia. *Environ Health Perspect*, 101: Suppl 677–84. doi:10.1289/ehp.93101s677 PMID:8020451

Rushton L & Romaniuk H (1997). A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med*, 54: 152–166. doi:10.1136/oem.54.3.152 PMID:9155776

Satin KP, Wong O, Yuan LA *et al.* (1996). A 50-year mortality follow-up of a large cohort of oil refinery workers in Texas. *J Occup Environ Med*, 38: 492–506. doi:10.1097/00043764-199605000-00010 PMID:8733641

Savitz DA & Andrews KW (1997). Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. *Am J Ind Med*, 31: 287–295. doi:10.1002/(SICI)1097-0274(199703)31:3<287::AID-AJIM4>3.0.CO;2-V PMID:9055951

Scélo G, Metayer C, Zhang L *et al.* (2009). Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. *Environ Health Perspect*, 117: 133–139. PMID:19165400

Schnatter AR, Armstrong TW, Nicolich MJ *et al.* (1996). Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian

petroleum distribution workers. *Occup Environ Med*, 53: 773–781. doi:10.1136/oem.53.11.773 PMID:9038803

Sheets PL, Yost GS, Carlson GP (2004). Benzene metabolism in human lung cell lines BEAS-2B and A549 and cells overexpressing CYP2F1. *J Biochem Mol Toxicol*, 18: 92–99. doi:10.1002/jbt.20010 PMID:15122651

Shen M, Lan Q, Zhang L *et al.* (2006). Polymorphisms in genes involved in DNA double-strand break repair pathway and susceptibility to benzene-induced hematotoxicity. *Carcinogenesis*, 27: 2083–2089. doi:10.1093/carcin/bgl061 PMID:16728435

Shu XO, Gao YT, Brinton LA *et al.* (1988). A population-based case-control study of childhood leukemia in Shanghai. *Cancer*, 62: 635–644. doi:10.1002/1097-0142(19880801)62:3<635::AID-CNCR2820620332>3.0.CO;2-3 PMID:3164642

Shu XO, Stewart P, Wen WQ *et al.* (1999). Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. *Cancer Epidemiol Biomarkers Prev*, 8: 783–791. PMID:10498397

Signer RA, Montecino-Rodriguez E, Witte ON *et al.* (2007). Age-related defects in B lymphopoiesis underlie the myeloid dominance of adult leukemia. *Blood*, 110: 1831–1839. doi:10.1182/blood-2007-01-069401 PMID:17554060

Singh KP, Casado FL, Opanashuk LA, Gasiewicz TA (2009). The aryl hydrocarbon receptor has a normal function in the regulation of hematopoietic and other stem/progenitor cell populations. *Biochem Pharmacol*, 77: 577–587. doi:10.1016/j.bcp.2008.10.001 PMID:18983985

Smith MT (1996). The mechanism of benzene-induced leukemia: a hypothesis and speculations on the causes of leukemia. *Environ Health Perspect*, 104: Suppl 61219–1225. PMID:9118896

Smith MT, Skibola CF, Allan JM, Morgan GJ (2004). Causal models of leukaemia and lymphoma. *IARC Sci Publ*, 157: 373–392. PMID:15055307

Smith MT & Zhang L (1998). Biomarkers of leukemia risk: benzene as a model. *Environ Health Perspect*, 106: Suppl 4937–946. PMID:9703476

Smith MT, Zhang L, Jeng M *et al.* (2000). Hydroquinone, a benzene metabolite, increases the level of aneusomy of chromosomes 7 and 8 in human CD34-positive blood progenitor cells. *Carcinogenesis*, 21: 1485–1490. doi:10.1093/carcin/21.8.1485 PMID:10910948

Smith MT, Zhang L, Wang Y *et al.* (1998). Increased translocations and aneusomy in chromosomes 8 and 21 among workers exposed to benzene. *Cancer Res*, 58: 2176–2181. PMID:9605763

Snyder CA, Goldstein BD, Sellakumar AR *et al.* (1980). The inhalation toxicology of benzene: incidence of hematopoietic neoplasms and hematotoxicity in ARK/J and C57BL/6J mice. *Toxicol Appl Pharmacol*, 54: 323–331. doi:10.1016/0041-008X(80)90202-1 PMID:6893503

Snyder CA, Sellakumar AR, James DJ, Albert RE (1988). The carcinogenicity of discontinuous inhaled benzene exposures in CD-1 and C57Bl/6 mice. *Arch Toxicol*, 62: 331–335. doi:10.1007/BF00293618 PMID:3242441

Snyder R (2004). Xenobiotic metabolism and the mechanism(s) of benzene toxicity. *Drug Metab Rev*, 36: 531–547. doi:10.1081/DMR-200033445 PMID:15554234

Sorahan T, Kinlen LJ, Doll R (2005). Cancer risks in a historical UK cohort of benzene exposed workers. *Occup Environ Med*, 62: 231–236. doi:10.1136/oem.2004.015628 PMID:15778255

Steinmaus C, Smith AH, Jones RM, Smith MT (2008). Meta-analysis of benzene exposure and non-Hodgkin lymphoma: biases could mask an important association. *Occup Environ Med*, 65: 371–378. doi:10.1136/oem.2007.036913 PMID:18417556

Stillman WS, Varella-Garcia M, Irons RD (2000). The benzene metabolite, hydroquinone, selectively induces 5q31- and -7 in human CD34+CD19- bone marrow cells. *Exp Hematol*, 28: 169–176. doi:10.1016/S0301-472X(99)00144-7 PMID:10706073

Stoner GD, Conran PB, Greisiger EA *et al.* (1986). Comparison of two routes of chemical administration on the lung adenoma response in strain A/J mice. *Toxicol Appl Pharmacol*, 82: 19–31. doi:10.1016/0041-008X(86)90433-3 PMID:3945940

Swerdlow SH, Campo E, Lee Harris N (2008). *WHO classification of tumours of haematopoietic and lymphoid tissues*, 4th edition. Lyon, France: IARC.

Thomadaki H & Scorilas A (2006). BCL2 family of apoptosis-related genes: functions and clinical implications in cancer. *Crit Rev Clin Lab Sci*, 43: 1–67. doi:10.1080/10408360500295626 PMID:16531274

Tough IM & Brown WM (1965). Chromosome Aberrations and Exposure to Ambient Benzene. *Lancet*, 1: 684 doi:10.1016/S0140-6736(65)91835-0 PMID:14258551

Valentine JL, Lee SS, Seaton MJ *et al.* (1996). Reduction of benzene metabolism and toxicity in mice that lack CYP2E1 expression. *Toxicol Appl Pharmacol*, 141: 205–213. PMID:8917693

van Steensel-Moll HA, Valkenburg HA, van Zanen GE (1985). Childhood leukemia and parental occupation. A register-based case-control study. *Am J Epidemiol*, 121: 216–224. PMID:3860001

van Wijngaarden E & Stewart PA (2003). Critical literature review of determinants and levels of occupational benzene exposure for United States community-based case-control studies. *Appl Occup Environ Hyg*, 18: 678–693. doi:10.1080/10473220301376 PMID:12909536

Vaughan AT, Betti CJ, Villalobos MJ *et al.* (2005). Surviving apoptosis: a possible mechanism of benzene-induced leukemia. *Chem Biol Interact*, 153-154: 179–185. doi:10.1016/j.cbi.2005.03.022 PMID:15935815

Verma DK, Johnson DM, McLean JD (2000). Benzene and total hydrocarbon exposures in the upstream petroleum oil and gas industry. *AIHAJ*, 61: 225–263.

Voltz R, Starck M, Zingler V *et al.* (2004). Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients. *Mult Scler*, 10: 472–474. doi:10.1191/1352458504ms1047cr PMID:15327049

Waidyanatha S, Rothman N, Fustinoni S *et al.* (2001). Urinary benzene as a biomarker of exposure among occupationally exposed and unexposed subjects. *Carcinogenesis*, 22: 279–286. doi:10.1093/carcin/22.2.279 PMID:11181449

Waidyanatha S & Rappaport SM (2005). Investigation of cysteinyl protein adducts of benzene diolepoxide. *Chem Biol Interact*, 153-154: 261–266. doi:10.1016/j.cbi.2005.03.033 PMID:15935825

Walter MJ, Payton JE, Ries RE *et al.* (2009). Acquired copy number alterations in adult acute myeloid leukemia genomes. *Proc Natl Acad Sci USA*, 106: 12950–12955. doi:10.1073/pnas.0903091106 PMID:19651600

Wang L, Roy SK, Eastmond DA (2007). Differential cell cycle-specificity for chromosomal damage induced by merbarone and etoposide in V79 cells. *Mutat Res*, 616: 70–82. PMID:17174356

Wang R, Zhang Y, Lan Q *et al.* (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. *Am J Epidemiol*, 169: 176–185. doi:10.1093/aje/kwn300 PMID:19056833

Whysner J, Reddy MV, Ross PM *et al.* (2004). Genotoxicity of benzene and its metabolites. *Mutat Res*, 566: 99–130. doi:10.1016/S1383-5742(03)00053-X PMID:15164977

Wiemels JL, Cazzaniga G, Daniotti M *et al.* (1999). Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet*, 354: 1499–1503. doi:10.1016/S0140-6736(99)09403-9 PMID:10551495

Wiemels JL, Xiao Z, Buffler PA *et al.* (2002). In utero origin of t(8;21) AML1-ETO translocations in childhood acute myeloid leukemia. *Blood*, 99: 3801–3805. doi:10.1182/blood.V99.10.3801 PMID:11986239

Williams PRD, Panko JM, Unice K *et al.* (2008). Occupational exposures associated with petroleum-derived products containing trace levels of benzene. *J Occup Environ Hyg*, 5: 565–574. doi:10.1080/15459620802282110 PMID:18615290

Williams PRD, Robinson K, Paustenbach DJ (2005). Benzene exposures associated with tasks performed on marine vessels (circa 1975 to 2000). *J Occup Environ Hyg*, 2: 586–599. doi:10.1080/15459620500339147 PMID:16234219

Wong O (1995). Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med*, 52: 380–384. doi:10.1136/oem.52.6.380 PMID:7627314

Wong O, Harris F, Smith TJ (1993). Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States. *Environ Health Perspect*, 101: Suppl 663–76. doi:10.1289/ehp.93101s663 PMID:8020450

Wong O & Raabe GK (1995). Cell-type-specific leukemia analyses in a combined cohort of more than 208,000 petroleum workers in the United States and the United Kingdom, 1937–1989. *Regul Toxicol Pharmacol*, 21: 307–321. doi:10.1006/rtph.1995.1044 PMID:7644720

Wong O & Raabe GK (1997). Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. *Regul Toxicol Pharmacol*, 26: 188–199. doi:10.1006/rtph.1997.1162 PMID:9356282

Wong O & Raabe GK (2000a). A critical review of cancer epidemiology in the petroleum industry, with a meta-analysis of a combined database of more than 350,000 workers. *Regul Toxicol Pharmacol*, 32: 78–98. doi:10.1006/rtph.2000.1410 PMID:11029272

Wong O & Raabe GK (2000b). Non-Hodgkin's lymphoma and exposure to benzene in a multinational cohort of more than 308,000 petroleum workers, 1937 to 1996. *J Occup Environ Med*, 42: 554–568. doi:10.1097/00043764-200005000-00016 PMID:10824308

Xu X, Wiencke JK, Niu M *et al.* (1998). benzene exposure, GSTT homozygous deletion and SCE *Am J Ind Med*, 33: 157–163. doi:10.1002/(SICI)1097-0274(199802)33:2<157::AID-AJIM7>3.0.CO;2-V PMID:9438048

Yin SN, Hayes RB, Linet MS *et al.* (1996). A cohort study of cancer among benzene-exposed workers in China: overall results. *Am J Ind Med*, 29: 227–235. doi:10.1002/(SICI)1097-0274(199603)29:3<227::AID-AJIM2>3.0.CO;2-N PMID:8833775

Yoon BI, Hirabayashi Y, Kawasaki Y *et al.* (2002). Aryl hydrocarbon receptor mediates benzene-induced hematotoxicity. *Toxicol Sci*, 70: 150–156. doi:10.1093/toxsci/70.1.150 PMID:12388843

Zhang L, Eastmond DA, Smith MT (2002). The nature of chromosomal aberrations detected in humans exposed to benzene. *Crit Rev Toxicol*, 32: 1–42. doi:10.1080/20024091064165 PMID:11846214

Zhang L, Rothman N, Li G *et al.* (2007). Aberrations in chromosomes associated with lymphoma and therapy-related leukemia in benzene-exposed workers. *Environ Mol Mutagen*, 48: 467–474. doi:10.1002/em.20306 PMID:17584886

Zhang L, Rothman N, Wang Y *et al.* (1999). Benzene increases aneuploidy in the lymphocytes of exposed workers: a comparison of data obtained by fluorescence in situ hybridization in interphase and metaphase cells. *Environ Mol Mutagen*, 34: 260–268. doi:10.1002/(SICI)1098-2280(1999)34:4<260::AID-EM6>3.0.CO;2-P PMID:10618174