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2. CANCER IN HUMANS

The published evidence on the association between benzene exposure and cancers of the lymphatic and haematopoietic system was last reviewed in *IARC Monographs* Volume 100F (IARC, 2012a), when it was concluded that there was *sufficient evidence* in humans for acute myeloid leukaemia (AML)/acute non-lymphocytic leukaemia (ANLL) and *limited evidence* for acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), and non-Hodgkin lymphoma (NHL).

This Working Group reviewed the association between benzene exposure and cancers of the lymphatic and haematopoietic system again, including those studies considered in *IARC Monographs* Volume 100F as well as studies published since that review in 2009. According to the 2017 *WHO Classification of Tumours of Haematopoietic and Lymphatic Tissues* (Swerdlow et al., 2017), the Working Group considered AML and myelodysplastic syndrome (MDS) as well as chronic myeloid leukaemia (CML) and myeloproliferative disorder (MPD) in the broader category of leukaemia; the category of lymphomas was considered to include NHL as well as its various subtypes (e.g. MM, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), and hairy cell leukaemia (HCL)), CLL, ALL, and Hodgkin lymphoma (HL). These studies are reviewed in Sections 2.1 and 2.2, respectively.

The Working Group also reviewed all available studies of the association between benzene exposure and other cancers in children and adults published before and after *IARC Monographs* Volume 100F. These reviews are presented in Sections 2.3 and 2.4, respectively.

Studies of adult cancers in occupational cohorts and in the general population are considered separately in Sections 2.1, 2.2, and 2.4, due to differences in approaches to the assessment of benzene exposure and the analysis of data according to the study setting.

Although tobacco smoke is an important source of benzene exposure for the population at large, accounting for half of population exposure to benzene in the USA (American Cancer Society, 2016), the Working Group did not review studies of smoking-related exposures, because tobacco smoke contains numerous correlated components that could confound the effects of benzene. Studies of tobacco smoking and exposure to secondhand tobacco smoke are reviewed in *IARC Monographs* Volume 100E (IARC, 2012b).

2.1 Adult leukaemia

2.1.1 Occupational cohort studies

(a) Introduction

This section reviews epidemiological studies of leukaemia in occupational cohorts, including occupational cohort studies and nested case–control analyses of such studies. Data on adult leukaemia in non-occupational cohort studies

and population-based case–control studies are reviewed in Section 2.1.2.

Benzene was first classified as a human carcinogen with *sufficient evidence* in *IARC Monographs* Supplement 1 and Volume 29 (IARC, 1982). Substantial support for this classification has since come from associations between exposure to benzene and leukaemia, particularly AML/ANLL, in several occupational cohorts described in *IARC Monographs* Supplement 7 (IARC, 1987) and later in *IARC Monographs* Volume 100F, compiled in 2009 (Baan et al., 2009; IARC, 2012a).

Among the studies that were published after the period covered by *IARC Monographs* Volume 100F, the Working Group chose not to consider results for broad aggregations of different cancer types, including "haematopoietic cancers", "leukaemia", or "myelogenous leukaemia" (Richardson, 2009; Merlo et al., 2010; Koh et al., 2011, 2014; Bonneterre et al., 2012); these diagnostic categories are not specific enough or sufficiently informative. Studies of occupational groups where exposure to benzene was not clearly documented and characterized were also excluded (Gudzenko et al., 2015). First, the main features of occupational cohort studies considered in this chapter are described (Table 2.1). Leukaemia risks associated with benzene exposure by histological type are described in the following sections for each of the cohort studies.

(b) Studies published since IARC Monographs Volume 100F

(i) Petroleum distribution workers

Three cohort studies of petroleum distribution workers conducted in Australia (Glass et al., 2003), Canada (Schnatter et al., 1996), and the United Kingdom (Rushton & Romaniuk, 1997) were updated with new cases of cancers of the lymphatic and haematopoietic system diagnosed up until December 2006 (Australia), 1994 (Canada), and 2005 (United Kingdom), and were pooled for reanalysis using a nested case–control study design (Schnatter et al., 2012). Only male cases and matched controls were included in the analysis (370 leukaemia cases and 1587 controls). All leukaemia diagnoses were reviewed by haematopathologists, who reclassified 8 leukaemia cases of the original publications to MDS or MPD. Benzene exposure was reassessed to allow comparability among the three studies, using exposure measurement data and individual work histories obtained from company records in Canada and the United Kingdom, or from trained interviewers in Australia. Six exposure metrics were derived: cumulative exposure (ppm-years), average intensity (ppm), maximum intensity (ppm, i.e. the highest job-specific exposure estimate), duration of employment (years), peak exposure (yes/no, when employed in a particular job for at least 1 year and having experienced > 3 ppm exposure for 15–60 minutes at least weekly), and dermal exposure (no, low, medium, high; defined as the highest job-specific probability of skin contact for at least 1 year). [The strengths of this study included the high quality of the assessment of benzene exposure and of diagnostic classification. The size of the study was relatively large, but small numbers were available in some subgroup analyses. Scarce or no information on potential confounders (e.g. smoking or multiple exposures other than benzene at the workplace) was available.]

(ii) Dow Chemical workers, Midland, Michigan

A retrospective cohort mortality study of 2266 workers exposed to benzene at Dow Chemical plant in Michigan (USA) (Bloemen et al., 2004) (included in *IARC Monographs* Volume 100F, Table 2.1, available at: http://publications.iarc.fr/123) was later updated (Collins et al., 2015). Vital status and cause of death were derived from the company's research database, regularly updated from several sources including the National Death Index. The follow-up, starting in 1940, was extended by

Table 2.1 Occupational cohort studies of exposure to benzene and leukaemia subtypes in adults

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schnatter et al. (2012) Australia, Canada, UK 1981–2006 (Australia), 1964–1994 (Canada), 1950–2005 (UK) Nested case–control	Cases: 370 diagnoses based on incidence and mortality data (hospital records, cancer registries, death certificates) Controls: 1587, 5 age-matched (Australia) or 4 age- and company-matched (Canada and UK) controls selected using incidence density-based sampling Exposure assessment method: quantitative measurements; exposure assessment was conducted at the job/ worksite/era level, based on routinely collected industry exposure measurements; work history was collected from company records (Canada and UK) or through interview and company records (Australia)	Leukaemia (AML)	Cumulative exposure tertiles (ppm-yr)			NR	Exposures are relatively low; MDS (potentially previously reported as AML) may be the more relevant health risk for such low exposure; strongest suggestion of a risk of MPD is for the exposure time window 2–20 yr (reported in Glass et al., 2014); based on limited data, smoking was unlikely to be a confounder Strengths: large study size; review of diagnosis by haematopathologists; re-assessment of exposure across the three studies Limitations: smoking data were incomplete
			≤ 0.348	20	1.00		
			0.348–2.93	19	1.04 (0.50–2.19)		
			> 2.93	21	1.39 (0.68–2.85)		
		Leukaemia (CML)	Cumulative exposure tertiles (ppm-yr)			NR	
			≤ 0.348	4	1.00		
			0.348–2.93	16	5.04 (1.45–17.50)		
			> 2.93	8	2.20 (0.63–7.68)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Collins et al. (2015) USA 1940–2009 Cohort	2266 workers exposed to benzene at a chemical plant Exposure assessment method: quantitative measurements; job titles were assigned to exposure categories by an industrial hygienist, based on IH measurements (JEM)	Leukaemia (AML): C92.0	Cumulative exposure (ppm-yr) 0–3.9 4.0–24.9 ≥ 25 Trend test *P* value, 0.88	 0 3 2	 0 (0–2.50) 1.87 (0.39–5.47) 1.39 (0.17–5.03)	Age, race, sex	Third update of the Dow Chemical plant retrospective cohort; one death for MDS, which was reported from the high-exposure group (SMR, 25.05; 95% CI, 0.63–139.58) Strengths: extensive benzene exposure monitoring; complete work history information; periodic medical examination at workplace; long and complete follow-up Limitations: mortality study based on death certificates

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Stenehjem et al. (2015) Norway 1965–1999/1999–2011 Cohort	24 917 male petroleum workers; offshore oil industry workers for at least 20 days during 1965–1999, all men, extracted from a cohort who responded to a survey conducted with postal questionnaires Exposure assessment method: quantitative measurements; a JEM was developed using monitoring data and job-specific information, giving semiquantitative estimates; JEM scores converted into corresponding ppm values	Leukaemia (myeloid): ICD-10 (codes C92, D45–7)	Cumulative exposure tertiles (ppm-yr)			Age, benzene exposure from other work, ever daily smoker	Nested case–cohort study based on an updated cohort of Norwegian offshore workers; evidence of dose-related patterns for cumulative exposure, exposure intensity and peak exposures for AML; weak links with duration; risks are higher for those with first exposure before 1980 Strengths: prospective case–cohort design; data from Cancer Registry of Norway ensure a high degree of completeness; independent exposure estimates developed for this cohort; analyses adjusted for some confounders Limitations: potential recall bias for distant occupations (non-differential); individual differences in exposure within each occupational group could not be taken into account
			T1 (< 0.001–0.037)	5	1.12 (0.31–4.01)		
			T2 (> 0.037–0.123)	4	1.12 (0.30–4.23)		
			T3 (0.124–0.948)	6	2.24 (0.65–7.71)		
			Trend test *P* value, 0.188				
		Leukaemia (AML): ICD-10 (code C92.0)	Cumulative exposure tertiles (ppm-yr)			Age, benzene exposure from other work, ever daily smoker	
			T1 (< 0.001–0.037)	2	1.40 (0.18–11.00)		
			T2 (> 0.037–0.123)	1	0.85 (0.08–9.29)		
			T3 (0.124–0.948)	5	4.85 (0.88–27.00)		
			Trend test *P* value, 0.052				
		NHL (CLL): ICD-10 (codes C83.0, C91.1)	Cumulative exposure tertiles (ppm-yr)			Age, benzene exposure from other work, ever daily smoker	
			T1 (< 0.001–0.037)	4	6.23 (0.71–54.00)		
			T2 (> 0.037–0.123)	2	3.08 (0.28–34.00)		
			T3 (0.124–0.948)	5	6.74 (0.75–60.00)		
			Trend test *P* value, 0.212				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhomberg et al. (2016) USA 1940–1996 Cohort	1696 workers from three rubber manufacturing plants (Pliofilm) for at least 1 d Exposure assessment method: quantitative measurements; updated benzene exposure estimates based on job classifications, reconstructed by additional interviews of former workers	Leukaemia (AML)	Cumulative exposure quintiles (ppm-yr)			NR	One of many re-evaluations of the Pliofilm cohort; evidence of a threshold effect and relevant exposure window (exposure within 10 yr of cancer onset appeared to be most relevant) Strengths: re-evaluated benzene exposure estimates based on quintiles Limitations: mortality-based; no control for potential confounders; low number of cases; no new cases; exposure reassessment for this cohort was based on few additional data and was supported by the chemical industry; elevated estimates increase the likelihood of observing an apparent threshold
			< 1.55	0	0 (0–8.88)		
			1.55–6.33	0	0 (0–8.68)		
			6.34–20.24	0	0 (0–8.57)		
			20.25–80.10	0	0 (0–7.53)		
			> 80.11	6	10.11 (3.71–22.01)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ireland et al. (1997) USA 1940–1977/ through 1991 Cohort	4172 hourly male chemical plant workers who began employment during 1940–1977 Exposure assessment method: expert judgement; benzene-using departments: nitrobenzene, phenol, chlorobenzene, muriatic acid, and alkylbenzene production; most exposures estimated by IH judgement with information on process changes	Leukaemia: all (AML, ALL, CML, CLL) ICD-8 (codes 204–207)	Cumulative exposure (ppm-mo)			Age	Cumulative exposures were low compared with rubber hydrochloride cohort Strengths: examined exposure categories and number of days with peak exposures Limitations: collection of exposure data began in 1980 when only chlorobenzene and muriatic acid departments were still running, so most exposure assignments were estimated by industrial hygienists (including during 1940s–1950s, when exposure data were very sparse); death certificates were the primary ascertainment source; some leukaemias likely missed or misclassified; possibility of exposure to contaminants in coal-tar-derived benzene used at facility; benzene exposures for maintenance workers could not be estimated
			Unexposed	5	1.1 (0.4–2.6)		
			< 12	2	2.5 (0.3–8.9)		
			12–72	0	0 (0–5.4)		
			≥ 72	3	4.6 (0.9–13.4)		
		Leukaemia: acute nonlymphatic	Cumulative exposure (ppm-mo)			Age	
			Unexposed	2	1.4 (0.2–5.0)		
			< 12	1	3.7 (0.1–20.6)		
			12–72	0	0 (0–44.1)		
			≥ 72	1	4.5 (0.1–25.3)		
		NHL (CLL)	Cumulative exposure (ppm-mo)			Age	
			Unexposed	1	1.0 (0–5.5)		
			< 12	1	5.9 (0.1–32.6)		
			12–72	0	0 (0–24.7)		
			≥ 72	1	6.7 (0.2–37.7)		
		Multiple myeloma	Cumulative exposure (ppm-mo)			Age	
			Unexposed	1	0.5 (0–2.8)		
			< 12	0	0 (0–10.1)		
			12–72	2	6.8 (0.8–2.5)		
			≥ 72	1	3.7 (0.1–20.1)		
		Hodgkin lymphoma	Cumulative exposure (ppm-mo)			Age	
			Unexposed	0	0 (0–3.3)		
			< 12	0	0 (0–16.8)		
			12–72	0	0 (0–21.4)		
			≥ 72	0	0 (0–27.4)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Linet et al. (2015) China, 12 cities 1972–1987/1972–1999 Cohort	73 789 benzene-exposed and 35 504 unexposed Chinese workers; spray and brush painting (coatings), rubber, chemical (including pharmaceutical manufacturing), shoemaking, and other (including printing and insulation) industries Exposure assessment method: records; workers dichotomized (benzene-exposed/unexposed) based on job titles and factory records of use of benzene-containing materials	Pharynx (nasopharynx): ICD-8 (code 147)	Exposed	29	1.9 (0.9–4.3)	Sex, attained age, attained calendar year	Update of the NCI-CAPM cohort; supersedes Yin et al. (1996a), Hayes et al. (1996); lag 2 yr for HLD, 10 yr for all other outcomes; no unexposed incident cases available for CLL Strengths: large sample size; follow-up of 28 yr Limitations: exposure dichotomized to exposed/unexposed only (no further classification); wide range of industrial processes included; limited control for confounders
		Stomach/gastric cancer	Exposed	211	1.0 (0.8–1.3)	Sex, attained age, attained calendar year	
		NHL (B-cell lymphoma): ICD-8 (codes 202–202); lymphomas and Hodgkin lymphoma	Exposed	31	4.0 (1.6–13.4)	Sex, attained age, attained calendar year	
		NHL (B-cell lymphoma): ICD-9 (codes 202–202); lymphomas and Hodgkin lymphoma	Exposed	31	3.2 (1.4–9.4)	Sex, attained age, attained calendar year	
		NHL (B-cell lymphoma): ICD-9 (codes 202, 202)	Exposed	30	3.9 (1.5–13.2)	Sex, attained age, attained calendar year	
		Multiple myeloma: ICD-9 (code 20)	Exposed	1	0.12 (0.01–0.96)	Sex, attained age, attained calendar year	
		Leukaemia: ICD-9 (codes 204–208)	Exposed	60	2.5 (1.4–4.9)	Sex, attained age, attained calendar year	
		Leukaemia (lymphoid): ICD-9 (codes 204.0, 204.1, 204.2)	Exposed	10	5.4 (1.0–99.3)	Sex, attained age, attained calendar year	

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Linet et al. (2015) (cont.)		Leukaemia (ALL): ICD-9 (code 204.0)	Exposed	18	4.5 (0.8–83.9)	Sex, attained age, attained calendar year	
		Leukaemia (myeloid): ICD-9 (codes 205, 206)	Exposed	39	2.2 (1.1–4.6)	Sex, attained age, attained calendar year	
		Leukaemia (AML): ICD-9 (codes 205.0, 206.0, 207.0, 207.1, 207.2)	Exposed	26	2.1 (0.9–5.2)	Sex, attained age, attained calendar year	
		Leukaemia (CML): ICD-9 (codes 205.1, 205.2)	Exposed	13	2.5 (0.8–10.7)	Sex, attained age, attained calendar year	
		Leukaemia: acute, NOS, ICD-9 (code 208.0)	Exposed	6	3.5 (0.6–66.1)	Sex, attained age, attained calendar year	
		Leukaemia: NOS, ICD-9 (codes 208.8, 208.9)	Exposed	5	2.4 (0.4–44.4)	Sex, attained age, attained calendar year	
		NHL (CLL): ICD-9 (codes 204.1, 204.2)	Exposed	2	NR	Sex, attained age, attained calendar year	
		NHL (CLL): ICD-9 (codes 204.1, 204.2)	Exposed	2	NR	Sex, attained age, attained calendar year	

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kirkeleit et al. (2008) Norway 1981–2003 Cohort	27 919 offshore petroleum workers registered to the Norwegian registry of employers and employees, and 366 114 matched controls from the general working population Exposure assessment method: other; location of work and job category	Leukaemia (ALL): ICD-9 (code 204.0)	Exposed in upstream offshore workers	1	2.20 (0.30–16.60)	Sex, age, year of first exposure, education	
		Leukaemia (AML)	Exposed in upstream offshore workers	6	2.89 (1.25–6.67)	Sex, age, year of first exposure, education	
		Leukaemia (CML)	Exposed in upstream offshore workers	1	1.44 (0.19–10.70)	Sex, age, year of first exposure, education	
Guénel et al. (2002) France 1978–1989 Nested case–control	Cases: 72 identified among male workers Controls: 285 controls matched to the cases by year of birth Exposure assessment method: expert judgement; JEM developed from expert judgement	Leukaemia (ALL): ICD-9 (code 204.0)	Exposure (benzene unit-yr)			Age matched	
			Never	9	1.0		
			> 0 to < 5.5	1	0.6 (0.1–5.3)		
			> 5.5	2	3.3 (0.3–43.3)		
			Trend test *P* value, 0.16				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wong et al. (1993) USA 1946–1985 Cohort	18 135 employees with potential exposure to gasoline for at least 1 yr at land-based terminals (n = 9026) or on marine vessels (n = 9109) Exposure assessment method: questionnaire	Leukaemia (ALL)	Land-based employees exposed to gasoline	2	1.3 (0.1–4.5)	NR	
			Marine-based employees exposed to gasoline	1	0.8 (0–4.4)		

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; d, day(s); HLD, haematopoietic, lymphoproliferative, and related disorders; ICD, International Statistical Classification of Diseases and Related Health Problems; IH, industrial hygiene; JEM, job-exposure matrix; MDS, myelodysplastic syndrome; mo, month(s); MPD, myeloproliferative disorder; NCI-CAPM, National Cancer Institute-Chinese Academy of Preventive Medicine; NHL, non-Hodgkin lymphoma;
NOS, not otherwise specified; NR, not reported; ppm, parts per million; SMR, standardized mortality ratio; yr, year(s)

13 years to the end of 2009. Industrial hygiene measurements of benzene were used to estimate job-specific exposures over time. The average exposure duration of cohort members was 4.9 years (range, 30 days–44.7 years), and cumulative exposure of the subjects was divided into three categories (0–3.9, 4.0–24.9, and ≥ 25 ppm-years). [The strengths of this study included its long and complete follow-up and comprehensive exposure assessment. However, it was based on mortality rather than incidence, there was no control for potential confounders, and the number of cases was small.]

(iii) Chinese workers

The incidence of and mortality from cancers of the lymphatic and haematopoietic system were studied in a large cohort of Chinese workers comprising 74 828 workers exposed to benzene and 35 805 unexposed workers (National Cancer Institute-Chinese Academy of Preventive Medicine (NCI-CAPM) cohort). The initial follow-up period of 1972–1987, which had a quantitative assessment for exposure to benzene (Hayes et al., 1997), was extended to 1999 using factory records, hospital records, and death certificates (Linet et al., 2015). Benzene exposure assessment was based on factory and job-specific information on the use of material containing benzene, and was limited to classification as ever (for at least 6 months) versus never exposed, preventing any dose–response evaluation. The study included 60 and 13 incident cases of leukaemia of all types in exposed and unexposed workers, respectively. [The strengths of this study included the large size of the cohort, which included both sexes and covered several different industries, and the long follow-up, with small numbers lost to follow-up. Control for potential confounders was limited to sex, age, and calendar period. The numbers of cases were relatively small in some subgroups, particularly among unexposed workers.]

(iv) Norwegian offshore oil workers

Kirkeleit et al. reported on a prospective cohort study of 27 919 workers listed as having been employed in the offshore oil industry in the Norwegian Registry of Employers and Employees between 1981 and 2003, and followed up for cancer incidence in the Cancer Registry of Norway until the end of December 2003 (Kirkeleit et al., 2008). No quantitative estimates of benzene exposure were derived.

Stenehjem et al. (2015) reported on 24 917 male petroleum workers with at least 20 days employment offshore between 1965 and 1999. The cohort was established by means of a postal questionnaire in 1998, asking participants to report on occupational history and potential confounding factors. About 50% of the offshore workers overlapped with the register-based cohort of male and female offshore workers followed up by Kirkeleit et al. (2008). The follow-up periods of the two studies overlapped by only 5 years out of a total of 31 years of observation; Kirkeleit et al. (2008) covered 1981–2003 and Stenehjem et al. (2015) covered 1999–2011. The overlap is described in (Stenehjem et al., 2014). Incident cancers were identified prospectively by linkage with the Cancer Registry of Norway (Stenehjem et al., 2015). A total of 112 cases of cancers of the lymphatic and haematopoietic system diagnosed during 1999–2011 were identified and compared with a reference subcohort of 1661 workers using a nested case–cohort design (Stenehjem et al., 2015). A job-exposure matrix (JEM) was developed to assess exposure to benzene. The JEM scores were then translated into corresponding ppm values estimated on the basis of industrial benzene measurement data in Norway (Steinsvåg et al., 2007; Bratveit et al., 2011). In all analyses, adjustment was made for benzene exposure from other work (coded as yes or no, depending on the self-reported job titles and/or industry sector where the worker had ever been employed, e.g. shipping, chemical industry,

painting and surface treatment, farming and forestry, or other industry) and smoking status (yes, no, unknown). [The main strengths of this study were the prospective design, the reliability of incidence data, and detailed exposure estimates (Steinsvåg et al., 2007).]

(v) Reassessment of the Pliofilm cohort study

The cohort of workers at three Pliofilm (rubber hydrochloride) manufacturing plants in Ohio (USA) consisted of 1696 workers followed up for mortality between 1940 and 1996 (Wong, 1995; Rinsky et al., 2002) included in *IARC Monographs* Volume 100F, Table 2.1 (available at: http://publications.iarc.fr/123). Methods of exposure assessment differed between investigators, leading to different distributions of benzene exposure in the cohort and different risk values depending on the exposure levels assigned to the cases. In a recent publication, Rhomberg and collaborators reassessed exposure to benzene using a probabilistic approach based on air sampling data and assumptions about how workplace concentrations decreased over time (Rhomberg et al., 2016). The uptake of benzene from dermal exposures was also estimated, and new exposure information was obtained through additional interviews of former workers (Williams & Paustenbach, 2003). Using these new estimates, the authors divided cohort members according to quantiles of benzene exposure distribution; about 20% of the cohort members were found to have cumulative exposures of more than 80.11 ppm-years. Previous investigators (Wong, 1995; Rinsky et al., 2002) had both used fixed cut-offs of 40, 200, and 400 ppm-years. [The Working Group noted that both the outcome categorization (leukaemia subtypes) and the exposure assessment methods and cut-offs were revised from multiple analyses reported from this cohort, and that this had an important impact on different risk estimates reported for the same set of study participants.]

(c) Acute non-lymphocytic leukaemia/acute myeloid leukaemia and myelodysplastic syndrome

Studies of AML and ANLL were reviewed by a previous Working Group in *IARC Monographs* Volume 100F. That review included studies also present in previous evaluations for Volume 29 (IARC, 1982) and Supplement 7 (IARC, 1987). The data reviewed in *IARC Monographs* Volume 100F (IARC, 2012a) were described as follows by that Working Group: "...analyses of 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). It was also noted that the NCI-CAPM cohort study [of Chinese workers exposed to benzene] found evidence of an increased risk for the combined category of ANLL and myelodysplastic syndromes (Hayes et al., 1997)".

New results on AML/ANLL and CML published since that time are described in the following and summarized in Table 2.1. Results regarding myelodysplastic syndromes (MDS) are also described in the text (not included in the table), as some cases of MDS can progress to AML and may have been classified in this way in earlier publications.

(i) Petroleum distribution workers

In the pooled analysis of three updated nested case–control studies of petroleum distribution workers from Australia, Canada, and the United Kingdom, 60 cases were classified as AML

(241 matched controls) and 29 as MDS (129 matched controls) (Schnatter et al., 2012).

Conditional logistic odds ratios (ORs) for AML were above unity for most exposure metrics, although none reached statistical significance (highest vs lowest cumulative exposure tertiles OR, 1.39; 95% confidence interval (CI), 0.68–2.85; average exposure intensity OR, 1.90; 95% CI, 0.86–4.18; maximum exposure intensity OR, 1.65; 95% CI, 0.75–3.73; duration of employment OR, 1.70; 95% CI, 0.75–3.87; peak exposure OR, 1.50; 95% CI, 0.82–2.75; dermal exposure OR, 1.15; 95% CI, 0.60–2.22), but no clear dose–response relationship could be demonstrated. In a further analysis of the same AML data, these associations were found to be more consistent in the subgroup of terminal workers who experienced higher exposure levels (Rushton et al., 2014). Finally, MDS showed a consistent monotonic trend for all benzene exposure metrics (e.g. for cumulative exposure, highest vs lowest tertile OR, 4.33; 95% CI, 1.31–14.3; *P* for trend, 0.01; based on 29 cases) (Schnatter et al., 2012).

[Quantitative exposure assessment and ascertainment of leukaemia subtypes were conducted carefully in this pooled analysis. The average exposure to benzene was found to be much lower than in studies of other populations exposed at higher levels, possibly explaining the non-statistically significant associations with AML. A monotonic trend was observed between benzene exposure and MDS. Previous studies relied upon an outcome classification where MDS was typically not identified (e.g. from death certificate). Some cases classified as AML in the original cohort studies were reclassified as MDS in the pooled analysis, leading to a more precise definition of outcomes, and therefore also likely contributing to the lack of associations with AML.]

(ii) Dow Chemical workers, Midland, Michigan

There were five deaths from AML in the cohort of 2266 workers exposed to benzene at a Dow Chemical plant, giving a standardized mortality ratio (SMR) of 1.11 (95% CI, 0.36–2.58) in the total population (*P* for trend, 0.88) (Collins et al., 2015). Standardized mortality ratios were similar when considering the whole ANLL subgroup (five deaths) or taking account of a latency period of more than 30 years (four deaths). No associations with AML were observed by tertiles of cumulative benzene exposure (in ppm-years). There was one MDS death in the group exposed to the highest concentrations of benzene. [This study had important limitations in terms of the small number of leukaemia cases, the use of mortality rather than incidence data, and the absence of an internal reference group.]

(iii) Chinese workers

Previously published results of ANLL incidence in this cohort of Chinese workers revealed statistically significantly elevated relative risks (RRs) for cumulative benzene exposure of 40 ppm-years or more (*P* for trend, 0.06). In analyses of ANLL/MDS, a significant positive trend was also observed (*P* for trend, 0.01) (Hayes et al., 1997). This updated study confirmed previous results, with more precise estimates (Linet et al., 2015). A total of 26 AML cases were ascertained among the subjects exposed to benzene and 7 among the unexposed, resulting in a relative risk of 2.1 (95% CI, 0.9–5.2). In addition, there were 8 MDS cases among the exposed and none among the unexposed group. Relative risks for AML/MDS were lower in 1988–1999 (RR, 1.3; 95% CI, 0.4–5.9) compared with 1972–1987 (RR, 3.7; 95% CI, 1.5–12.8), but the difference was not significant. [The strengths of this study included the large size of the cohort and the long and complete follow-up, with small numbers of subjects lost to follow-up. The main limitation was the lack of analysis of quantitative exposure

to benzene, as workers were simply categorized as exposed or not exposed.]

(iv) Norwegian offshore oil workers

A study based on a Norwegian cohort of offshore oil industry workers (included in *IARC Monographs* Volume 100F, Table 2.1, available at: http://publications.iarc.fr/123) showed an increased risk of AML (RR, 2.89; 95% CI, 1.25–6.67) compared with the general working population (Kirkeleit et al., 2008).

In a later, partially overlapping cohort study analysed using a case–cohort approach (Stenehjem et al., 2015), the hazard ratio (HR) of AML for offshore workers ever exposed versus never exposed to benzene was 2.18 (95% CI, 0.47–10.00). The risk estimate was substantially higher in the highest tertile of cumulative exposure (0.124–0.948 ppm-years) compared with the lowest tertile (< 0.001–0.037 ppm-years), with a hazard ratio of 4.85 (95% CI, 0.88–27.00; *P* for trend, 0.052). Regarding other metrics evaluated, hazard ratios were greatest in the highest tertile of average intensity (HR, 3.21; 95% CI, 0.63–19; *P* for trend, 0.092), cumulative peak (HR, 3.61; 95% CI, 0.59–26.00; *P* for trend, 0.166), and average peak (HR, 4.87; 95% CI, 0.90–26.00; *P* for trend, 0.056). No clear pattern was observed for duration of exposure in years.

[The main strengths of these studies included the prospective design, the reliability of incidence data, and the detailed exposure estimates. Stenehjem et al. (2015) included new cases of AML diagnosed during 1999–2011 but not the cases included in the earlier follow-up; this led to a relatively small number of cases. The narrow distribution of benzene exposure was an important limitation.]

(v) Reassessment of the Pliofilm cohort study

After reassessment of exposure to benzene in the Pliofilm cohort study in Ohio, all six deaths from AML were observed in the highest quintile of benzene exposure (SMR, 10.11; 95% CI, 3.71–22.01), possibly indicating a threshold effect of benzene exposure of more than 80.11 ppm-years (Rhomberg et al., 2016). By contrast, using fixed cut-offs for categories of benzene exposure (based on a balanced distribution of cases), Rinsky et al. (2002) classified four deaths from exposure to benzene at more than 400 ppm-years, giving an unstable standardized mortality ratio of 34.79 (95% CI, 9.48–89.09) in this exposure category. In the analysis using lag times of 0, 5, 10, 15, or 20 years, Rhomberg et al. (2016) found that the highest risk of AML mortality remained in the highest category of exposure, and the observations were consistent with an association with benzene exposure within the past 10 years. [The elevated exposure estimates increased the likelihood of observing an apparent threshold by assigning exposed workers to a higher exposure category; these results were questioned by the Working Group, however, due to the retrospective reassessment of exposure and the use of simulation methods.]

(d) Chronic myeloid leukaemia and myeloproliferative disorder

Studies of CML and occupational exposure to benzene were also reviewed in *IARC Monographs* Volume 100F. Occupational cohort studies available at that time were described as follows: "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)".

Additional data for CML/MPD in occupational cohorts that have become available since that time are described here and summarized in Table 2.1.

(i) Petroleum distribution workers

The pooled analysis of updated case–control studies nested within three occupational cohorts of petroleum distribution workers from Australia, Canada, and the United Kingdom exposed to low concentrations of benzene included 28 cases of CML (characterized by the presence of the Philadelphia chromosome, a specific genetic abnormality in chromosome 22) and 30 cases of MPD (Schnatter et al., 2012). Matched controls included 122 and 124 men for CML and MPD, respectively. For CML, compared with the lowest tertile, the odds ratio for cumulative exposure was 5.04 (95% CI, 1.45–17.50) in the second tertile (exposure of 0.34–2.93 ppm-years) and 2.20 (95% CI, 0.63–7.68) in the highest tertile (*P* for trend, 0.02). No clear indication of the existence of a monotonic dose–response relationship emerged when incorporating the additional exposure metrics considered in the study (see Section 2.1.1(b)(i)).

For MPD, odds ratios for cumulative exposure were 1.28 (95% CI, 0.47–3.98) in the second tertile and 1.79 (95% CI, 0.68–4.74) in the upper tertile; the trend was not significant (*P* for trend, 0.49). No strong relationship was shown with any other metrics for the whole exposure period. After restricting the exposure window to 2–20 years before diagnosis, statistically or borderline significant dose–response trends were found for cumulative exposure, dermal exposure, maximum intensity, and average intensity. An odds ratio of 3.81 (95% CI, 1.36–10.70) was reported for peak exposure, based on 18 cases ever exposed to more than 3 ppm for 1 year or more (Schnatter et al., 2012; Glass et al., 2014). [This study was the first to examine CML and MPD as separate entities. The Working Group noted that exposure to benzene was relatively low in these cohorts.]

(ii) Chinese workers

The incidence of CML in the NCI-CAPM cohort of Chinese workers was non-significantly elevated in exposed workers compared with non-exposed workers (13 exposed cases; OR, 2.5; 95% CI, 0.8–10.7) (Linet et al., 2015). Results for mortality were almost identical (not reported). [No dose–response relationship was reported, because workers were simply classified as exposed or unexposed to benzene.]

2.1.2 General-population studies

See Table 2.2

General-population studies of leukaemia in adults and exposure to benzene were also reviewed in *IARC Monographs* Volume 100F, reporting the following for ANLL: "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, available at: http://publications.iarc.fr/123). 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)." Regarding CML, Volume 100F reported: "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://publications.iarc.fr/123)".

For the current evaluation, the Working Group included all general-population cohort studies and case–control studies published in 2009 or later that examined the relationship between benzene exposure (assessed quantitatively or qualitatively) and AML or CML. Studies were excluded if they did not specifically address benzene exposure, but instead used other indicators of traffic-related air pollution (Raaschou-Nielsen et al., 2016) or residential proximity to

Table 2.2 General-population studies of exposure to benzene and leukaemia in adults

Reference, location, follow-up/ enrolment period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kaufman et al. (2009) Bangkok, Thailand 1997–2003 Case–control	Cases: 87 incident cases at Siriraj Hospital, Bangkok Controls: 756 initially age- and sex-matched hospital patients with diagnoses "considered generally unrelated to the exposures of interest" Exposure assessment method: questionnaire	Leukaemia (AML)	Ever exposed Unexposed Exposed	 81 6	 1.0 4.9 (1.4–17.0)	Age, sex, income, use of cellphones, occupational and nonoccupational pesticide exposure, pesticides used near the home, working with powerlines, living near powerlines	Strengths: high response (100%) Limitations: small study; self-reported ever/never exposure; potentially substantial selection and/ or recall bias
Wong et al. (2010a) Shanghai 2003–2007 Case–control	Cases: 722 newly diagnosed AML cases in 29 hospitals; response 94.6% Controls: 1444 patients without malignant diseases and without diseases of the lymphatic and haematopoietic system admitted to the same hospital as the individually matched case (2 controls per case); response 99.0% Exposure assessment method: expert judgement; exposure classification carried out on a job-by-job basis (jobs identified by questionnaire) by an expert committee (blind for case–control status)	Leukaemia (AML)	Benzene exposure (yr) Never (reference) Ever ≤ 10 > 10 to < 20 > 20 Benzene exposure (mg/m³) Group 1: < 1 Group 2: 1–10 Groups 3, 4: >> 10 Period of first exposure 1940–1959 1960–1979 1980–1999 after 2000 Trend test *P* value, 0084 (length of exposed job); 0.01 (maximum exposure)	 644 78 43 21 14 40 20 18 8 22 36 12	 1.00 1.43 (1.05–1.93) 1.99 (1.29–3.07) 1.44 (0.82–2.51) 0.74 (0.39–1.39) 1.18 (0.79–1.76) 1.63 (0.90–2.94) 2.05 (1.05–3.98) 1.33 (0.54–3.26) 0.97 (0.57–1.62) 1.57 (1.00–2.46) 4.18 (1.56–11.15)	Age, sex, hospital	Funding: Benzene Health Effects Consortium Strengths: large study; complete occupational histories with expert assessment Limitations: hospital-based study including potential for selection bias; expert assessment of benzene exposure based on self-reported questionnaire data

Table 2.2 (continued)

Reference, location, follow-up/ enrolment period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Saberi Hosnijeh et al. (2013) 23 centres in 10 European countries 1992–2000 Cohort	241 465 men and women aged 35–70 yr at recruitment, with no prevalent cancer Exposure assessment method: expert judgement; occupational exposures of high-risk occupations estimated by linking them to a general-population JEM originally developed for another study; exposure to benzene classified as "high", "low", and "no exposure" based on job code; 113 cases of AML, but not specified by exposure	Leukaemia (AML)	No exposure	NR	1.00	Sex, smoking status, alcohol intake, age at recruitment, country	Strengths: large cohort with long follow-up; detailed information on confounders Limitations: lack of occupational histories in large number of participants; different procedures to identify cases; exposure classification not very detailed
			Low exposure	NR	1.06 (0.63–1.81)		
			High exposure	NR	1.52 (0.78–2.98)		
			Trend test *P* value, 0.28				
		Leukaemia (CML)	No exposure	NR	1.00	Sex, smoking status, alcohol intake, age at recruitment, country	
			Low exposure	NR	1.00 (0.45–2.22)		
			High exposure	NR	1.97 (0.75–5.19)		
			Trend test *P* value, 0.30				
		NHL (CLL)	No exposure	NR	1.00	Sex, smoking status, alcohol intake, age at recruitment, country	
			Low exposure	NR	1.11 (0.78–1.58)		
			High exposure	NR	0.56 (0.27–1.14)		
			Trend test *P* value, 0.37				
Talibov et al. (2014) Finland, Iceland, Norway, Sweden 1961–2005 Nested case–control	Cases: 15 332 incident cases Controls: 76 660 randomly selected among cohort members who were alive and free from AML on the date of diagnosis of the matched index case (5 controls per case) Exposure assessment method: other; NOCCA JEM based on FINJEM; quantitative assessment (ppm-yr)	Leukaemia (AML)	Cumulative exposure (ppm-yr)			Year of birth, sex, country	The study was funded by Doctoral Programs in Public Health (DPPH)/ Academy of Finland Strengths: very large nested study; selection bias improbable Limitations: exposure classification by JEM relatively unprecise; "cross-sectional" information on jobs held (based on census records); no adjustment for smoking or genetic factors
			50th and 90th percentiles: unexposed	NR	1.00		
			≤ 3.7	430	1.02 (0.84–1.24)		
			3.7–13.6	310	0.88 (0.71–1.11)		
			> 13.6	68	0.80 (0.56–1.15)		
			Trend test *P* value, 0.33				

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; FINJEM, Finnish job-exposure matrix; JEM, job-exposure matrix; NHL, non-Hodgkin lymphoma; NOCCA, Nordic Occupational Cancer Study; NR, not reported; ppm, parts per million; yr, year(s)

gasoline plume (Talbott et al., 2011), or if they only combined benzene exposure with exposure to other solvents (Poynter et al., 2017), even if the text explicitly referred to "benzene exposure".

Since 2009, one new cohort study in the general population (European Prospective Investigation into Cancer and Nutrition study by Saberi Hosnijeh et al., 2013), one nested case–control study in the Nordic Occupational Cancer Study cohort (Talibov et al., 2014), and two new case–control studies (Kaufman et al., 2009; Wong et al., 2010a) have investigated the relationship between occupational benzene exposure and adult leukaemia.

A large cohort study with 241 465 participants covering 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) identified 113 AML cases by either population cancer registries, health insurance records, pathology registries, or active contact with study subjects or next of kin (Saberi Hosnijeh et al., 2013). Occupational exposure to benzene was assessed through a general-population JEM based on self-reported occupations of high risk. Exposure to benzene was classified as either "no exposure", "low exposure", or "high exposure". In the high-exposure category, the hazard ratio for AML was 1.52 (95% CI, 0.78–2.98; *P* for trend, 0.28). The same study reported on CML (46 cases in total) and found an increased hazard ratio of 1.97 in the high-exposure group (95% CI, 0.75–5.19; *P* for trend, 0.37). [The strengths of this study included its large size, its long follow-up, and the detailed information about confounders. The limitations included the lack of complete occupational histories in large numbers of participants, different procedures for case identification, and the lack of specificity in the exposure classification.]

Talibov et al. (2014) conducted a very large case–control study nested within the Nordic Occupational Cancer Study cohort. The study in Finland, Iceland, Norway, and Sweden comprised 15 332 AML cases and 76 660 control subjects. The authors did not find an association between occupational benzene exposure, as assessed by a JEM, and AML. With occupational unexposed workers as a reference, the hazard ratios of those exposed to benzene at 3.7 or less, 3.7–13.6, and more than 13.6 ppm-years was 1.02 (95% CI, 0.84–1.24), 0.88 (95% CI, 0.71–1.11), and 0.80 (95% CI, 0.56–1.15), respectively (*P* for trend, 0.33). [The strengths of this study included its very large size and its nested design, making selection bias improbable. The limitations included incomplete work histories for many participants and the imprecise exposure classification by JEM.]

In a hospital-based case–control study in Shanghai, China, Wong et al. (2010a) compared 722 newly diagnosed AML cases with 1444 control subjects without malignant diseases or diseases of the lymphatic and haematopoietic system. The authors found a monotonic exposure–response relationship between maximum occupational benzene exposure and AML (*P* for trend, 0.01). The odds ratios were 1.18 (95% CI, 0.79–1.76), 1.63 (95% CI, 0.90–2.94), and 2.05 (95% CI, 1.05–3.98) for maximum exposure to benzene at less than 1, 1–10, and more than 10 mg/m^3, respectively. Individuals with a first diagnosis after the year 2000 had a higher risk than individuals with an earlier date of first diagnosis. [The strengths of this study included its large size, as well as complete occupational history with job-specific questions, and expert assessment of exposures. The limitations included the potential for selection bias as a consequence of the hospital-based control selection.]

In a small hospital-based case–control study in Bangkok, Thailand, 87 AML cases were compared with 756 patients of the same hospital (Kaufman et al., 2009). For self-reported occupational benzene exposure, an elevated odds ratio of 4.9 (95% CI, 1.4–17.0) was found. [The high response rate was a strength of this study. Limitations included the potential for selection and recall bias as a consequence of the

hospital-based control selection and the use of self-reported benzene exposure (ever vs never).]

2.2 Adult lymphoma

This section presents the Working Group's review of studies of NHL and HL in adults. Because most of the available studies did not group the entities now included within NHL according to the current WHO classification (Swerdlow et al., 2017), the disease entities presented here are those used in the original publications. For occupational cohort studies, which were more numerous, data are presented for total NHL as defined in the original studies and MM when separate risk data were reported (in the same subsection), for CLL, for ALL, and for HL.

2.2.1 Occupational cohort studies

(a) Non-Hodgkin lymphoma and multiple myeloma

Twenty-one studies on the association between NHL, including MM, and exposure to benzene in occupational cohorts were included in *IARC Monographs* Volume 100F (see Table 2.9, available at: http://publications.iarc.fr/123). The purpose of the current update is to establish whether new studies contribute to the causal assessment of the overall evidence. Several articles on adult lymphomas included in *IARC Monographs* Volume 100F or published later were excluded by the Working Group either because the exposure assessment was considered inadequate to determine whether workers were exposed to benzene (Guberan & Raymond, 1985; Cuzick & De Stavola, 1988; La Vecchia et al., 1989; Blair et al., 1993; Walker et al., 1993; Lagorio et al., 1994; Satin et al., 1996; Lynge et al., 1997; Anttila et al., 1998; Gérin et al., 1998; Lundberg & Milatou-Smith, 1998; Divine et al., 1999b; Persson & Fredrikson, 1999; Mao et al., 2000; Wong et al., 2001a, b; Sorahan et al., 2002; Kauppinen et al., 2003; Xu et al., 2003; Dryver et al., 2004; Huebner et al., 2004; Punjindasup et al., 2015), or because these were either methodological articles or focused on mechanisms (Vineis et al., 2007; Barry et al., 2011; Faisandier et al., 2011).

Studies in occupational cohorts published after the compilation of *IARC Monographs* Volume 100F that are included for evaluation here are those published by Koh et al. (2011, 2014), Collins et al. (2015), Linet et al. (2015), and Stenehjem et al. (2015). These studies are summarized in Table 2.3.

Most studies reported a small number of NHL cases as a result of exposure to benzene, usually less than 20, and generally presented mortality as an outcome, leading to low sensitivity of ascertainment for NHL. The exceptions are the studies by Hayes et al. (1997), Nilsson et al. (1998), Glass et al. (2003), Sorahan et al. (2005), Kirkeleit et al. (2008), Koh et al. (2011, 2014), Linet et al. (2015), and Stenehjem et al. (2015), which identified incident cases. To broadly characterize the available studies, exposure contexts included a variety of manufacturing processes including the petroleum industry, chemical plants, or others, as well as different exposure assessment methods (see Section 1.4.1 on Occupational exposure). Among the studies published before the previous evaluation in *IARC Monographs* Volume 100F, the current Working Group considered those with high-quality exposure assessment, case ascertainment, and follow-up, as well as a large sample size and adjustment for confounders, to be the most informative. None of the studies in the previous Monograph fulfilled all these criteria. All the studies considered in the evaluation are described below (chronologically), but only studies published after *IARC Monographs* Volume 100F are included in Table 2.3.

Wong (1987a) studied male workers from seven chemical plants in the USA, where jobs were classified based on past quantitative measurements. An apparent dose–response

Table 2.3 Occupational cohort studies of exposure to benzene and lymphoma in adults

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Collins et al. (2015) USA 1940–2009 Cohort	2266 chemical industry workers exposed to benzene as solvent and raw material Exposure assessment method: quantitative measurements; job-specific exposure estimated from measurements taken from 1944 to the late 1970s	NHL: ICD-10 (codes C82–C85.9)	Cumulative exposure (ppm-yr)			Age, race, sex	Third update of the Dow Chemical plant retrospective cohort Strengths: extensive benzene exposure monitoring; complete work history information; periodic medical examination at workplace; long and complete follow-up Limitations: small cohort; mortality data (based on death certificates) for a period over which diagnosis and classification were uncertain
			> 30 yr latency	12	1.02 (0.53–1.78)		
			0–3.9	6	1.23 (0.45–2.69)		
			4–24.9	6	1.10 (0.41–2.40)		
			≥ 25	3	0.58 (0.12–1.69)		
			Trend test *P* value, 0.26				
		Hodgkin lymphoma: ICD-10 (code C81)	Cumulative exposure (ppm-yr)			Age, race, sex	
			> 30 years latency	1	1.32 (0.03–7.36)		
			0–3.9	0	0 (0–5.28)		
			4–24.9	2	2.63 (0.32–9.51)		
			≥ 25	0	0 (0–4.85)		
			Trend test *P* value, 0.35				
Linet et al. (2015) China 1972–1987/1972–1999 Cohort	35 804 benzene-exposed workers in 672 factories (spray and brush painting, rubber, chemical, shoemaking, and other) Exposure assessment method: records; factory and job title-specific information on the use of benzene-containing materials formed the basis for determining benzene-exposed or unexposed jobs; no quantitative assessment	Multiple myeloma: ICD-9 (code 203)	Exposed/unexposed			Sex, age, calendar year	Strengths: very large cohort; few losses to follow-up; long follow-up (28 yr); very careful ascertainment of haematolymphopoietic malignancies Limitations: no quantitative assessment of exposure; wide range of industrial processes included; coexposures vary and were not addressed in the analyses; very small numbers for CLL (zero unexposed cases)
			Mortality	1	0.10 (0.01–1.00)		
			Incidence	1	0.12 (0.01–0.96)		
		NHL: ICD-9 (codes 200, 202)	Exposed/unexposed			Sex, age, calendar year	
			Mortality	31	4.0 (1.6–13.4)		
			Incidence	30	3.9 (1.5–13.2)		
		NHL (CLL): ICD-9 (codes 204.1, 204.2)	Exposed/unexposed			Sex, age, calendar year	
			Incidence	2	NR		
		Leukaemia (ALL): ICD-9 (code C204.0)	Exposed/unexposed			Sex, age, calendar year	
			Incidence	8	4.5 (0.8–83.9)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Koh et al. (2011) Korea 1960–2007 Cohort	8866 male workers in refinery/petrochemical complex in Korea producing benzene or using benzene as a raw material Exposure assessment method: other; job title	NHL	Subgroups of workers (exposure-based) in the petrochemical complex			Age, calendar period	Strengths: incidence data Limitations: small number of cases; exposure assessment based on job title
			Manufacturing workers	2	0.70 (0.08–2.52)		
Koh et al. (2014) Korea 2002–2007 (2002–2005 for incidence) Cohort	14 698 male workers registered in a regional petrochemical plant maintenance workers union Exposure assessment method: none; job title	NHL: ICD-10 (codes C82–C85)	Maintenance workers, incidence	3	1.83 (0.38–5.34)	Age	Limitations: very small number of cases
		NHL: ICD-10 (codes C82–C85)	Maintenance workers, mortality	2	1.24 (0.15–4.47)	Age	
Stenehjem et al. (2015) Norway 1965–1999/1999–2011 Cohort	24 917 male petroleum workers; offshore oil industry workers for at least 20 d during 1965–1999, extracted from a cohort who responded to a survey conducted with postal questionnaires Exposure assessment method: quantitative measurements; a JEM was developed using monitoring data and job-specific information, giving semiquantitative estimates; JEM scores then translated into corresponding ppm values	NHL (B-cell lymphoma): ICD-10 (codes C82–C91)	Exposed/unexposed			Age, benzene exposure from other work, ever daily smoker	Nested case–cohort study based on an updated cohort of Norwegian offshore workers Strengths: prospective case–cohort design; data from Norway cancer registry ensure a high degree of completeness; independent exposure estimates developed for this cohort; analyses adjusted for some confounders Limitations: potential recall bias for distant occupations (non-differential); individual differences in exposure within each occupational group could not be taken into account
			Exposed	61	1.49 (0.90–2.48)		
			Trend test *P* value, 0.245				
		Multiple myeloma: ICD-10 (code C90.0)	Exposed/unexposed			Age, benzene exposure from other work, ever daily smoker	
			Exposed	13	1.64 (0.55–4.89)		
			Trend test *P* value, 0.024				
		NHL (CLL): ICD-10 (codes C83.0, C91.1)	Cumulative exposure tertile (ppm-yr)			Age, benzene exposure from other work, ever daily smoker	
			T1 (< 0.001–0.037)	4	6.23 (0.71–54.00)		
			T2 (> 0.037–0.123)	2	3.08 (0.28–34.00)		
			T3 (0.124–0.948)	5	6.74 (0.75–60.00)		
			Trend test *P* value, 0.212				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Collins et al. (2015) USA 1940–2009 Cohort	2266 workers exposed to benzene at a chemical plant Exposure assessment method: quantitative measurements; job titles were assigned to exposure categories by an industrial hygienist, based on IH measurements (JEM)	Leukaemia: ICD-10 (codes C91–C95)	Cumulative exposure (ppm-yr)			NR	Third update of the Dow Chemical plant retrospective cohort; one death for MDS, and it was in the high-exposure group (SMR 25.05; 95% CI: 0.63–139.58) Strengths: extensive benzene exposure monitoring; complete work history information; periodic medical examination at workplace; long and complete follow-up Limitations: mortality study based on death certificates; no evaluation of possible confounders
			0–3.9	3	0.60 (0.12–1.76)		
			4.0–24.9	7	1.23 (0.49–2.53)		
			≥ 25	10	1.72 (0.86–3.17)		
			Trend test *P* value, 0.15				
		Leukaemia (myeloid): ICD-10 (code C92)	Cumulative exposure (ppm-yr)			NR	
			0–3.9	0	0 (0–1.79)		
			4.0–24.9	4	1.78 (0.48–4.54)		
			≥ 25	4	1.93 (0.53–4.94)		
			Trend test *P* value, 0.24				
		Leukaemia (AML): ICD-10 (code C92.0)	Cumulative exposure (ppm-yr)			NR	
			0–3.9	0	0 (0–2.50)		
			4.0–24.9	3	1.87 (0.39–5.47)		
			≥ 25	2	1.39 (0.17–5.03)		
			Trend test *P* value, 0.88				
		Leukaemia (lymphoid): ICD-10 (code C91)	Cumulative exposure (ppm-yr)			NR	
			0–3.9	1	0.78 (0.02–4.36)		
			4.0–24.9	1	0.68 (0.02–3.78)		
			≥ 25	2	1.31 (0.16–4.72)		
			Trend test *P* value, 0.53				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schnatter et al. (2012) Australia, Canada, UK 1981–2006 (Australia), 1964–1994 (Canada), 1950–2005 (UK) Nested case–control	Cases: 370 diagnoses based on incidence and mortality data (hospital records, cancer registries, death certificates) Controls: 1587; 5 age-matched (Australia) or 4 age- and company-matched (Canada and UK) controls selected using incidence density-based sampling Exposure assessment method: quantitative measurements; conducted at the job/ worksite/era level, based on routinely collected industry exposure measurements; work history was collected from company records (Canada and UK) or through interview and company records (Australia)	NHL (CLL)	Cumulative exposure (ppm-yr) ≤ 0.348 0.348–2.93 > 2.93 Trend test *P* value, 0.9	 24 32 24	 1.00 1.49 (0.81–2.76) 1.05 (0.56–1.98)	NR	Exposures are relatively low; based on limited data, smoking was unlikely to be a confounder Strengths: large study size; review of diagnosis by haematopathologists; reassessment of exposure across the three studies Limitations: Smoking data were incomplete

ALL, acute lymphoblastic/lymphocytic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; ICD, International Statistical Classification of Diseases and Related Health Problems; IH, industrial hygiene; JEM, job-exposure matrix; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NR, not reported; ppm, parts per million;
SMR, standardized mortality ratio; yr, year(s)

relationship between NHL and cumulative exposure to benzene was observed, with a relative risk of 3.7 (*P* value, < 0.04) for continuous or intermittent benzene exposure, and one of 3.8 (*P* value, < 0.04) for continuous benzene exposure compared with no exposure. [The Working Group noted the very small number of subjects in this study and that 95% confidence intervals were not reported.] Wong & Raabe (1997) conducted a nested case–control study on MM in gasoline distribution workers (17 MM deaths among the exposed). Total hydrocarbon concentrations in air were used as a surrogate measure of exposure to benzene. *P* values for trend were 0.06 for exposure duration, 0.77 for cumulative exposure to total, and 0.08 for peak exposure. [The Working Group considered the use of indirect estimates of exposure to benzene and the very small number of MM deaths to be strong limitations of this study.]

Schnatter et al. (1996) and Glass et al. (2003) both report on NHL and MM or NHL/MM, and were later included in a pooled analysis (Schnatter et al., 2012). Schnatter et al. (1996) conducted a nested case–control study of petroleum distribution workers in Canada where benzene exposure was quantitatively assessed and standardized mortality ratios were reported. Eight deaths from NHL were observed, and exposure–response analyses based on these showed no consistent pattern. Similarly, the study found non-significant standardized mortality ratios for MM based on seven deaths only (Schnatter et al., 1996). [The Working Group noted the adjustment for several potential confounders, but the very small sample size of the study.] Glass et al. (2003) conducted a nested case–control study in the petroleum industry in Australia, and did not observe a relationship between cumulative exposure to benzene and NHL/MM.

Consonni et al. (1999) report on a cohort of 1583 male oil refinery workers employed during 1949–1982 and followed up to May 1991. Comparing exposed with non-exposed workers, a standardized mortality ratio of 2.12 (95% CI, 0.68–4.95) was found based on 5 exposed NHL cases. The excess risk was significantly increased among workers with 15 years or more of employment, and 30 years or more since first employment.

Using a JEM based on air sampling data, Rinsky et al. (2002) assessed quantitative exposure to benzene for a cohort of workers manufacturing Pliofilm in the USA; the number of NHL or MM cases was very limited, however (5 for each, based on death certificates). The standardized mortality ratio for white males was 1.00 (95% CI, 0.32–2.33) for NHL and 2.12 (95% CI, 0.69–4.96) for MM (reference group unexposed). [The Working Group noted that exposure–response for NHL was not modelled because of the small numbers of cases.] Using the same Pliofilm cohort reported by Rinsky et al. (2002), Wong (1995) focused specifically on MM. Results were reported in terms of levels of cumulative exposure, and no increased mortality risk was observed. [The Working Group noted that results were based on extremely small numbers; 4 MM cases in total were categorized across four exposure strata.]

Collins et al. (2003) reported on NHL and MM in a small study with long follow-up (from 1940 to 1997) at a single chemical plant that was studied previously by Bond et al. (1986). The study was based on individual exposure measurements, and no increased risks for NHL mortality were observed (25 exposed cases in total). An increased standardized mortality ratio was reported for MM, but with a dose–response relationship that did not reach statistical significance (reference group unexposed). [The Working Group noted the generally low exposure levels ranging from less than 1 ppm-years to 632 ppm-years, but with a median of 3 ppm-years.]

Sorahan et al. (2005) reported on a cohort of workers considered occupationally exposed to benzene based on records of the Factory Inspectorate in the United Kingdom. A total of

15 NHL deaths (SMR, 0.94; 95% CI, 0.53–1.56) and 24 incident NHL cases (standardized incidence ratio (SIR), 1.00; 95% CI, 0.64–1.49) occurred in the exposed workers compared with the unexposed. Additionally, based on 8 incident cases and six deaths, the same study found no increased risk of MM. [The Working Group noted the small numbers for MM and that the exposure assessment was limited, although exposure levels were historically high.]

Kirkeleit et al. (2008) reported on a large cohort of more than 27 000 offshore petroleum workers in Norway (see Section 2.1.1(b)(iv) for further details). Compared with the reference unexposed group, the overall relative risk was 1.01 for incident NHL (95% CI, 0.58–1.75) and 2.49 for incident MM (95% CI, 1.21–5.13). [This study overlaps partially with Stenehjem et al. (2015), described below. No quantitative assessment of benzene exposure was available.]

Several new studies reporting pertinent data for NHL or MM and benzene exposure in occupational settings have been published since the previous *IARC Monographs* Volume 100F (Table 2.3).

Stenehjem et al. (2015) studied 61 NHL incident cases. Overall, compared with a reference unexposed group, there was a slight excess of NHL cases among the exposed subjects (RR, 1.49; 95% CI, 0.9–2.48), and a stronger but not statistically significant association with specific histological type. No *P* trend was observed for NHL (*P* trend of 0.245 based on tertiles of exposure). The incidence of MM (13 exposed cases) was increased among exposed workers (RR, 1.64; 95% CI, 0.55–4.89), and a significant dose–response relationship with exposure tertiles was found (*P* for trend, 0.024). [The Working Group noted the very low levels of exposure in these workers: the upper values of average intensity and cumulative exposure were estimated to be 0.040 ppm and 0.948 ppm-years, respectively.]

Linet et al. (2015) updated the study by Hayes et al. (1997) that was based on 35 804 male and female workers exposed to benzene in 672 factories in China, with a long follow-up (28 years) and good case ascertainment. This study did not assess benzene exposure quantitatively. A total of 31 NHL deaths (RR, 4.0; 95% CI, 1.6–13.4) and 30 incident cases (RR, 3.9; 95% CI, 1.5–13.2) were reported. Only one death and 1 incident case of MM were recorded. [The Working Group considered this a strong study due to the robust case ascertainment and long follow-up.] Data on exposure–response relationships in the same cohort were reported earlier by Hayes et al. (1996) (see *IARC Monographs* Volume 100F, Table 2.9, available at: http://publications.iarc.fr/123). The relative risk of mortality from NHL for those exposed to benzene for more than 10 years, compared with a reference unexposed group, was 4.2 (95% CI, 1.1–15.9) based on 11 exposed cases. A non-monotonic dose–response relationship was observed with average (*P* for trend, 0.04) and cumulative (*P* for trend, 0.02) benzene exposure.

Collins et al. (2015) updated a cohort study previously reported by Bloemen et al. (2004) on mortality among 2266 chemical workers in the USA. Controlled for age, sex, and gender, the standardized mortality ratio for NHL observed in workers with more than 30 years latency (n = 12) was 1.02 (95% CI, 0.53–1.78). [The Working Group noted the robust exposure assessment but very small numbers, particularly in analyses by cumulative exposure.]

(b) Chronic lymphocytic leukaemia

The data on the association between CLL and exposure to benzene that were available at the time (until 2009) were reviewed in *IARC Monographs* Volume 100F and described as follows: "Several cohort studies in the petroleum industry [subsequently included in a pooled analysis by Schnatter et al. (2012)] showed mixed results, with some non-significantly increased risks reported and other studies showing no association (see Table 2.7, available at http://publications.iarc.fr/123). 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)".

The current Working Group reviewed these studies and determined that several did not meet the criteria established for inclusion (see Section 2.1.1(a)) (McCraw et al., 1985; Satin et al., 1996; Lynge et al., 1997; Divine et al., 1999b; Divine & Hartman, 2000; Wong et al., 2001a; Lewis et al., 2003; Bloemen et al., 2004; Huebner et al., 2004). One study reviewed previously was superseded by later updates (Glass et al., 2003).

Three of the five occupational cohort studies published after *IARC Monographs* Volume 100F and described in Section 2.2.1(b) (petroleum distribution workers in Australia, Canada, and the United Kingdom; Chinese workers; and Norwegian offshore oil workers) presented data on CLL and benzene exposure (Table 2.3), as described in the following sections.

(i) Petroleum distribution workers in Australia, Canada, and the United Kingdom

Exposure to benzene was compared between 80 cases of CLL and 345 matched controls in the pooled analysis of updated case–control studies nested in occupational cohorts of petroleum distribution workers (Schnatter et al., 2012; Rushton et al., 2014). When compared with subjects in the lowest exposure tertile of cumulative exposure (< 0.348 ppm-years), the odds ratio of CLL was more elevated in the intermediate exposure tertile (0.348–2.93 ppm-years; OR, 1.49; 95% CI, 0.81–2.76; 32 cases) than in the highest exposure tertile (> 2.93 ppm-years; OR, 1.05; 95% CI, 0.56–1.98; 24 cases). No clear indication of an association was shown with the other exposure metrics reported in this study (see Section 2.1.1(b)). No dose–response relationship was observed for CLL, except with duration of employment (*P* for spline, < 0.03). Refinery workers (mainly from the Australian study) showed a higher risk of CLL compared with subjects who had never worked as a refinery operator or craftsman (RR, 1.99; 95% CI, 0.87–4.57).

(ii) Chinese workers exposed to benzene

The large NCI-CAPM cohort of Chinese workers included only two CLL cases among the workers exposed to benzene and none among the unexposed; no relative risk could be computed (Linet et al., 2015).

(iii) Norwegian offshore oil workers

In the nested case–cohort study on Norwegian offshore oil industry workers, 12 cases of CLL were compared with 1661 reference workers from the same cohort (Stenehjem et al., 2015). A five-fold hazard ratio of CLL for workers ever versus never exposed to benzene was reported (HR, 5.4; 95% CI, 0.7–41.0). The risk estimates for cumulative exposure were substantially higher in the exposed subjects with respect to the unexposed (HR in the upper tertile, 6.74; 95% CI, 0.75–60.00; 5 cases), but no exposure–response relationship was found (*P* for trend, 0.212). Hazard ratios were consistently elevated when considering all the other metrics reported in the study (see Section 2.1.1(b)), although the highest risks were often in the intermediate tertiles of exposure (e.g. the HR for the middle tertile of average peak exposure was 6.66; 95% CI, 1.32–34.00; 6 exposed cases) and no statistically significant dose–response trend was observed for any of the

metrics. [The Working Group noted that exposure levels in the study were generally low.]

(c) Acute lymphocytic leukaemia

ALL is a rare cancer in adults, and this makes it difficult to study its association with exposure to benzene. The maximum number of exposed cases in the studies included in *IARC Monographs* Volume 100F was 8 (IARC, 2012a; Table 2.3, available at: http://publications.iarc.fr/123). The evidence for the association between ALL in adults and benzene exposure that was available at the time of the previous evaluation was described as follows: "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; Yin et al., 1996a; Divine et al., 1999b; Guénel et al., 2002; Lewis et al., 2003; Gun et al., 2006; Kirkeleit et al., 2008)".

The Working Group reviewed these studies and determined that most (Rushton, 1993; Satin et al., 1996; Divine et al., 1999b; Lewis et al., 2003; Gun et al., 2006) did not meet the criteria for inclusion (see Section 2.1.1(a)) in the current evaluation.

The Working Group identified one earlier study that met the inclusion criteria, but had not been reviewed in *IARC Monographs* Volume 100F: Sorahan et al. (2005). In this study, which was conducted in the United Kingdom, no cases of ALL were observed (0.83 expected) in a cohort of 5514 male and female workers exposed to benzene.

Only one new study with pertinent data for adult ALL and benzene exposure has been published since the previous IARC review. Eight cases of incident ALL were ascertained in the NCI-CAPM cohort of Chinese workers among those who held jobs entailing exposure to benzene, and one among the unexposed (Linet et al., 2015). An elevated relative risk for incidence of 4.5 (95% CI, 0.8–83.9) was found. Formal statistical significance was reached in the "all lymphoid leukaemia" group (9th International Statistical Classification of Diseases and Related Health Problems (ICD-9), code 204), that is, after the addition of 2 cases of CLL among the exposed (RR, 5.4; 95% CI, 1.0–99.3) based on a total of 10 cases. A dose–response evaluation was not conducted, because benzene exposure assessment was limited to a categorization of ever versus never exposed.

Among the included studies (except Sorahan et al., 2005, which had no ALL cases), the risk estimates for ALL as a result of benzene exposure ranged from 0.8 to 4.5, and all the 95% confidence intervals included the null.

(d) Hodgkin lymphoma

The evidence for HL was reviewed in *IARC Monographs* Volume 100F. At that time the Working Group noted that the data on HL in studies of cohorts exposed to benzene were sparse, with most studies having very small numbers of cases and reporting no association (see Table 2.13, available at: http://publications.iarc.fr/123). The evidence from these studies was judged to be *inadequate*.

With the exception of the study by Collins et al. (2015) (described in Section 2.1.1(b) and summarized in Table 2.3), which found no association between HL mortality and cumulative exposure to benzene based on only 2 cases of HL, no additional data have been reported on the association between HL and exposure to benzene.

2.2.2 General-population studies

This review included all published, peer-reviewed epidemiological studies reporting a risk estimate for the association between exposure to benzene and NHL, CLL, DLBCL, follicular lymphoma, HCL, MM, ALL, or HL in study populations enrolled from the population at large, distinct from industry-based cohorts. Relevant studies by Clavel et al. (1996), Orsi et al.

(2010), and Wong et al. (2010b) were not included in *IARC Monographs* Volume 100F but have been added to this chapter, in addition to Bassig et al. (2015) (all summarized in Table 2.4). One study by Jiao et al. (2012) on a gene-environment interaction with a BRCA2 variant was excluded as it did not report overall risks for benzene exposure. All the studies were of a case–control design, with the exception of a cohort study from Shanghai (Bassig et al., 2015). The case–control studies were a mixture of hospital-based and population-based designs. The quality of the population controls varied extensively; studies conducted within the USA were often based on random digit dialling (Wang et al., 2009) or driving licence rosters (Kato et al., 2005), often obtaining low response rates. All studies included newly diagnosed incident cases, usually with a re-examination of diagnoses. Histological reviews were performed in the studies by Scherr et al. (1992), Fritschi et al. (2005), and Miligi et al. (2006) (see *IARC Monographs* Volume 100F, Table 2.10, for details of studies included, available at: http://publications.iarc.fr/123). Exposure contexts for the studies reviewed here mainly included occupational exposure of the subjects. The assessment of benzene exposure ranged from a self-report ascertained by questionnaire [which the Working Group did not deem to be of sufficient quality for assessing exposure to benzene] to expert judgement based on quantitative measurements in factories (Bassig et al., 2015), although most studies used a JEM (see Section 1.3 and Section 1.6 for further information). The studies judged most informative by the Working Group were those that scored high for exposure assessment features, with a large sample size and high-quality design (including a histological review of cases and high response rates). Several studies were excluded due to small sample size (Linet et al., 1987; Kato et al., 2005; Ruckart et al., 2013) or because the exposure assessment was very limited (Micheli et al., 2014).

Clavel et al. (1996) found no association between exposure to benzene and HCL [currently classified as a subtype of NHL]. Exposure assessment was based on a JEM. [The Working Group noted that the response rate was low among controls, at around only 57%.]

The large European multicentre Epilymph study (Cocco et al., 2010), which included population- and/or hospital-based controls depending on the areas and used a JEM to assess benzene exposure, was previously included in *IARC Monographs* Volume 100F. Cocco et al. (2010) found no association between exposure to benzene and NHL, DLBCL, follicular lymphoma, or MM; a positive association between CLL and benzene exposure was observed, but there was no evidence of a dose–response relationship (OR of exposed versus never exposed to benzene isolated from other organic solvents, 1.8; 95% CI, 1.0–3.2; *P* for trend, 0.14). [The Working Group noted that the response rate was low in the population controls, at around only 52%. An earlier study by Seidler et al. (2007), which was already included in the Epilymph analysis, reported no association with NHL.]

Fritschi et al. (2005) found no association between NHL and exposure to benzene in a population-based study in Australia that included 68 exposed cases. Exposure to benzene was assessed by a JEM. [The Working Group noted the relatively low response rate among the population-based controls, at around only 61%.]

Miligi et al. (2006) describe a well-conducted population-based study on more than 1400 NHL cases and 1500 controls from the general population, with high response rates of 79%. Cases were examined by a panel of pathologists. Exposure assessment was based on detailed questionnaires, expert judgement, and a JEM (with assessment of probability and intensity of exposure). Positive associations were found for medium and high benzene exposure versus very low and low benzene exposure (OR, 1.6; 95% CI; 1.0–2.4) based on 58 cases, as well as a non-significant

Table 2.4 Epidemiological studies of exposure to benzene and adult lymphoma in the general population

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bassig et al. (2015) China (Shanghai) 1996–2000/until 2009 Cohort	73 087 women only, aged 40–70 yr; Shanghai Women's Study (population-based), with 92.7% response rate Exposure assessment method: quantitative measurements; JEM that combined benzene measurements in factories (since 1954) plus questionnaire data and other information; probability and intensity of exposure assigned	NHL	Cumulative exposure (mg/m^3)-yr) Unexposed (reference) Ever exposed Tertile 1: ≤ 35.2 Tertile 2: 35.21–102.4 Tertile 3: > 102.4 Trend test *P* value, 0.006 for duration, 0.005 for cumulative exposure	 78 24 3 9 12	 1.00 1.86 (1.17–2.96) 0.92 (0.29–2.94) 2.20 (1.10–4.41) 2.16 (1.17–4.00)	Ever smoking, alcohol intake, BMI, education, age	Strengths: highly representative of the general female population in Shanghai; accurate data on exposure; accurate data from cancer registry on incident cancers (very low losses to follow-up) Limitations: only 24 NHL among the exposed
Clavel et al. (1996) France 1980–1990 Case–control	Cases: 226 hairy cell leukaemia patients recruited in 18 French hospitals; only living cases included (60% of 368 eligible) Controls: 425 hospital-based, matched to cases by sex, birth date, admission date, residence; mainly from orthopaedic and rheumatology departments; response rate, 57% Exposure assessment method: expert judgement; JEM that assessed a score for ppm of exposure to benzene; exposure blindly assigned to cases and controls	NHL (HCL)	Unexposed Cumulative benzene exposure (ppm-yr) < 1 (score) 1–5 (score) ≥ 5	189 15 10 7	1.0 0.7 (0.4–1.3) 0.7 (0.3–1.4) 0.5 (0.2–1.2)	Matching variables age and sex, smoking status, residence, admission date	Strengths: large series of rare tumour; good exposure assessment Limitations: low response rate among controls; only living cases (prevalent) included, meaning potential source of bias

Table 2.4 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Orsi et al. (2010) France 2000–2004 Case–control	Cases: 244 NHL, 87 HD, 56 MM; hospital-based, men only (aged 20–75 yr); incident cases; response rate, 95% Controls: 456 mainly from orthopaedic and rheumatology departments, residing in hospital catchment area; matched by age, sex, centre; cancers excluded, as well as diseases related to occupation, alcohol, or smoking; response rate, 91.2% Exposure assessment method: expert judgement; job-specific questionnaires evaluated by chemical engineer; experts derived ppm estimates from previously published intensity measurement campaigns	NHL	All benzene, exposed vs unexposed	94	1.0 (0.7–1.5)	Age, centre, socioeconomic status	Strengths: good exposure assessment by expert; very high response rate Limitations: hospital-based study
			Benzene > 1 ppm-yr	70	1.4 (0.9–2.1)		
			Pure benzene	6	3.0 (0.8–11.2)		
			Pure benzene, definite exposure	5	3.4 (0.8–15.0)		
			Latency 30 yr, pure benzene	5	5.5 (1.0–30.7)		
			High intensity of exposure	4	2.6 (0.6–11.2)		
			Same, diffuse large cell lymphoma	4	7.2 (1.6–33.2)		

Table 2.4 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wong et al. (2010b) Shanghai 2003–2008 Case–control	Cases: 649 hospital-based from 25 hospitals; response rate, 76% Controls: 1298 hospital-based controls matched by age and sex, with exclusion of blood malignancies; response rate, NR Exposure assessment method: expert judgement; exposure assessment conducted by experts by estimating ppm of exposure	NHL	Maximum exposure to benzene			Age, sex, hospital	Limitations: hospital-based study
			Score 1	32	1.14 (0.73–1.78)		
			Score 2	9	0.75 (0.35–1.64)		
			Score 3–4	9	1.21 (0.53–2.76)		
			Trend test *P* value, 0.76 for maximum exposure, 0.80 for duration of exposure				

BMI, body mass index; CI, confidence interval; HCL, hairy cell leukaemia; HD, Hodgkin disease; JEM, job-exposure matrix; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; ppm, parts per million; vs, versus; yr, year(s)

threefold increased risk for exposure duration of more than 15 years (OR, 2.9; 95% CI, 0.9–9.0) based on 14 cases.

In a hospital-based case–control study of men only with very high response rates (83%) conducted in France, Orsi et al. (2010) reported no increased NHL risk with exposure to benzene compared with no exposure (OR, 1.0; 95% CI, 0.7–1.5), and a positive association for those exposed to "pure benzene" (OR, 3.0; 95% CI, 0.8–11.2) based on 6 exposed cases. No associations were observed for HL and MM. [The Working Group noted an unclear choice of controls and the small numbers for the different exposure metrics, for example, "pure benzene".]

A population-based case–control study in the Boston metropolitan area by Scherr et al. (1992), with high response rates of 80% and including a review of pathological material (slides), found no significant association with NHL in ever versus never exposed cases (OR, 1.2; 95% CI, 0.5–2.6). [The Working Group noted the potential for information bias due to the use of self-reported exposure via questionnaires, as well as the small sample size.]

In a population-based case–control study of women aged 21–84 years, Wang et al. (2009) used a JEM (with assessment of probability and intensity of exposure) to report slightly elevated, non-statistically significant risks for NHL in the group exposed to medium to high concentrations of benzene, particularly for specific histological types (*P* for trend, 0.04 for DLBCL, 0.08 for CLL, and 0.18 for follicular lymphoma). [The Working Group noted generally low response rates.]

A hospital-based study by Wong et al. (2010b), including 649 cases and 1298 matched controls, found no association between NHL and benzene exposure assessed by experts based on job questionnaires, and a significant association for follicular lymphoma (based on 7 cases only).

A population-based cohort study conducted after the publication of *IARC Monographs* Volume 100F evaluated the association between benzene exposure and NHL: Bassig et al. (2015) followed up 73 087 women in the Shanghai general population for NHL incidence through the Cancer Registry, and used a quantitative JEM based on actual benzene measurements (with assessment of probability and intensity of exposure to benzene). Response rates were very high (93%). The overall hazard ratio for the ever exposed versus the unexposed group was 1.86 (95% CI, 1.17–2.96) based on 24 exposed cases, and an exposure–response relationship was reported with both duration of exposure to benzene (*P* for trend, < 0.006) as well as cumulative exposure (*P* for trend, < 0.005). A case–control study in Italy showed evidence of a dose–response relationship between exposure to benzene for a duration of more than 15 years and CLL (*P* for trend, 0.05) (Costantini et al., 2008).

In a case–control study in residents in Shanghai (532 cases and 502 controls from the general population), a significant 3.9-fold increased risk for ALL was reported for the group with 15 years or more of self-reported occupational exposure to benzene, based on 5 exposed cases in this category (Adegoke et al., 2003); no association was observed in another study in the USA, with only 3 cases in the highest exposure group (see *IARC Monographs* Volume 100F, Table 2.4, available at: http://publications.iarc.fr/123).

2.3 Childhood cancer

Age-specific incidence rates for several types of childhood cancer peak at ages < 5 years, indicating that risk factors exist in the early life environment or might be inherited. Few risk factors have been identified, with the exception of ionizing radiation and chemotherapy, meaning that the majority of cases are unexplained.

It is known that benzene causes AML/ANLL in adults. Positive associations have also been observed between exposure to benzene and ALL, CLL, MM, and NHL (IARC, 2012a). Leukaemia

is the most common type of childhood cancer, leading to the hypothesis that benzene could also cause leukaemia in children. Benzene often occurs as part of mixed exposures, such as in utero in pregnant women who smoke, or from second-hand smoke and traffic exhaust in ambient air. Studies of childhood cancers have used various indicators of such mixtures, for example, traffic (von Behren et al., 2008; Amigou et al., 2011), petrol stations, and automotive repair garages near the residence (Steffen et al., 2004; Brosselin et al., 2009). Studies of parental occupational exposures and childhood cancer have also used indicators for mixed exposure which may include benzene, such as "solvent use" (van Steensel-Moll et al., 1985; Carlos-Wallace et al., 2016). [The Working Group is aware of these studies but decided to review only those specifically assessing exposure to benzene. The Working Group noted that, even in studies where benzene is specifically assessed, benzene is often one of many correlated air pollutants; confounding from such correlated air pollutants can rarely be excluded.]

Ecological studies have compared incidence rates of childhood leukaemia (Whitworth et al., 2008; Senkayi et al., 2014) and tumours of the central nervous system (CNS) (Danysh et al., 2015) with benzene levels assessed at census tracts or county level. These studies were not reviewed by the current Working Group because of the usual limitations of the ecological design for causal inference.

The Working Group reviewed a series of case–control studies that quantified ambient benzene levels, either assessed at the exact address or as a mean for the area where childhood cancer cases and controls lived. A case–control study that assessed exposure by measuring a benzene metabolite in urine from childhood cases and controls (Jiang et al., 2016) was also reviewed. One additional case–control study (Ruckart et al., 2013) was not reviewed, because the information that could be extracted was limited because the study included only 13 verified childhood cases of cancer of the haematopoietic system (11 leukaemia and 2 NHL) and because exposure to benzene was not quantified. Another case–control study that investigated the distance from the residence to industries emitting benzene was not reviewed because benzene concentrations were not quantified (García-Pérez et al., 2015).

The Working Group also reviewed a series of case–control studies and two cohort studies that compared the occupational exposure to benzene of the parents of childhood cancer cases and controls. Table 2.5 includes only relevant studies of cancer sites with sufficient or limited evidence that were either not included in, or published after, *IARC Monographs* Volume 100F (IARC, 2012a).

2.3.1 Childhood exposure to benzene in outdoor air

Four case–control studies assessed benzene concentrations at the exact address(es) where childhood cancer cases and controls lived (see Table 2.5).

In a population-based study included in *IARC Monographs* Volume 100F, Raaschou-Nielsen et al. (2001) identified 1989 cases (age, 0–14 years) of leukaemia, lymphoma, and tumours of the CNS in the Danish Cancer Registry, and selected 5506 controls at random among the whole Danish childhood population using the Danish Population Registry. Controls were matched to cases by sex, age, and calendar time. The residential history of each child was traced from 9 months before birth to the time of diagnosis. Benzene exposure was calculated from a dispersion model based on traffic and the configuration of the street and buildings at the address. The analyses adjusted for urban development, geographical region, type of residence, low-frequency electromagnetic fields (power lines and transformer stations), mother's age, and birth order. For exposure to benzene during childhood between the 90th and 99th percentile

Table 2.5 Epidemiological studies of exposure to benzene and childhood leukaemia in the general population

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Crosignani et al. (2004) Province of Varese, Italy 1978–1997 Case–control	Cases: 120 from cancer registry Controls: 480 population-based from Health Service Archives Exposure assessment method: other; modelled concentration of benzene outside the residence at time of diagnosis	Leukaemia: ICD-9 (codes 204.0–208.9), lymphoid leukaemia, myeloid leukaemia, monocytic leukaemia, other specified and unspecified leukaemia	Benzene concentration (μg/m³) < 0.1 0.1–10 > 10 Trend test *P* value, 0.005	 88 25 7	 1.0 1.5 (0.9–2.5) 3.9 (1.4–11.3)	Sex, age, SES of municipality	Incidence, ages 0–14 yr Strengths: population-based; exposure model Limitations: small number of cases; only address at diagnosis; non-differential misclassification of exposure

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vinceti et al. (2012) Emilia-Romagna region, northern Italy 1998–2009 Case–control	Cases: 83 from cancer registry Controls: 332 population-based from Health Service Archives Exposure assessment method: other; CALINE4 dispersion model estimating exposure to benzene from road traffic; based on address at diagnosis; exposure categories are approximate quartiles of annual average benzene concentrations	Leukaemia: acute leukaemia	Benzene concentration (μg/m³)			Sex, age, province of residence, PM_{10} concentration	Incidence within previous 0–14 yr; validation of dispersion model reported; linear trends were not statistically significant; stronger and statistically significant associations with AML for children < 5 yr (OR, 5.46; 95% CI, 1.12–26.51; 11 cases) Strengths: population-based, exposure model Limitations: small number of cases; only address at diagnosis; limited confounder adjustment; non-differential misclassification of exposure
			< 0.10	16	1.0		
			0.10 to < 0.25	18	0.8 (0.5–2.6)		
			0.25 to < 0.50	17	1.1 (0.5–2.6)		
			≥ 0.50	32	1.7 (0.8–3.6)		
		Leukaemia (ALL)	OR per 1 μg/m³ increase in average benzene concentration and with a 10 μg/m³ increase in average PM_{10} concentration	64	0.97 (0.49–1.93)	Sex, age, province of residence, PM_{10} concentration	
		Leukaemia (AML)	OR per 1 μg/m³ increase in average benzene concentration and with a 10 μg/m³ increase in average PM_{10} concentration	19	1.92 (0.64–5.78)	Sex, age, province of residence, PM_{10} concentration	

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Houot et al. (2015) Île-de-France, France 2002–2007 Case–control	Cases: 517 from cancer registry Controls: 6147 population-based, from tax databases Exposure assessment method: records; modelled concentration of benzene outside the residence at time of diagnosis	Leukaemia (ALL)	Benzene concentration (μg/m³)			Age	Incidence within previous 0–14 yr Strengths: population-based; exposure model Limitations: small number of AML cases; only address at diagnosis; limited confounder adjustment; non-differential misclassification of exposure
			< 1.3	215	1.0		
			≥ 1.3	210	0.9 (0.7–1.0)		
		Leukaemia (AML)	Benzene concentration (μg/m³)			Age	
			< 1.3	33	1.0		
			≥ 1.3	59	1.6 (1.0–2.4)		
Heck et al. (2014) California, USA 1990–2007 Case–control	Cases: 66 ALL and 41 AML from cancer registry Controls: 2627 for ALL and 17 299 for AML, randomly from population with California birth certificates Exposure assessment method: other; air toxics measured at monitoring station nearest to home address at time of birth (ALL, ≤ 2 km; AML, ≤ 6 km)	Leukaemia (ALL)	OR per IQR increase in benzene concentration (1.2 ppb) during pregnancy			Year of birth, mother's birth place, parity, neighbourhood SES, mother's race/ethnicity	Incidence within previous 0–5 yr; exploratory study of 22 air toxics Strengths: population-based; monitoring-based exposure assessment Limitations: small number of cases; no address history; multiple testing; non-differential misclassification of exposure
			1st trimester	66	0.85 (0.58–1.26)		
			2nd trimester	66	1.16 (0.80–1.67)		
			3rd trimester	66	1.50 (1.08–2.09)		
			Entire pregnancy	66	1.44 (0.84–2.48)		
			1st year of life	61	1.23 (0.62–2.43)		
		Leukaemia (AML)	OR per IQR increase in benzene concentration (1.2 ppb) during pregnancy			See above	
			1st trimester	41	1.13 (0.64–2.01)		
			2nd trimester	41	1.30 (0.74–2.28)		
			3rd trimester	41	1.75 (1.04–2.93)		
			Entire pregnancy	41	1.94 (0.89–4.19)		
			1st year of life	25	2.61 (0.97–6.99)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Janitz et al. (2017) Oklahoma, USA 1997–2012 Case–control	Cases: acute leukaemia, 307; ALL, 228; AML, 79; cancer registry Controls: 1013 population with Oklahoma birth certificates Exposure assessment method: other; USEPA National Air Toxics Assessment database modelled benzene 2005 concentration of the census tract where living at time of birth; exposure level cut-points were based on quartiles of benzene concentration (μg/m³) among controls	Leukaemia: ALL and AML combined	Benzene concentration (μg/m³)			Week of birth, race/ ethnicity, age at diagnosis, sex, birth order, electromagnetic fields, urbanization, maternal education, smoking during pregnancy	Incidence within previous 0–19 yr; an alternative exposure categorization showed substantially lower ORs in association with the very highest exposures (above 95th percentile, 1.33–2.03 μg/m³) Strengths: population-based exposure model Limitations: small number of cases; no address history; exposure assessment for only 1 yr, non-differential misclassification of exposure
			0.11 to < 0.39	73	1.00		
			0.39 to < 0.67	71	1.06 (0.71–1.58)		
			0.67 to < 0.91	77	1.21 (0.79–1.87)		
			0.91–2.03	86	1.28 (0.83–1.97)		
		Leukaemia (ALL): childhood ALL	Benzene concentration (μg/m³)			Week of birth, race/ ethnicity, age at diagnosis, sex, birth order, electromagnetic fields, urbanization, maternal education, smoking during pregnancy	
			0.11 to < 0.39	NR	1.00		
			0.39 to < 0.67	NR	0.91 (0.58–1.44)		
			0.67 to < 0.91	NR	1.07 (0.66–1.76)		
			0.91–2.03	NR	1.06 (0.65–1.74)		
		Leukaemia (AML): childhood AML	Benzene concentration (μg/m³)			Week of birth, race/ ethnicity, age at diagnosis, sex, birth order, electromagnetic fields, urbanization, maternal education, smoking during pregnancy	
			0.11 to < 0.39	NR	1.00		
			0.39 to < 0.67	NR	1.60 (0.67–3.82)		
			0.67 to < 0.91	NR	1.92 (0.77–4.74)		
			0.91–2.03	NR	2.42 (0.98–5.96)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Spycher et al. (2017) Switzerland 1990 or 2000/ until end of 2008 Cohort	1 664 801 children aged < 16 yr Exposure assessment method: other; census data on parental occupation and JEM (based on ISCO-88) to categorize potential for benzene exposure	Leukaemia (ALL) Leukaemia (AML)	Maternal occupational exposure Ever exposed Maternal occupational exposure Ever exposed	19 3	1.92 (1.18–3.13) 1.05 (0.32–3.48)	Sex; year of birth; census; education; household crowding; neighbourhood SES; background ionizing radiation and electromagnetic fields from radio and TV transmitters; distance to nearest highway, petroleum refinery, petrol station, motor vehicle service station	No associations with AML or ALL and paternal exposure were observed Strengths: population-based study with data on incidence; models adjusted for a range of socioeconomic, perinatal, and environmental factors; accurate and complete outcome ascertainment Limitations: no adjustment for maternal smoking; small number of exposed AML cases

ALL, acute lymphoblastic/lymphocytic leukaemia; AML, acute myeloid leukaemia; CALINE4, California Line Source Dispersion model, version 4; CI, confidence interval; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; ISCO, International Standard Classification of Occupations; JEM, job-exposure matrix; NR, not reported; OR, odds ratio; PM, particulate matter; ppb, parts per billion; SES, socioeconomic status; USEPA, United States Environmental Protection Agency; yr, year(s)

of the distribution of exposure, or above the 99th percentile compared with below the 50th percentile, the respective adjusted relative risks were 0.9 (95% CI, 0.6–1.5) and 0.4 (95% CI, 0.1–1.6) for leukaemia, 1.1 (95% CI, 0.7–1.8) and 0.6 (95% CI, 0.2–1.7) for tumours of the CNS, and 0.8 (95% CI, 0.4–1.8) and 0.4 (95% CI, 0.1–2.0) for lymphomas. The results also indicated no associations between benzene concentrations at the address(es) during pregnancy and cancer risk, although the group exposed to the second-highest levels of benzene was associated with a relative risk for lymphomas of 2.2 (95% CI, 1.2–3.9). This higher risk for lymphomas in association with benzene concentrations during pregnancy was restricted to HL; based on 19 exposed cases, a relative risk of 4.3 (95% CI, 1.5–12.4) was observed in association with exposure above the 90th percentile compared with below the 50th percentile (see *IARC Monographs* Volume 100F, Table 2.14, available at: http://publications.iarc.fr/123). [The strengths of this study included the population-based design, the large sample size, the assessment of cumulative exposure over all addresses during pregnancy and childhood, and the objective, model-based exposure assessment method. However, the study was limited by the non-differential misclassification of exposure.]

A small study of leukaemia incidence was undertaken in Varese, Italy (Crosignani et al., 2004). A total of 120 incident cases were identified from the population-based Lombardy Cancer Registry, and 480 population controls, matched to cases by age and sex, were selected from the population-based Health Service Archives. Benzene concentration at the address at diagnosis was calculated on the basis of traffic density on surrounding roads and distances from the home address to roads with heavy traffic. When comparing children exposed to high concentrations of benzene (estimated annual average, benzene at > 10 μg/m^3) with children not exposed to road traffic emissions (estimated annual average, benzene at < 0.1 μg/m^3), the relative risk was 3.9 (95% CI, 1.4–11.3) based on 7 exposed cases, and 4.3 (95% CI, 1.5–12.6) after adjustment for socioeconomic status of the municipality. There was a trend across the three exposure categories (*P* for trend, < 0.005). [The strengths of the study included the population-based design and the objective, model-based, exposure assessment method. The limitations included the small number of cases, the use of only the address at diagnosis for exposure assessment, and the non-differential misclassification of exposure.]

In the Emilia-Romagna region, northern Italy, Vinceti et al. (2012) identified 83 incident cases of acute leukaemia among children (age, 0–14 years) in the population-based Italian Association of Paediatric Haematology and Oncology cancer registry. A total of 332 population controls, individually matched to cases by sex, year of birth, and province of residence during the diagnosis year, were selected. Traffic-related benzene and PM_{10} (particulate matter of diameter ≤ 10 μm) concentrations were estimated by the California Line Source Dispersion model, version 4 (CALINE4), at the address at time of diagnosis. Modelled benzene concentrations were validated against those measured at fixed-site monitoring stations, showing a correlation coefficient of 0.43 (95% CI, −0.48–0.89) for annual mean values. The odds ratio for acute leukaemia was 1.7 (95% CI, 0.8–3.6) for the highest (≥ 0.50 μg/m^3) compared with the lowest (< 0.10 μg/m^3) category of benzene exposure, after adjustment for PM_{10}. Linear analyses adjusted for PM_{10} showed odds ratios of 0.97 (95% CI, 0.49–1.93; 64 cases) and 1.92 (95% CI, 0.64–5.78; 19 cases) for ALL and AML, respectively, in association with a 1 μg/m^3 increase in average benzene concentration. Restricting the linear analyses to children diagnosed when aged 0–4 years yielded odds ratios of 1.95 (95% CI, 0.58–6.50; 27 cases) and 5.46 (95% CI, 1.12–26.51; 11 cases) for ALL and AML, respectively. [A strength of this study was the population-based design and the objective exposure assessment by

use of a validated exposure model, although the correlation between calculated and measured benzene was relatively low. Limitations included the small sample size resulting in wide confidence intervals, the use of only the address at the time of diagnosis for exposure assessment, and non-differential misclassification of exposure.]

Houot et al. (2015) estimated benzene concentrations at the addresses at the time of diagnosis of 517 incident acute leukaemia cases (age, 0–14 years) and 6147 control children living in the Île-de-France region in France. Cases were identified from the National Registry of Childhood Haematopoietic Malignancies, and control children were selected from a population-based tax database. The benzene modelling took into account contributions from both urban background pollution and local traffic. The subjects were classified on the basis of the benzene exposure estimate at their home being either less than 1.3 μg/m^3 (median exposure for the controls) or 1.3 μg/m^3 or more. When comparing the two groups, the odds ratio for ALL was 0.9 (95% CI, 0.7–1.0; based on 210 exposed cases) and for AML was 1.6 (95% CI, 1.0–2.4; $P < 0.05$, based on 59 exposed cases). The analyses were adjusted for age. [Strengths included the population-based design and the objective, model-based exposure assessment method. Limitations included the limited adjustment for potential confounders, the use of only the address at the time of diagnosis for exposure assessment, the non-differential misclassification of exposure, and the limited contrast in the analysis of exposures to above versus below the median.]

A series of studies from California, USA, studied the association between a wide range of air toxics (including benzene) measured at 39 different sites and different types of childhood cancers. Cases (age, 0–5 years) were identified from the California Cancer Registry, and population controls were selected randomly from the California birth records. Birth addresses of cases and control children were allocated to 1 of the 39 monitoring stations if the address was within a certain distance, and the measured air toxic concentration was averaged over certain time periods; both the distance and the time period differed between the studies. Odds ratios were calculated for one interquartile range (IQR) increase in benzene concentration, corresponding to 1.2 ppb (3.8 μg/m^3). Heck et al. (2013) compared benzene concentrations during pregnancy for 74 neuroblastoma cases and 13 115 control children, and observed an odds ratio of 1.36 (95% CI, 0.82–2.25) per IQR increase of benzene concentration after adjustment for year of birth, maternal race/ethnicity, maternal age, and method of payment for prenatal care. Shrestha et al. (2014) studied 337 cases of Wilms tumour and 96 514 control children, and found an odds ratio of 1.07 (95% CI, 0.84–1.36) per IQR of benzene concentration during pregnancy after adjustment for birth year, maternal age, maternal race/ethnicity, parity, and census-based socioeconomic status. Heck et al. (2014) included 66 cases of ALL and 41 cases of AML, and found odds ratios of 1.44 (95% CI, 0.84–2.48) for ALL and 1.94 (95% CI, 0.89–4.19) for AML per IQR increase of benzene concentration during the entire pregnancy. Results were adjusted for year of birth, maternal race/ethnicity, mother's birthplace, parity, and neighbourhood socioeconomic status. Exposure during the third trimester was associated with statistically significant odds ratios. Odds ratios in association with benzene concentration during the first year of life were similar to those reported for exposure during pregnancy. Heck et al. (2015) included 88 retinoblastoma cases and 25 144 control children, and found a significant odds ratio of 1.67 (95% CI, 1.06–2.64) per IQR increase of benzene concentration during pregnancy after adjustment for year of birth, maternal race and birthplace, paternal age, and method of payment for prenatal care. Von Ehrenstein et al. (2016) investigated the risk for tumours of the CNS based on 168 cases and 27 199 control children; odds

ratios of 2.14 (95% CI, 1.12–4.06; 38 cases) for primitive neuroectodermal tumour, 0.82 (95% CI, 0.36–1.87; 30 cases) for medulloblastoma, and 0.83 (95% CI, 0.53–1.29; 100 cases) for astrocytoma per IQR increase of benzene concentration during pregnancy were reported. Results were adjusted for year of birth, maternal race/ethnicity, maternal age, birthplace, and education. [The strengths of these studies included the population-based design and the objective, monitoring-based exposure assessment method. Limitations included the small sample sizes, the assessment of exposure at only one address, the non-differential misclassification of exposure, and the explorative nature including analyses of many pollutants. Not adjusting for smoking at home, and especially maternal smoking during pregnancy, were other common limitations of many studies. The results for neuroblastoma and retinoblastoma appear to be generating, rather than testing, hypotheses.]

Symanski et al. (2016) identified 1248 cases (age, 0–4 years) of ALL from the Texas Cancer Registry and selected 12 172 population-based control children from birth certificates. The address at birth was used to allocate each child to a census tract. Concentrations of benzene, 1,3-butadiene and polycyclic organic matter at census tract level were extracted from the United States Environmental Protection Agency National-Scale Air Toxics Assessment (NATA), which provided modelled concentrations for years 1996, 1999, 2002, and 2005; each address was allocated to an exposure quartile for the year closest in time. The statistical models adjusted for time of birth, census tract (random effect), maternal age, infant birth weight, sex, and maternal race/ethnicity, and reported odds ratios of 1.19 (95% CI, 1.00–1.41), 1.16 (95% CI, 0.98–1.38), and 1.17 (95% CI, 0.98–1.39) for the second, third, and fourth exposure quartiles compared with the first. Models including both benzene and 1,3-butadiene showed associations between childhood cancer and exposure to 1,3-butadiene, but not to benzene. [The Working Group noted that it is difficult to disentangle the effect of correlated pollutants. The strengths of this study included: the population-based design; the large sample size; the objective, model-based exposure assessment method; and the mutual adjustment for other air pollutants. Limitations included the lack of information about address history and non-differential misclassification of exposure. Further, the transformation of absolute exposure concentrations into quartiles based on 4 different years makes a quantitative interpretation of the results difficult: for example, the third exposure quartile for benzene in 1996 has a lower range of benzene levels than the second exposure quartile in 1999.]

Janitz et al. (2017) studied benzene and acute leukaemia including 228 cases of ALL and 79 of AML (age, 0–19 years) from the Oklahoma Central Cancer Registry, USA. A total of 28% of identified cases were excluded, however, because they could not be linked to birth certificates. Population controls (n = 1013) were selected from birth certificates, matched by week of birth. Address at birth was allocated to the census tract, and benzene concentrations for 2005 for each census tract were extracted from the NATA database. Children were divided into quartiles of exposure and, in a secondary analysis, the cut-off point at the 40th (0.53 μg/m^3), 60th (0.78 μg/m^3), and 95th (1.33 μg/m^3) percentiles were used to form exposure categories. The results indicated no association between benzene and ALL, with an odds ratio for the highest quartile compared with the lowest of 1.06 (95% CI, 0.65–1.74) and that for above the 95th percentile compared with below the 40th percentile being 0.67 (95% CI, 0.28–1.62). In contrast, the two corresponding odds ratios for AML were 2.42 (95% CI, 0.98–5.96) and 1.58 (95% CI, 0.53–4.69), with an indication of an exposure–response relationship over quartiles but not over the alternative exposure categorization. The analyses adjusted for time of birth, race/ethnicity, age at diagnosis, sex, birth order,

exposure to electromagnetic fields, urbanization, and maternal education and smoking during pregnancy. [The strengths included the population-based design and the objective, model-based exposure assessment method. Limitations included the limited sample size, the lack of information about address history, the exposure assessment being based on only 1 year, and the non-differential misclassification of exposure. The Working Group noted the exclusion of cases that could not be linked to a birth certificate as a potential source of selection bias.]

Jiang et al. (2016) measured the benzene metabolite *trans*,*trans*-muconic acid (*t*,*t*-MA) in urine samples from 71 cases of ALL identified at the Shenzhen Children's Hospital, China, and from those of 142 control children selected from the orthopaedics section and matched to cases by sex and age. A higher proportion was above the detection limit among cases compared with controls, and higher *t*,*t*-MA concentration was associated with an increased risk (OR, 1.09; 95% CI, 1.00–1.19). [The Working Group noted that the related exposure contrast was not reported in the article. Other limitations included: the risk for reverse causation because urine was collected after the ALL diagnosis; a lack of translation between concentrations of *t*,*t*-MA in urine (which only reflect exposure during the few hours before urine collection) and exposure to benzene, meaning that the use of *t*,*t*-MA in this context did not provide a good context for exposure to benzene and the validity of this exposure assessment method is low (see Section 1.3); and the non-differential misclassification of exposure.]

2.3.2 Parental occupational exposure to benzene

Nine case–control and two cohort studies assessed the occupational exposure to benzene of parents of childhood cancer cases and controls. In 8 of the 11 studies, the exposure assessment was based on information about parental occupation, industry, or exposure collected by interviews with parents after their child received a diagnosis of cancer. Three other studies used information from birth certificates (Shaw et al., 1984) or census data (Feychting et al., 2001; Spycher et al., 2017), which could not be influenced differently by parents of cases and controls. Exposure was assessed in two (yes/no) or three (e.g. no/possible/probable) categories either by parents themselves or by experts or JEM, but was never quantified. [The Working Group noted that the interview-based exposure assessment in 8 of the 11 studies implied a risk for recall and interviewer bias. Differential participation among parents of cases and controls may also have biased the results. Other general limitations were the low numbers of exposed parents, leading to imprecise risk estimates, and the lack of quantification of benzene exposure. For these reasons, the Working Group gave little weight to this group of studies when evaluating benzene as a potential cause of childhood cancer.]

The results from the 11 studies are inconsistent. Shaw et al. (1984) used information about job from birth certificates in a case–control study in California, USA, and reported no difference in childhood leukaemia risk between case and control groups for paternal occupation with potential for benzene exposure. In a cohort study in Sweden, Feychting et al. (2001) reported no association between parental job (2–26 months before the child's birth, obtained from census data) with the potential for benzene exposure (possible and probable exposure combined) and the risk for leukaemia (RR, 1.23; 95% CI, 0.39–3.85; 3 cases) or tumours of the CNS (RR, 0.91; 95% CI, 0.23–3.70; 2 cases) in their children. The risk of leukaemia in children younger than 5 years was 2.0 (95% CI, 0.6–6.3) based on 3 exposed cases [although benzene exposure was too rare for a meaningful analysis].

In a nationwide cohort study in Switzerland, Spycher et al. (2017) used census data about parental occupation and a JEM to categorize

potential for benzene exposure (Table 2.5). In association with maternal exposure to benzene, the study showed a hazard ratio for ALL of 1.92 (95% CI, 1.18–3.13; 19 exposed cases) using the partially adjusted model and 2.63 (95% CI, 1.58–4.38) using the fully adjusted model, which included 14 variables but not maternal smoking. No association between maternal exposure to benzene and risk for AML (3 exposed cases only), lymphoma, NHL, tumours of the CNS, or glioma (Table 2.5) was found. The study also found no association between paternal benzene exposure and risk for ALL or AML, although an increased non-significant risk was observed for AML (HR, 2.66; 95% CI, 0.79–9.00; 3 exposed cases in the upper exposure category). [The Working Group considered this study to be informative because of: the lack of potential for participation, recall, or interviewer bias; the objective assessment of benzene exposure using a JEM; the proper adjustment for potential confounders; and the greater number of cases with exposed parents compared with most other studies. No adjustment was made for parental smoking, however, and there was potential for exposure misclassification.]

Among the eight case–control studies with subjective (interview-based) information about benzene exposure, three found statistically significant associations, two found increased odds ratios without statistical significance, and three found no association.

Shu et al. (1988) (see Table 2.4 in *IARC Monographs* Volume 100F, available at: http://publications.iarc.fr/123) investigated parental exposures in relation to childhood leukaemia in Shanghai and found an association between maternal exposure during pregnancy and risk for ANLL (OR, 4.0; 95% CI, 1.8–9.3; 11 cases) but not for ALL (OR, 1.3; 95% CI, 0.5–3.0; 8 cases).

McKinney et al. (1991), evaluated in *IARC Monographs* Volume 100F, investigated the associations between parental exposure to benzene and risk for leukaemia and NHL (combined) in north England; statistically significant associations with paternal preconceptional exposure (OR, 5.8; 95% CI, 1.7–26.4; 12 cases) and with maternal preconceptional exposure (OR, 4.0; 95% CI, 0.3–118.0; 2 cases) were found.

Castro-Jiménez & Orozco-Vargas (2011) investigated parental benzene exposure and risk for ALL in Columbia, and reported unadjusted odds ratios of 3.0 (95% CI, 1.3–7.1) and 1.6 (95% CI, 0.8–3.1) in association with maternal and paternal exposure, respectively, before conception, and an unadjusted odds ratio of 1.9 (95% CI, 0.8–4.2) in association with maternal exposure during pregnancy. After adjustment for maternal age, parental preconception smoking status, and maternal socioeconomic status during pregnancy, odds ratios of 5.50 (95% CI, 1.38–21.92) and 11.65 (95% CI, 2.98–45.59) were observed for exposure to benzene by mother only and by both parents, respectively.

Feingold et al. (1992) investigated childhood cancer in Denver, Colorado, USA, and reported odds ratios in association with paternal occupational benzene exposure during the year before the child's birth of 0.7 (95% CI, 0.1–3.1) for tumours of the CNS and 1.6 (95% CI, 0.5–5.8) for ALL. Peters et al. (2014) investigated childhood tumours of the brain in Australia, and reported odds ratios of 2.4 (95% CI, 0.2–25.7) and 2.7 (95% CI, 0.9–7.9) in association with maternal exposure in the year before birth and paternal exposure in the year before conception.

Kaletsch et al. (1997) studied childhood leukaemia and lymphoma in Germany, and found no association with parental occupational exposure to benzene.

Shu et al. (1999) investigated parental occupational exposures and risk of ALL in offspring (see Table 2.4 in *IARC Monographs* Volume 100F, available at: http://publications.iarc.fr/123). The authors reported odds ratios of 0.7 (95% CI, 0.3–1.8), 0.5 (95% CI, 0.1–1.6), and 0.6 (95% CI, 0.2–1.6) for maternal exposure to benzene before conception, during pregnancy, and after birth, respectively. Corresponding odds ratios for

paternal occupational exposure to benzene were 1.2 (95% CI, 0.8–1.2), 1.0 (95% CI, 0.6–1.7), and 1.2 (95% CI, 0.7–1.9).

Infante-Rivard et al. (2005) studied childhood ALL in Canada and reported an odds ratio of 0.8 (95% CI, 0.2–3.1) in association with maternal benzene exposure during the 2 years before birth, and one of 1.4 (95% CI, 0.3–6.3) in association with maternal exposure during pregnancy.

[Treating all leukaemias as a single entity is a limitation of several of the preceding studies, given the evidence of etiological heterogeneity.]

2.4 Other cancers

This section describes epidemiological studies on benzene exposure and cancer in adults in sites other than in the lymphohaematopoietic system. The tables (Table 2.6 and Table 2.7) include only relevant studies of cancer sites with sufficient or limited evidence that either were not included in *IARC Monographs* Volume 100F (IARC, 2012a) or were published later.

2.4.1 Occupational cohort studies

Several occupational cohort studies have reported results for multiple solid tumour sites. Some earlier studies were updated for specific outcomes, most often leukaemia or lymphomas, but results for other cancers were not reported in the updates.

The Working Group included occupational cohort studies that reported risk estimates specifically for benzene, based on either individual estimates of exposure or identification of subcohorts exposed to benzene. Studies were excluded if they did not meet these inclusion criteria (Guberan & Raymond, 1985; Dagg et al., 1992; Rushton, 1993; Schnatter et al., 1993; Tsai et al., 1993, 1996, 2003; Walker et al., 1993; Honda et al., 1995; Collingwood et al., 1996; Fu et al., 1996; Satin et al., 1996; Järvholm et al., 1997; Lynge et al., 1997; Lundberg & Milatou-Smith, 1998; Pukkala, 1998; Consonni et al., 1999; Divine et al., 1999a, b; Wong et al., 2001a, b; Sorahan et al., 2002; Kauppinen et al., 2003; Lewis et al., 2003; Huebner et al., 2004; Gun et al., 2006; Bonneterre et al., 2012), were superseded by updates (Ott et al., 1978), presented results only for excessively broad outcome groupings, or had very small study populations (Decouflé et al., 1983).

Studies publicly available at the time were reviewed in *IARC Monographs* Volume 100F, and a new search of the literature for this review identified a few additional studies in occupational cohorts. The following studies available at the time of the previous IARC review are included in the current evaluation: Tsai et al. (1983), Wilcosky et al. (1984), Bond et al. (1986), Wong (1987a, b), Wong et al. (1993), Greenland et al. (1994), Hayes et al. (1996), Bulbulyan et al. (1999), and Sorahan et al. (2005). A brief description of these cohorts is provided in the following section.

(a) Description of occupational cohorts

Bond et al. (1986) studied mortality among 956 workers from a chemicals production plant in Michigan, USA, exposed to benzene (see Section 2.1.1). Industrial hygiene data were used to weight jobs as incurring very low, low, moderate, or high levels of exposure, a representative time-weighted average exposure value was assigned to each level, and cumulative dose indices were calculated for each worker by summing daily time-weighted average values over the work history. Exposure–response analyses were made both including and excluding workers who were exposed to arsenic, asbestos, or high levels of vinyl chloride. Updated results for this cohort were reported by Collins et al. (2015) (see Section 2.1.1(b)), but data were not provided for all cancer sites.

Bulbulyan et al. (1999) reported cancer mortality among women in the Russian printing

Table 2.6 Occupational cohort studies of exposure to benzene and cancer of the lung

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Linet et al. (2015) China, 12 cities 1972–1987/1972–1999 Cohort	74 827 benzene-exposed and 35 504 unexposed Chinese workers; spray and brush painting (coatings), rubber, chemical (including pharmaceutical manufacturing), shoemaking, and other (including printing and insulation) industries Exposure assessment method: records; workers dichotomized (benzene exposed/unexposed) based on job titles and factory records on use of benzene-containing materials	Lung: ICD-9 (code 162)	Exposed	351	1.5 (1.2–1.9)	Sex, attained age, attained calendar year	Supersedes Yin et al. (1996a), Hayes et al. (1996); lag of 2 yr for HLD and 10 yr for all other outcomes; MDS RR mortality, infinity (1.5–infinity), $n = 7$; incidence, infinity (1.9–infinity), $n = 8$ Strengths: large sample size, 28-yr follow-up Limitations: exposure dichotomized to exposed/unexposed only (no further classification); wide range of industrial processes included; coexposures vary and were not addressed in the analyses
Koh et al. (2014) Republic of Korea 2002–2007 Cohort	14 698 male workers registered in a regional petrochemical plant maintenance workers union 2002–2007 Exposure assessment method: none; benzene-exposed workers	Lung: ICD-10 (codes C33–34) Lung: ICD-10 (codes C33–34)	SMR exposed SIR exposed	9 5	0.68 (0.31–1.29) 0.73 (0.24–1.71)	Age Age	Strengths: good coverage of target population Limitations: short follow-up time; no quantitative exposure assessment; occupational histories and specific tasks not available; tobacco exposure history not available
Koh et al. (2011) Republic of Korea 1992–2007 follow-up (16 yr) Cohort	8866 male workers at seven petrochemical plants producing or using benzene Exposure assessment method: none; classified by job	Lung (mortality) Lung (incidence) 	All workers Manufacturing workers Office workers All workers Manufacturing workers Office workers	5 3 2 8 2 6	0.35 (0.11–0.83) 0.31 (0.06–0.91) 0.44 (0.05–1.95) 0.60 (0.26–1.17) 0.22 (0.03–0.78) 1.42 (0.52–3.09)	Age and calendar period Age and calendar period 	Strengths: the first investigation of cancer risk of workers in a refinery/petrochemical complex in the Republic of Korea; data from cancer registry; ICD-10 coding Limitations: no control for smoking; short follow-up; small number of cases; healthy worker effect

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Collins et al. (2015) USA 1940–2009 Cohort	2266 workers exposed to benzene at a chemical plant Exposure assessment method: quantitative measurements; job titles were assigned to exposure categories by an industrial hygienist, based on IH measurements (JEM)	Lung: ICD-10 (codes C33–C34)	Ever exposed 0–3.9 ppm-yr	146	1.05 (0.89–1.24)	Age, race, sex	Third update of the Dow Chemical plant retrospective cohort Strengths: extensive benzene exposure monitoring; complete work history information; periodic medical examination at workplace; long and complete follow-up Limitations: mortality study based on death certificates

CI, confidence interval; HLD, haematopoietic, lymphoproliferative, and related disorders; ICD, International Statistical Classification of Diseases and Related Health Problems; IH, industrial hygiene; JEM, job-exposure matrix; MDS, myelodysplastic syndrome; ppm, parts per million; RR, relative risk; SIR, standard incidence ratio; SMR, standardized mortality ratio; yr, year(s)

Table 2.7 Epidemiological studies of exposure to benzene and cancer at other sites in adults in the general population

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bove et al. (2014) USA (California) 1975–1985/1979–2008 Cohort	309 901 marine and naval personnel who began service during 1975–1985 and were stationed anytime during this period in one of two camps, one of them having contaminated drinking-water and the other not Exposure assessment method: records; monthly average estimates of contaminant concentrations in drinking-water, published in peer-reviewed agency record; each individual was assigned estimated exposure based on residence	Lung: trachea, bronchus, and lung; ICD-9 (code 162)	Camp Pendleton (referent, non-contaminated water)	216	0.81 (0.71–0.93)	Age, sex, race, rank, education	Despite the possible healthy veteran effect bias, elevations in SMR were observed in the exposed camp Strengths: large cohorts; low loss to follow-up Limitations: exposure misclassification; for a mortality endpoint a longer follow-up is necessary; 97% of the Camp Lejeune cohort was of age < 55 yr and < 6% had died by the end of the study
			Camp Lejeune (exposure to contaminated drinking-water)	237	0.92 (0.80–1.04)		
Yuan et al. (2014) China, Shanghai 1986–1989 Nested case–control	Cases: 82 men, lifelong non-smokers aged 45–64 yr at enrolment Controls: 83 members of the Shanghai Cohort study without cancer, non-smokers and alive at the time of cancer diagnosis of the case; matched by age at enrolment (±2 yr), year, month of urine sample collection (±1 month), and neighbourhood of residence at recruitment Exposure assessment method: other; levels of urinary PAH and VOCs (SPMA for benzene) prospectively analysed	Lung	Quartiles of SPMA (metabolite of benzene)			Age at baseline, neighbourhood of residence at enrolment, years of sample storage, urinary cotinine level	Strengths: active follow-up with annual in-person interviews; after 22 yr loss of follow-up low (only 5%); urinary cotinine was also quantified to confirm non-smoking status Limitations: relatively small sample size; 26% of cases not histologically confirmed; small number of cases of SCC (n = 16); urinary samples were only collected at baseline
			1st quartile (ref)	17	1.00		
			2nd quartile	18	1.03 (0.39–2.69)		
			3rd quartile	19	1.10 (0.44–2.78)		
			4th quartile	20	1.57 (0.65–3.80)		
			Trend test P value, 0.31				
		Lung (SCC)	Tertiles of SPMA			Age at baseline, neighbourhood of residence at enrolment, years of sample storage, urinary cotinine level	
			1st tertile (ref)	NR	1.00		
			2nd tertile	NR	1.97 (0.31–12.65)		
			3rd tertile	NR	5.76 (1.11–28.96)		
			Trend test P value, 0.023				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (2014) Toronto, Canada 1997–2002 Case–control	Cases: 445 incident cases of cancer of the trachea, bronchus, or lung; men and women aged 20–84 yr; non-smokers were oversampled (35%); recruited from four tertiary-care hospitals in Toronto Controls: 948 (425 population and 523 hospital); one control series was population-based (from tax assessment files), the other control series was recruited from a nonspecialized family medicine clinic Exposure assessment method: other; land-use regression models linked to residential addresses; questionnaire on exposures	Lung: trachea, bronchus, and lung; ICD-9 (code 162) Lung: trachea, bronchus, and lung; ICD-9 (code 162)	IQR increase in time-weighted average benzene concentration IQR increase ($0.15\ \mu g/m^3$) Residential benzene exposure, 10 yr before interview IQR increase ($0.15\ \mu g/m^3$)	NR NR	1.84 (1.26–2.68) 1.58 (1.15–2.16)	Controls frequency-matched to cases by ethnicity, age, sex, pack-years of smoking (continuous variable, summed over pipe, cigar, and cigarette use), exposure to second-hand smoke, BMI, family history of cancer, neighbourhood measures of unemployment, median family income	The exposure profile among hospital controls would be expected to be higher than that in population controls (because of residential location of the hospital) Strengths: good exposure assessment including smoking history Limitations: low participation rate of population controls (59%) and lung cancer cases (62%)

BMI, body mass index; CI, confidence interval; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; NR, not reported; PAH, polycyclic aromatic hydrocarbon; SCC, squamous cell cancer; SMR, standardized mortality ratio; SPMA, *S*-phenylmercapturic acid; VOCs, volatile organic compounds; yr, year(s)

industry; the occupation of bookbinding was known to have used benzene until 1958. [The Working Group noted that many women in the bookbinding group probably did not work during the time when benzene was used.]

Greenland et al. (1994) followed up 1821 male workers at a transformer assembly facility from 1969 to 1984. Interviews with long-term employees were used to develop JEMs for seven types of exposure, including benzene, classified as none, indirect (nearby), or direct. [The notable limitations of this study included work history records not being available for many (34%) of the workers, so the size of the underlying cohort was unknown.]

Hayes et al. (1996) examined mortality among a cohort of Chinese workers from multiple industries, of whom 74 828 were exposed to benzene and 35 805 were unexposed. The study provided relative risk estimates and assessed trends across several cumulative exposure categories (0, < 10, 10–39, 40–99, 100–400, and > 400 ppm-years) for a subset of outcomes.

A total of 5514 workers from 233 facilities in the United Kingdom who were judged by their employers to be exposed to benzene were followed up for cancer incidence (1971–2001) and mortality (1968–2002) by Sorahan et al. (2005). No exposure assessment was included in the analyses because air sampling data were from 1966/1967 and only available from 130 of the facilities. [The study was retained by the Working Group as each cohort member was reported as exposed. Some under-ascertainment in the incidence component of the study was reported.]

Tsai et al. (1983) reported on 454 male benzene workers ever employed at a refinery in Texas, USA. Exposure evaluation used 1973–1982 air sampling data to determine which employees worked in benzene areas and for what duration.

Wilcosky et al. (1984) examined 6678 active and retired rubber industry workers from Akron, Ohio, USA. The study assigned worker exposures based on employment in a process area where a specific solvent was authorized for use, but the authors acknowledged that the solvents may not have been used in some of the areas.

Wong (1987a, b) reported on a study of 4602 workers exposed to benzene and 3074 unexposed workers in seven chemical plants in the USA. Wong (1987a) reported results for exposure characterized as intermittent or continuous. A companion paper presented results for this same population by cumulative exposure category for select outcomes, in which Mantel–Haenszel extension χ^2 trend test results were given (Wong, 1987b).

Wong et al. (1993) reported data for a cohort of gasoline distribution workers in the USA, 9026 of whom were based on land and 9109 who operated on marine vessels between 1946 and 1985, who were followed up for mortality outcomes until 1989. The exposure assessment for this study developed metrics for cumulative and peak exposures to total hydrocarbons as a surrogate for benzene exposure to components of gasoline.

Many of these cohort studies had limitations. In some of the occupational settings, all or subsets of workers had potential exposure to other substances such as asbestos, dust, other solvents, and industrial chemicals. Bond et al. (1986) addressed some of these additional exposure types in the analysis, in this case by removing workers exposed to arsenic, asbestos, or high levels of vinyl chloride. None of these studies adjusted for covariates other than demographic factors. The studies were also inconsistent in addressing latency; some presented results by time since first exposed or employed.

Of the more recent studies included in this evaluation, Stenehjem et al. (2017) prospectively followed up a cohort of 24 917 offshore petroleum workers in Norway (see Section 2.2.1(b)) for 13.5 years for incident cases of cancer, including cancer of the skin (melanoma and squamous cell carcinoma of the forearm and hand). An update of a cohort of Chinese workers from multiple industries (see Section 2.2.1(b)) (Linet et al.,

2015) provided rate ratios comparing outcomes between ever- and never-exposed workers. Koh et al. (2014) followed up 14 698 temporary maintenance workers in a refinery/petrochemical complex in the Republic of Korea for mortality from 2002 to 2007 and for incidence from 2002 to 2005; the workers' exposure to benzene was characterized by Chung et al. (2010). [The Working Group noted the short follow-up time as a limitation of this study.] Koh et al. (2011) also examined cancer mortality during 1992–2007 and incidence during 1997–2005 among 8866 male workers in units of a refinery/petrochemical complex in the Republic of Korea that produced or used benzene. Results were given separately for production, maintenance, laboratory, and office workers, but the authors were not able to quantify exposures because they lacked adequate job history and exposure records.

(b) Cancer sites reviewed in IARC Monographs Volume 100F

(i) Cancer of the lung

The evidence from occupational cohort studies of an association between exposure to benzene and cancer of the lung that was available at the time of publication of *IARC Monographs* Volume 100F was judged to be *inadequate*. Cohort studies available at that time, with information on potential or estimated benzene exposure and cancer of the lung, are described in Table 2.15 of Volume 100F (available at: http://publications.iarc.fr/123).

Bond et al. (1986) reported that among 956 chemical manufacturing plant workers in the USA, who had been employed for 1 month or longer during 1938–1978 and followed up through 1982, overall mortality from cancer of the lung was not increased (SMR, 0.99; 95% CI, 0.59–1.57; 18 deaths). Among cumulative exposure categories, an excess risk (SMR, 2.04; 5 deaths) was observed for the category of 500–599 ppm-months, while no excess risk was observed for the categories of 0–499 ppm-months (SMR, 0.62; 6 deaths) and 1000 ppm-months or more (SMR, 0.49; 2 deaths) [95% CIs were not reported]. In an update of this cohort (see Table 2.6), Collins et al. (2015) reported that among 2266 United States chemical manufacturing plant workers beginning employment during 1940–1982 and followed up through 2009, no excess risk of cancer of the lung (including lung, trachea, and bronchus; ICD-10, codes C33–C34) was observed (SMR, 1.05; 95% CI, 0.89–1.24; 146 deaths).

Collins et al. (2003) reported that among 4417 chemical manufacturing hourly workers in Illinois, USA, who began employment during 1940–1977 and were followed up through 1997, a 60% excess risk of cancer of the lung was observed among those with cumulative exposure to benzene at more than 6 ppm-years (SMR, 1.6; 95% CI, 1.2–2.1; based on 55 deaths). There was a monotonic trend in standardized mortality ratios across cumulative exposure groups exposed to benzene at less than 1 ppm-years (SMR, 1.1; 95% CI, 0.7–1.5), 1–6 ppm-years (SMR, 1.3; 95% CI, 1.0–1.8), and more than 6 ppm-years (SMR, 1.6; 95% CI, 1.2–2.1), although the reference group also presented an elevated risk for cancer of the lung (SMR, 1.3; 95% CI, 1.1–1.5).

Sorahan et al. (2005) reported that among 5514 workers exposed to benzene in 233 factories in the United Kingdom during 1966/1967 or earlier, followed up for mortality during 1968–2002, there was a significant increase in mortality from cancer of the lung (SMR, 1.21; 95% CI, 1.07–1.35; based on 294 deaths) and in incidence of cancer of the lung (SIR, 1.19; 95% CI, 1.06–1.34; based on 293 cases). There was no clear evidence of heterogeneity by type of industry, despite exposure of some of these workers to other carcinogens such as asbestos and polycyclic aromatic amines. [The Working Group noted that some of the deaths coded to cancer of the lung may actually have been due to mesothelioma. Some cancer cases may have been missed or misclassified.]

Wong (1987a, b) reported a standardized mortality ratio of 1.12 (95% CI, 0.90–1.39; *n* = 86), but no exposure–response relation was observed. Among land-based gasoline distribution and marine distribution workers, Wong et al. (1993) reported standardized mortality ratios of 0.66 (95% CI, 0.57–0.77; *n* = 165) and 1.07 (95% CI, 0.94–1.21; *n* = 208), respectively.

The Working Group identified several other pertinent studies that were available at the time, but not included in the previous review (see Table 2.6). Tsai et al. (1983) reported a standardized mortality ratio of 0.52 (95% CI, 0.06–1.86; *n* = 2) in a study of refinery workers. Greenland et al. (1994) observed an odds ratio of 0.58 (95% CI, 0.31–1.07) when directly comparing exposed transformer repair workers with their indirectly exposed or unexposed counterparts. Bulbulyan et al. (1999) reported a standardized mortality ratio of 0.7 (95% CI, 0.1–2.0; *n* = 3) among female bookbinders.

Additional data were available for several more recent studies. Linet et al. (2015) (see Section 2.1.1(b) for details) updated data on cancer among Chinese workers exposed to benzene, studied previously by Hayes et al. (1996). Workers exposed to benzene demonstrated a significant excess of mortality from cancer of the lung (RR, 1.5; 95% CI, 1.2–1.9; *n* = 351). The highest relative risk for mortality from cancer of the lung was for workers in the rubber and coatings industries. Relative risks for death from cancer of the lung were significantly elevated and of the same magnitude in the early (1972–1987) and later (1988–1999) follow-up periods. All analyses were stratified according to sex, attained age, and attained calendar year. [The Working Group noted that there was no control for potential confounding by smoking or other occupational exposures. However, the authors noted that associations were similar in women and men, although the prevalence of smoking is generally much lower among Chinese women.] Hayes et al. (1996) and Yin et al. (1996b) previously reported data for this cohort. Mortality from cancer of the lung (also including trachea and bronchus; ICD-9, code 162) was in excess in the cohort overall (RR, 1.4; 95% CI, 1.0–2.0) due to men (RR, 1.5; 95% CI, 1.0–2.2; 109 cases) but not women (RR, 1.0; 95% CI, 0.4–2.9; 16 cases), and it was increased among workers with greater estimated cumulative benzene exposure (RR, 1.7 for those with ≥ 400 ppm-years exposure vs no exposure; *P* value for trend, 0.01).

Koh et al. (2011) reported on a study of cancer mortality and incidence among petrochemical workers at plants producing or using benzene; no excess in cancer of the lung mortality (SMR, 0.31; 95% CI, 0.06–0.91) or incidence (SIR, 0.22; 95% CI, 0.03–0.78) was reported in manufacturing workers. [The Working Group noted the presence of a healthy worker effect and the short follow-up time.]

Koh et al. (2014) reported on a study of cancer mortality and incidence among temporary maintenance workers at a refinery/petrochemical complex in the Republic of Korea; no excess in cancer of the lung mortality (SMR, 0.68; 95% CI, 0.31–1.29) or incidence (SIR, 0.73; 95% CI, 0.24–1.71) was observed.

(ii) Cancer of the kidney

The evidence available on the association between occupational exposure to benzene and cancer of the kidney was reviewed in *IARC Monographs* Volume 100F, and judged to be *inadequate* at that time; pertinent occupational cohort studies reviewed in Volume 100F are described in Table 2.17 (available at: http://publications.iarc.fr/123). The results of these studies generally do not show a consistent association, although several studies did report elevated but not statistically significant risks for cancer of the kidney (Wong, 1987a, b; Tsai et al., 1993; Sorahan et al., 2005).

Wong et al. (1993) reported on a nested case–control study of United States land-based or marine petroleum distribution workers for

exposure to gasoline containing 2–3% benzene (Wong et al., 1999); several quantitative indices of gasoline exposure (duration of exposure, cumulative exposure, frequency of peak exposure, age at first exposure, and year of first exposure) were used for analysis, but an excess mortality risk was not found for cancer of the kidney. [The Working Group noted potential exposure misclassification and a healthy worker effect.]

Wong (1987a, b) observed a standardized mortality ratio of 0.85 (95% CI, 0.27–1.98; $n = 5$), and did not observe any association between level of exposure and increased risk of cancer of the kidney: no cases were reported in the highest cumulative exposure category.

An odds ratio of 4.29 (95% CI, 1.33–13.8) for death from cancer of the kidney was reported for transformer manufacturing facility workers directly exposed to benzene compared with workers who were unexposed or indirectly exposed (Greenland et al., 1994).

Bulbulyan et al. (1999) reported a standardized mortality ratio of 1.9 (95% CI, 0.4–5.6; $n = 3$) among female bookbinders exposed to benzene.

Collins et al. (2015) reported no excess of death from cancer of the kidney (SMR, 0.78; 95% CI, 0.34–1.55; $n = 8$).

(c) Other cancer sites

Data for other cancer sites were not reviewed in detail in *IARC Monographs* Volume 100F. The key findings of pertinent studies that reported data for several additional types of cancer are reported in the following sections.

(i) Cancers of the nasal cavity, pharynx, larynx, and other respiratory sites

Several studies have reported data on other cancers of the respiratory tract, including the nasal cavity, buccal cavity, pharynx, and larynx (Tsai et al., 1983; Wong, 1987b; Greenland et al., 1994; Hayes et al., 1996; Bulbulyan et al., 1999; Sorahan et al., 2005; Koh et al., 2011, 2014; Linet et al., 2015). Results were based on small numbers of cases or deaths and were generally close to expectation. Two studies reported increased, albeit non-significant, relative risks for cancer of the nasopharynx. Among temporary maintenance workers at a refinery/petrochemical complex in the Republic of Korea, excess mortality (SMR, 5.88; 95% CI, 1.21–17.2; based on 3 deaths) and incidence (SIR, 8.33; 95% CI, 1.72–24.50; based on 3 cases) of cancer of the nasopharynx were reported. The relative risk of death from cancer of the nasopharynx was also elevated (RR, 1.9; 95% CI, 0.9–4.3; $n = 29$) in the Chinese cohort of workers exposed to benzene (Linet et al., 2015), although there was no evidence of a trend with cumulative benzene exposure (Hayes et al., 1996).

(ii) Cancer of the oesophagus

Chinese worker cohorts reported a P value for trend of 0.09 for the association between mortality from cancer of the oesophagus and cumulative exposure to benzene (Hayes et al., 1996). An elevated risk (RR, 1.6; 95% CI, 1.0–2.5; 70 exposed deaths) was reported when comparing workers exposed to benzene with unexposed workers in an updated analysis of the Chinese worker cohort (Linet et al., 2015). Greenland et al. (1994) reported an odds ratio of 1.23 (95% CI, 0.26–5.72) for mortality from cancer of the oesophagus among directly exposed workers compared with indirectly exposed or unexposed workers. Bulbulyan et al. (1999) observed an increase in female bookbinders (SMR, 4.1; 95% CI, 1.0–10.4; $n = 4$). Wong (1987a) observed no excess mortality from cancer of the oesophagus in workers continuously exposed to benzene, and no dose–response relationship was detected for the four deaths observed (Wong, 1987b). Sorahan et al. (2005) reported incidence and mortality results that were not statistically significant and were near or below expectation. Koh et al. (2014) observed a standardized mortality ratio of 0.51 (95% CI, 0.01–2.85; $n = 1$) and no incident cases.

(iii) Cancer of the stomach

The results from most studies of cancer of the stomach are generally at or below expectation. Hayes et al. (1996) reported a *P* value for trend of 0.63 for the association between mortality from cancer of the stomach and cumulative benzene exposure. Greenland et al. (1994) observed an odds ratio of 0.32 (95% CI, 0.04–2.42) for directly exposed workers compared with indirectly exposed or unexposed workers. A cancer of the stomach mortality deficit was reported by Wong (1987a) for workers exposed to benzene (SMR, 0.43; 95% CI, 0.16–0.94; $n = 6$). Tsai et al. (1983) reported a non-significantly elevated standardized mortality ratio of 2.32 for men working 1 year or more in areas exposed to benzene, based on a single case. Sorahan et al. (2005) reported a standardized mortality ratio of 1.06 (95% CI, 0.80–1.37; $n = 57$) and a similar standardized incidence ratio. Bulbulyan et al. (1999) reported a significantly elevated mortality from cancer of the stomach among press operators (SMR, 2.2; 95% CI, 1.0–4.2; $n = 9$) but no elevation among bookbinders (SMR, 1.0; 95% CI, 0.5–1.8; $n = 12$). Wilcosky et al. (1984) reported an odds ratio of 1.3 (based on 12 exposed cases) comparing male workers with potential cumulative benzene exposure of more than 1 year with those with no benzene exposure. Linet et al. (2015) reported no excess risk (RR, 1.0; 95% CI, 0.8–1.3; 211 exposed deaths) for mortality from cancer of the stomach when comparing exposed workers with those not exposed. Koh et al. (2014) reported a standardized mortality ratio of 0.83 (95% CI, 0.41–1.48; $n = 11$) and a standardized incidence ratio of 0.99 (95% CI, 0.56–1.64; $n = 15$). Koh et al. (2011) found significant deficits of mortality from cancer of the stomach in all workers (SMR, 0.24; 95% CI, 0.06–0.60; $n = 4$) and in manufacturing workers (SMR, 0.25; 95% CI, 0.05–0.74; 3 cases), as well as in all-cause mortality and all-cancer mortality among all workers and manufacturing workers.

(iv) Cancers of the colon, rectum, and anus

A study of the Chinese worker cohort reported no evidence (*P* for trend, 0.91) of an exposure–response relationship between exposure to benzene and cancers of the colon and rectum (Hayes et al., 1996). In the update of that study, Linet et al. (2015) observed a relative risk of 1.5 (95% CI, 1.0–2.3; 79 exposed deaths) for cancers of the colon and rectum. Greenland et al. (1994) reported deficits in odds ratios for mortality from cancers of the colon (OR, 0.74; 95% CI, 0.33–1.66) and rectum (OR, 0.85; 95% CI, 0.29–2.47) in directly exposed workers compared with those who were indirectly or not exposed. Wong (1987a) reported a standardized mortality ratio of 1.08 (95% CI, 0.52–1.98; $n = 10$) in continuously exposed workers; no significant exposure–response relationships for cancer of the colon were reported (Wong, 1987b). Sorahan et al. (2005) reported a deficit for mortality (SMR, 0.81; 95% CI, 0.57–1.11; 38 cases) from and incidence (SIR, 0.86; 95% CI, 0.65–1.10; 60 cases) of cancer of the colon. However, for cancer of the rectum increased risks for mortality (SMR, 1.05; 95% CI, 0.71–1.48; $n = 31$) and incidence (SIR, 1.13; 95% CI, 0.86–1.45; $n = 61$) were reported. Among women exposed to benzene while employed as bookbinders, Bulbulyan et al. (1999) reported standardized mortality ratios of 1.3 (95% CI, 0.6–2.6; $n = 8$) for cancer of the colon and 1.3 (95% CI, 0.4–3.1; $n = 5$) for cancer of the rectum. Tsai et al. (1993) reported a standardized mortality ratio for cancer of the colon of 0.94 (95% CI, 0.60–1.40; $n = 24$). For cancers of the intestine and anus, Koh et al. (2014) reported a standardized mortality ratio of 0.33 (95% CI, 0.04–1.20; $n = 2$) and a standardized incidence ratio of 0.91 (95% CI, 0.37–1.88; $n = 7$) among temporary maintenance workers. Koh et al. (2011) reported a standardized mortality ratio of 0.49 (95% CI, 0.06–1.78; $n = 2$) for cancers of the colon and anus among manufacturing workers.

(v) Cancers of the liver and biliary tract

When analysing mortality from cancers of the liver and gall bladder among Chinese workers by cumulative benzene exposure, no notable exposure–response relationships or elevations in exposed versus unexposed workers were observed by Hayes et al. (1996) (*P* for trend, 0.16). Linet et al. (2015) reported a relative risk for cancers of the liver, gallbladder, and bile duct of 1.2 (95% CI, 0.9–1.4; 286 exposed deaths) in the updated study of Chinese benzene workers. Greenland et al. (1994) reported a non-significant odds ratio of 2.76 (95% CI, 0.68–11.20; $n = 9$) for cancers of the liver, gallbladder, and biliary tract combined among workers directly exposed to benzene compared with their unexposed or indirectly exposed counterparts. Elevations in mortality (SMR, 1.54; 95% CI, 0.74–2.84; $n = 10$) and morbidity (SIR, 1.31; 95% CI, 0.57–2.59; $n = 8$) from cancer of the liver were reported by Sorahan et al. (2005); regarding cancer of the gallbladder, the same study reported deficits in mortality (SMR, 0.60; 95% CI, 0.08–2.26; two deaths) and morbidity (SIR, 0.66; 95% CI, 0.14–1.92; three deaths). Bulbulyan et al. (1999) reported 1 observed death from liver cancer, compared with 1.2 cases expected in bookbinders. Wong (1987b) reported no excess risk or exposure–response trends among chemical workers in the USA. Koh et al. (2014) reported a standardized mortality ratio of 0.82 (95% CI, 0.51–1.25; $n = 21$) and a standardized incidence ratio of 1.07 (95% CI, 0.58–1.79; $n = 14$) for cancer of the liver. Koh et al. (2011) reported a standardized mortality ratio of 0.64 (95% CI, 0.34–1.09; $n = 13$) for cancers of the liver and biliary tract among manufacturing workers.

(vi) Cancer of the prostate

Greenland et al. (1994) reported an odds ratio of 1.02 (95% CI, 0.49–2.12) for directly exposed workers compared with indirectly exposed or unexposed workers. No associations were seen by Wong (1987a) (SMR, 0.93; 95% CI, 0.34–2.03; 6 deaths) or Wilcosky et al. (1984) (OR, 0.73; 11 deaths; CI not reported). Sorahan et al. (2005) reported a standardized mortality ratio of 0.94 (95% CI, 0.70–1.24; $n = 50$) and a standardized incidence ratio of 1.10 (95% CI, 0.91–1.32; $n = 121$). Koh et al. (2014) reported a standardized mortality ratio of 2.51 (95% CI, 0.06–14.00; $n = 1$) and a standardized incidence ratio of 1.20 (95% CI, 0.03–6.71; $n = 1$). Koh et al. (2011) observed no deaths from cancer of the prostate in manufacturing workers.

(vii) Cancer of the bladder

No association between exposure to benzene and cancer of the bladder was seen by Greenland et al. (1994) or Wong (1987a). Sorahan et al. (2005) reported a standardized mortality ratio of 1.00 (95% CI, 0.66–1.46; 27 cases) and a standardized incidence ratio of 1.04 (95% CI, 0.81–1.31; 69 cases). Bulbulyan et al. (1999) observed 1 death from cancer of the bladder in bookbinders, where 0.5 was expected. Among press operators, standardized mortality ratio was 12.5 (95% CI, 1.5–45.1; $n = 2$). Linet et al. (2015) reported a relative risk for cancer of the bladder for exposed versus unexposed workers of 0.9 (95% CI, 0.4–2.2; 18 exposed deaths). Koh et al. (2011) observed no deaths from cancer of the bladder.

(viii) Cancer of the skin

Bond et al. (1986) found four deaths from cancer of the skin, all in the lowest exposure category (0–499 ppm-months). The overall standardized mortality ratio for cancer of the skin was 4.41 unlagged and 6.22 with a 15-year lag. Wong (1987a) observed a non-significant deficit in workers continuously exposed to benzene, with the single exposed case (of 3 cases in total) occurring in the lowest exposure category (Wong, 1987b). For all cancers of the skin, Koh et al. (2014) reported a standardized mortality ratio of 5.05 (95% CI, 0.13–28.20; $n = 1$) and no incident cases. No deaths from cancer of the skin were observed by Koh et al. (2011) in manufacturing workers.

For non-melanoma cancer of the skin, Sorahan et al. (2005) reported one observed death (SMR, 0.55; 95% CI, 0.01–3.05). Stenehjem et al. (2017) reported an adjusted odds ratio of 3.51 (95% CI, 0.45–27.00; n = 6) for squamous cell carcinoma of the forearm and hand after adjustment for age, sunburn frequency, and education.

For malignant melanoma, Sorahan et al. (2005) reported a standardized mortality ratio of 0.81 (95% CI, 0.22–2.06; n = 4) and a standardized incidence ratio of 1.21 (95% CI, 0.64–2.07; n = 13). Among women potentially exposed to benzene, Bulbulyan et al. (1999) reported an elevated risk (SMR, 8.7; 95% CI, 1.1–31.3; n = 2) among press operators and no melanoma deaths among bookbinders. In offshore petroleum workers, Stenehjem et al. (2017) reported an odds ratio for benzene exposure of 2.43 (95% CI, 0.30–20.00; n = 5) for melanomas of the forearm and hand after adjustment for age, sunburn frequency, and education. [The Working Group noted that adjustment for sunburn was not a good proxy for adjusting for occupational exposure to ultraviolet radiation. There may also have been potential confounding as a result of other co-exposures.]

(ix) Cancers of the brain and central nervous system

Wong (1987a) reported an increased mortality from cancer of the CNS (ICD-8, code 191–912) for workers continuously exposed to benzene (SMR, 1.54; 95% CI, 0.56–3.35; n = 6), with no linear trend by cumulative exposure (Wong, 1987b) or overall elevation for the three exposure categories.

An odds ratio of 2.11 (95% CI, 0.66–6.73; n = 16) was reported for transformer assembly workers directly exposed to benzene compared with those indirectly exposed or unexposed (Greenland et al., 1994). These results include both malignant and unspecified tumours of the brain.

An exposure–response analysis for the Chinese cohort (Hayes et al., 1996) saw no trend (P for trend, 0.48), but did find an elevation in the highest exposure category (RR, 2.3; five deaths) with deficits in two intermediate exposure categories. In an update of the study, Linet et al. (2015) reported a relative risk of 0.8 (95% CI, 0.4–1.6; 18 exposed deaths) for benign and malignant tumours of the brain for any exposure to benzene.

For cancers of the brain and spine, Koh et al. (2014) reported a standardized mortality ratio of 1.21 (95% CI, 0.15–4.36; n = 2) and a standardized incidence ratio of 2.36 (95% CI, 0.29–8.52; n = 2). Koh et al. (2011) observed no deaths from neurological cancers in manufacturing workers. Collins et al. (2015) reported a standardized mortality ratio of 1.01 (95% CI, 0.48–1.86; 10 deaths) for cancer of the CNS among chemical production workers.

Several older studies provided only summary standardized mortality ratio results for these cancers. Bulbulyan et al. (1999) reported a standardized mortality ratio of 2.6 (95% CI, 0.5–4.6; n = 3) for cancers of the brain and nervous system among women employed as bookbinders. Tsai et al. (1983) included benign neoplasms of the brain and other parts of the nervous system, and neoplasms of an unspecified nature of the eye, brain, and other parts of the nervous system, and reported a standardized mortality ratio of 3.23 (95% CI, 0.04–17.95; n = 1) among men employed as refinery workers. Sorahan et al. (2005) reported non-significant increases in mortality (SMR, 1.05; 95% CI, 0.60–1.70; n = 16) and morbidity (SIR, 1.16; 95% CI, 0.68–1.83; n = 18) for malignant neoplasms of the brain and other parts of the nervous system.

(x) Cancer of the pancreas

A study of male chemical workers observed a standardized mortality ratio below expectation (Wong 1987a) and no exposure–response association between exposure to benzene and cancer

of the pancreas (Wong, 1987b). Greenland et al. (1994) reported an odds ratio of 0.58 (95% CI, 0.18–1.93; *n* = 33) when comparing transformer assembly workers who had been directly exposed to benzene with those indirectly exposed or unexposed. Elevated risks for mortality (SMR, 1.21; 95% CI, 0.85–1.68; *n* = 36) and incidence (SIR, 1.29; 95% CI, 0.90–1.79; *n* = 36) were observed by Sorahan et al. (2005). Bulbulyan et al. (1999) reported a standardized mortality ratio of 1.1 (95% CI, 0.2–3.3; *n* = 3) in female bookbinders and one of 2.0 (95% CI, 0.3–7.4; *n* = 2) among female press operators potentially exposed to benzene. Koh et al. (2014) observed a standardized mortality ratio of 0.57 (95% CI, 0.07–2.07; *n* = 2) and a standardized incidence ratio of 1.41 (95% CI, 0.17–5.09; *n* = 2) in temporary maintenance workers in a refinery/petrochemical complex in the Republic of Korea. For refinery/petrochemical facility manufacturing workers, Koh et al. (2011) reported a standardized mortality ratio of 1.21 (95% CI, 0.25–3.52; *n* = 3) for cancer of the pancreas. Linet et al. (2015) reported a relative risk of 1.7 (95% CI, 1.0–3.1; 45 exposed deaths) for the Chinese benzene worker cohort.

(xi) Additional cancers

Cancers assessed by less than four studies each include the following malignancies: other urinary and genitourinary (Sorahan et al., 2005); other endocrine (Sorahan et al., 2005); small intestine (Sorahan et al., 2005); testis (Sorahan et al., 2005); ovary (Bulbulyan et al., 1999, Sorahan et al., 2005); uterine corpus (Bulbulyan et al., 1999; Sorahan et al., 2005; Linet et al., 2015); uterine cervix (Bulbulyan et al., 1999; Sorahan et al., 2005); thyroid (Sorahan et al., 2005); pleural cancer and mesothelioma (Sorahan et al., 2005); breast (Bulbulyan et al., 1999; Sorahan et al., 2005; Linet et al., 2015); bone (Wong, 1987a, b; Sorahan et al., 2005); lip (Sorahan et al., 2005); and tongue (Sorahan et al., 2005; Koh et al., 2014). Small numbers of cases or deaths were observed for most of these sites. Exceptions included: a standardized mortality ratio of 2.9 (95% CI, 1.5–5.0; *n* = 12) for cancer of the ovary among bookbinders (Bulbulyan et al., 1999); a relative risk of 2.6 (95% CI, 0.9–10.9; *n* = 19) for death from cancer of the uterus; and a relative risk of 1.2 (95% CI, 0.6–2.5; *n* = 32) for death from cancer of the breast among Chinese workers exposed to benzene (Linet et al., 2015).

2.4.2 General-population studies

(a) Cancer of the lung

One cohort study of environmental exposure and three case–control studies examined cancer of the lung in relation to indicators of exposure to benzene (Table 2.7).

Bove et al. (2014) reported on cancer of the lung in the cohort study of United States military personnel exposed to contaminated drinking-water. No quantitative estimate of benzene or other agents was derived. There was an elevated hazard ratio (adjusted for sex, race, rank, and education, but not for smoking) for cancer of the lung among the personnel exposed to drinking-water contaminated with solvents, including benzene (HR, 1.16; 95% CI, 0.96–1.40; 10-year lag time), where the elevation was due entirely to those with higher cumulative exposures. The standardized mortality ratio was 0.92 (95% CI, 0.80–1.04; 237 deaths), and most people in the cohort were younger than 55 years at the end of follow-up.

A case–control study in Montreal reviewed in *IARC Monographs* Volume 100F showed no association between exposure to benzene and overall cancer of the lung (*n* = 857) or for histological subtypes (see Table 2.16, available at: http://publications.iarc.fr/123). Covariates adjusted for in the study included cumulative smoking index, and exposure to arsenic, asbestos, chromium VI, nickel, crystalline silica, beryllium, cadmium, and polycyclic aromatic hydrocarbons (Gérin et al., 1998).

Villeneuve et al. (2014) reported on a case–control study of 445 incident cases of cancer of the lung, trachea, and bronchus, and 948 hospital- and population-based controls in Toronto (1997–2002). Exposure to ambient volatile organic compounds, including benzene, from outdoor air pollution was assessed using land-use regression models and residential history data. The investigators collected information on confounders including tobacco use and exposure to cigarette smoke. An interquartile range increase in estimated time-weighted average benzene exposure across previous residences was associated with cancer of the lung only when using population-based controls (OR, 1.84; 95% CI, 1.26–2.68). Associations were also positive when using exposure 10 years before interview (OR, 1.58; 95% CI, 1.15–2.16) or at the time of interview (OR, 1.51; 95% CI, 1.13–2.01), but smaller in magnitude.

Yuan et al. (2014) reported on a nested case–control study of 82 cases of cancer of the lung and 83 controls among lifelong non-smoking Chinese men in the Shanghai Cohort Study, aged 45–64 years at enrolment. Prospective urine samples were taken and levels of urinary metabolites of polycyclic aromatic hydrocarbons and volatile organic compounds were examined for an association with risk of cancer of the lung. None of the metabolites of volatile organic compounds were associated with overall risk of cancer of the lung. However, elevated urinary *S*-phenylmercapturic acid (SPMA, a metabolite of benzene) was associated with an increased risk of squamous cell carcinoma of the lung (16 cases); odds ratios for the second and third tertiles of SPMA were 1.97 (95% CI, 0.31–12.65) and 5.76 (95% CI, 1.11–28.96), respectively. Overall, there was a monotonic but non-significant trend in odds ratios across quartiles of SPMA (ORs, 1.00, 1.03, 1.10, and 1.57; *P* for trend, 0.31). [The Working Group noted that the study size was small and, although specific to benzene, SPMA was measured at a single point in time and is not a good proxy for occupational benzene exposure (half-life, 9.1 hours). Results also appear to be sensitive to the grouping of the exposure data.]

(b) Cancer of the kidney

In the previous review of the evidence for associations between exposure to benzene and cancer of the kidney, *IARC Monographs* Volume 100F identified two case–control studies in the general population. In the first study, conducted in Germany, an association was found between exposure to benzene and an increased risk for cancer of the kidney (specifically, renal cell carcinoma; Pesch et al., 2000). The study included 935 incident cases and 4298 controls interviewed between 1991 and 1995, with exposure estimated according to occupational history and a JEM. Results indicated that employment durations exceeding the 90th percentile (classified as "very long exposures") in the chemical, rubber, and printing industries were associated with renal cell carcinoma. Substantial exposure to organic solvents was a significant risk factor for both men and women. In the second study in Montreal, Canada, benzene exposure levels were low for most exposed subjects, and there was little evidence of an association between medium and high levels of exposure and risk of cancer of the kidney (OR, 1.3; 95% CI, 0.7–2.4; $n = 12$) (Gérin et al., 1998). The evidence available at the time was judged to be *inadequate*.

Subsequently, Bove et al. (2014) reported on a cohort study of United States marine ($n = 154\,932$) and naval ($n = 154\,969$) personnel who began service during 1975–1985 and were stationed at two United States military bases. Drinking-water systems in Camp Lejeune, North Carolina, were contaminated with solvents, and drinking-water in Camp Pendleton, South Carolina, was uncontaminated. Although the study population was an occupational group, the exposure of interest was environmental; the agents of primary concern were perchloroethylene and trichloroethylene in drinking-water. Benzene was also a contaminant,

with monthly average concentrations above the current United States maximum contaminant levels for 63 months. Personnel in Camp Lejeune had an elevated mortality for cancer of the kidney (HR, 1.35; 95% CI, 0.84–2.16) and, within the cohort, a monotonic categorical cumulative exposure trend was observed for cancer of the kidney and total contaminants. A risk estimate for the association between benzene exposure and mortality from cancer of the kidney was not reported. Less than 6% of the cohort had died, but a risk estimate for the association between benzene exposure and cancer of the kidney was not reported.

(c) Additional cancers

Several studies of associations between various cancers and environmental exposures to benzene have been published recently.

Bove et al. (2014) reported no excess mortality from cancer of the oral cavity or larynx among marine and naval personnel exposed to contaminated drinking-water.

Garcia et al. (2015) reported on a cohort study of 112 378 participants in the California Teachers Study, including 5676 women diagnosed with cancer of the breast. Modelled annual average air concentrations of 24 mammary gland carcinogen pollutants were derived from the NATA database; the mean benzene concentration was 1.40 μg/m^3. There was little evidence for a trend in the hazard of breast cancer overall with estimated benzene concentration (*P* value for trend, 0.38). Analyses restricted to tumours that were both estrogen-receptor and progesterone-receptor negative (704 cases) suggested increased risk of cancer of the breast with exposure to benzene, with a hazard ratio for the highest quintile of benzene concentration of 1.45 (95% CI, 1.15–1.83; *P* for trend, 0.016). Confining the analysis to never smokers did not weaken the association.

Cigarette smoking is the most important environmental factor for cancer of the pancreas. Among smokers, 90% of benzene exposure comes from smoking (National Cancer Institute, 2015). Antwi et al. (2015) reported on a case–control study based at the Mayo Clinic in Minnesota on environmental exposures and risk of cancer of the pancreas; the study included 2092 cases and 2316 hospital-based matched controls from primary care clinics with self-reported exposure in the form of questionnaire responses. Self-reported regular exposure to benzene was associated with cancer of the pancreas, adjusted for age, sex, smoking, diabetes, body mass index, and education (OR, 1.70; 95% CI, 1.23–2.35). [The Working Group noted that significant risks associated with regular exposure to asbestos (OR, 1.54; 95% CI, 1.23–1.92) and chlorinated hydrocarbons (OR, 1.63; 95% CI, 1.32–2.02) were reported. Exposure assessment in the study was limited by self-reported exposure to benzene.]

2.5 Quantitative data

Following the recommendation of an Advisory Group on quantitative risk characterization (IARC, 2014), the Working Group carried out meta-analyses and meta-regression analyses of quantitative associations between occupational benzene exposure and several cancers of the haematopoietic tissues. These analyses update and extend those published earlier by Vlaanderen et al. (2010, 2011, 2012). The association between occupational benzene exposure and the development of AML and CLL was estimated in meta-analyses. Meta-regression analyses investigating the slope and shape of exposure–disease functions were conducted for AML. Studies were selected for inclusion in these analyses using the criteria applied throughout this section; the analytical approach was similar to that previously reported by Vlaanderen et al. (2010, 2011).

2.5.1 Data extraction

Risk ratios, odds ratios, and standardized mortality or incidence ratios were extracted from published studies. The term "relative risk" will be used to refer to these measures of association collectively. Where both mortality and incidence data were reported, the incidence data were used for analysis.

For the meta-regression analyses, only relative risk estimates reported for cumulative exposure to benzene (expressed in ppm-years or ppm-months) were used.

2.5.2 Statistical analysis

(a) Meta-analysis

Random-effects meta-analyses were performed to pool relative risks for AML and CLL. To allow the inclusion of studies without quantitative exposure estimates, only relative risks for "any occupational benzene exposure" versus "background benzene exposure" were used in the meta-analysis. For those studies which included exposure estimates, relative risks for categories of exposure were pooled either by summing observed and expected cases for studies that reported standardized mortality ratios, or by conducting a within-study random-effects meta-analysis of the non-reference exposure groups for studies which reported relative risks or odds ratios.

(b) Meta-regression

The data extracted for use in meta-regression analysis were relative risk estimates for categories of cumulative benzene exposure. Each exposure category relative risk was assigned a specific cumulative exposure value for the purpose of regression analysis, defined as the mid-point of the exposure category. If an open-ended exposure category was reported for the highest exposure group, then the Working Group assigned it an exposure value equal to the reported lower limit for that exposure category plus one half the width of the previous exposure category. The variance of each relative risk was estimated using the reported confidence intervals under the assumption of Wald-type bounds. As risk estimates of a study based on a common internal reference group will be correlated, the covariance between different risk estimates within a study were estimated. For studies that reported standardized mortality ratios, covariance was not estimated.

Meta-regression analyses were performed on the natural logarithm of the reported relative risk estimates, fitting a linear model as well as natural spline models with knots at the 20th, 50th, and 80th percentiles of the benzene exposure distribution. All statistical analyses were performed using the MIXED and IML procedures in SAS 9.4; the meta-analysis was conducted using the "metafor" package in R, version 3.1.2 (Viechtbauer, 2010).

2.5.3 Results

(a) Meta-analysis

Results of the meta-analysis of selected studies on adult AML and CLL are shown in Fig 2.1, stratified by outcome assessment (incidence, mortality, and both combined).

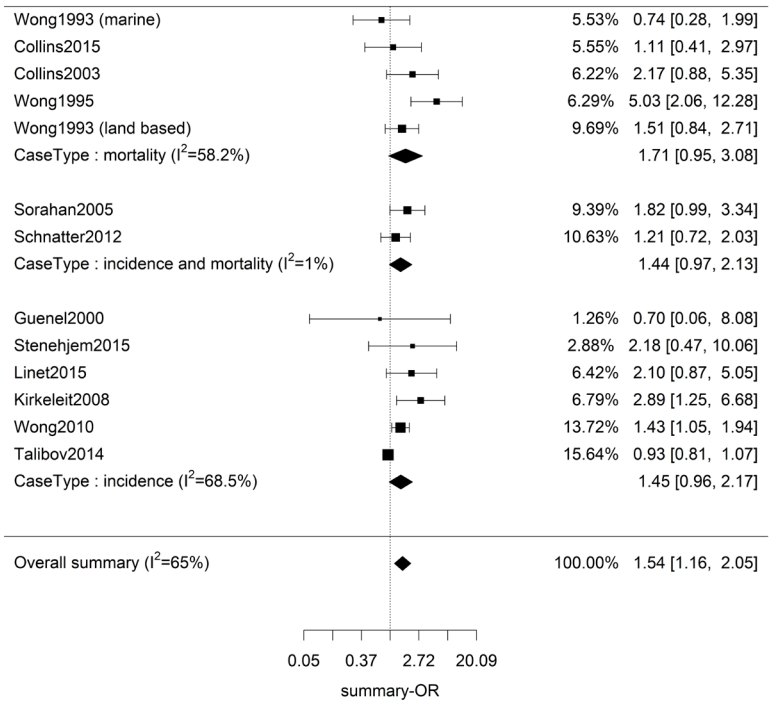
(b) Meta-regression

Visual examination of the natural spline of the cumulative benzene exposure and AML function, including six occupational cohort studies, strongly supported a linear model, as did a statistical comparison of the linear and spline models with respect to goodness of model fit. Subsequent meta-regression analysis focused on results for the linear model, presented in Fig. 2.2.

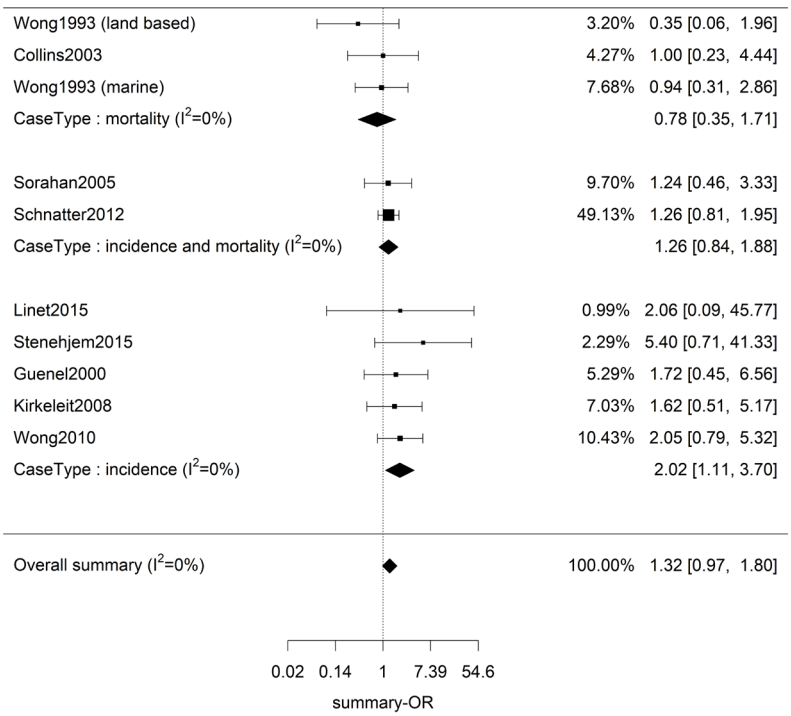
The sensitivity of the exposure–response trend to a single influential study was assessed by refitting the model upon exclusion of one study at a time (Table 2.8). These results indicate that the exposure–response estimate is robust for

Fig. 2.1 Forest plots of (A) AML and (B) CLL stratified by type of outcome (incidence or mortality)

A

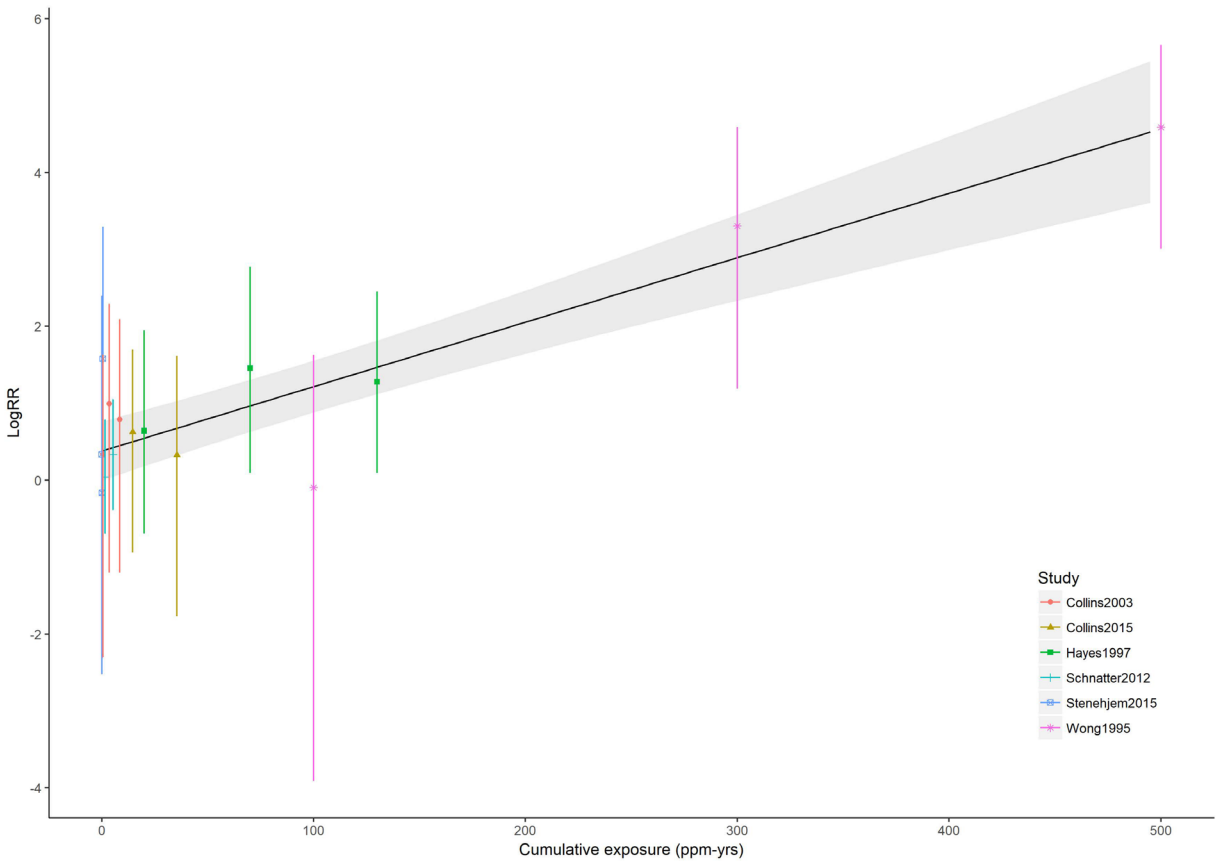


B



AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; OR, odds ratio
Compiled by the Working Group

Fig. 2.2 Meta-regression model of cumulative benzene exposure and AML, including fitted curve and confidence bands



AML, acute myeloid leukaemia
Compiled by the Working Group

Table 2.8 Sensitivity analyses of the linear function of cumulative exposure to benzene (ppm-yr) and AML by sequential exclusion of individual cohort studies

Studies	Intercept	Slope (/100)
All studies	0.38 (0.20)	0.84 (0.11)
Excluding Stenehjem et al. (2015)	0.34 (0.20)	0.85 (0.11)
Excluding Collins et al. (2015)	0.40 (0.22)	0.84 (0.11)
Excluding Schnatter et al. (2012)	0.50 (0.25)	0.81 (0.11)
Excluding Hayes et al. (1997)	0.36 (0.21)	0.86 (0.11)
Excluding Collins et al. (2003)	0.28 (0.23)	0.86 (0.11)
Excluding Wong (1995)	0.45 (0.21)	0.59 (0.40)

AML, acute myeloid leukaemia; ppm, parts per million; yr, year(s)

the exclusion of all individual studies, with the exception of Wong (1995) (reanalysis of Pliofilm manufacturing plants in Ohio), which leads to an overall lower estimated association (0.59 vs 0.85). The Stenehjem et al. (2015) study, which seems to indicate higher risks at low levels of exposure, and the Wong (1995) study were particularly influential on the exposure–response function due to the high exposure estimates. The observed instability in the derivation of the meta-exposure–response association underscores some uncertainty in these results.

References

Adegoke OJ, Blair A, Shu XO, Sanderson M, Jin F, Dosemeci M, et al. (2003). Occupational history and exposure and the risk of adult leukemia in Shanghai. *Ann Epidemiol*, 13(7):485–94. doi:10.1016/S1047-2797(03)00037-1 PMID:12932623

American Cancer Society (2016). Benzene and cancer risk. Available from: https://www.cancer.org/cancer/cancer-causes/benzene.html, accessed 21 September 2018.

Amigou A, Sermage-Faure C, Orsi L, Leverger G, Baruchel A, Bertrand Y, et al. (2011). Road traffic and childhood leukemia: the ESCALE study (SFCE). *Environ Health Perspect*, 119(4):566–72. doi:10.1289/ehp.1002429 PMID:21147599

Anttila A, Pukkala E, Riala R, Sallmén M, Hemminki K (1998). Cancer incidence among Finnish workers exposed to aromatic hydrocarbons. *Int Arch Occup Environ Health*, 71(3):187–93. doi:10.1007/s004200050269 PMID:9591160

Antwi SO, Eckert EC, Sabaque CV, Leof ER, Hawthorne KM, Bamlet WR, et al. (2015). Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. *Cancer Causes Control*, 26(11):1583–91. doi:10.1007/s10552-015-0652-y PMID:26293241

Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al.; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens–Part F: chemical agents and related occupations. *Lancet Oncol*, 10(12):1143–4. doi:10.1016/S1470-2045(09)70358-4 PMID:19998521

Barry KH, Zhang Y, Lan Q, Zahm SH, Holford TR, Leaderer B, et al. (2011). Genetic variation in metabolic genes, occupational solvent exposure, and risk of non-hodgkin lymphoma. *Am J Epidemiol*, 173(4):404–13. doi:10.1093/aje/kwq360 PMID:21228414

Bassig BA, Friesen MC, Vermeulen R, Shu XO, Purdue MP, Stewart PA, et al. (2015). Occupational exposure to benzene and non-Hodgkin lymphoma in a population-based cohort: The Shanghai Women's Health Study. *Environ Health Perspect*, 123(10):971–7. doi:10.1289/ehp.1408307 PMID:25748391

Björk J, Albin M, Welinder H, Tinnerberg H, Mauritzson N, Kauppinen T, et al. (2001). Are occupational, hobby, or lifestyle exposures associated with Philadelphia chromosome positive chronic myeloid leukaemia? *Occup Environ Med*, 58(11):722–7. doi:10.1136/oem.58.11.722 PMID:11600728

Blair A, Linos A, Stewart PA, Burmeister LF, Gibson R, Everett G, et al. (1993). Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case-control study. *Am J Ind Med*, 23(2):301–12. doi:10.1002/ajim.4700230207 PMID:8427258

Bloemen LJ, Youk A, Bradley TD, Bodner KM, Marsh G (2004). Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. *Occup Environ Med*, 61(3):270–4. doi:10.1136/oem.2003.007013 PMID:14985523

Bond GG, McLaren EA, Baldwin CL, Cook RR (1986). An update of mortality among chemical workers exposed to benzene. *Br J Ind Med*, 43(10):685–91. PMID:3465366

Bonneterre V, Mathern G, Pelen O, Balthazard AL, Delafosse P, Mitton N, et al. (2012). Cancer incidence in a chlorochemical plant in Isère, France: an occupational cohort study, 1979-2002. *Am J Ind Med*, 55(9):756–67. doi:10.1002/ajim.22069 PMID:22692930

Bove FJ, Ruckart PZ, Maslia M, Larson TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. *Environ Health*, 13(1):10. doi:10.1186/1476-069X-13-10 PMID:24552493

Bratveit M, Kirkeleit J, Hollund BE, Vagnes KS, Abrahamsen EH (2011). Retrospective JEM for benzene in the Norwegian oil and gas industry. Conference abstract. *Occup Environ Med*, 68(Suppl 1):A26. doi:10.1136/oemed-2011-100382.83

Brosselin P, Rudant J, Orsi L, Leverger G, Baruchel A, Bertrand Y, et al. (2009). Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). *Occup Environ Med*, 66(9):598–606. doi:10.1136/oem.2008.042432 PMID:19213757

Bulbulyan MA, Ilychova SA, Zahm SH, Astashevsky SV, Zaridze DG (1999). Cancer mortality among women in the Russian printing industry. *Am J Ind Med*, 36(1):166–71. doi:10.1002/(SICI)1097-0274(199907)36:1<166::AID-AJIM24>3.0.CO;2-P PMID:10361603

Carlos-Wallace FM, Zhang L, Smith MT, Rader G, Steinmaus C (2016). Parental, in utero, and early-life exposure to benzene and the risk of childhood leukemia: A meta-analysis. *Am J Epidemiol*, 183(1):1–14. doi:10.1093/aje/kwv120 PMID:26589707

Castro-Jiménez MÁ, Orozco-Vargas LC (2011). Parental exposure to carcinogens and risk for childhood acute lymphoblastic leukemia, Colombia, 2000-2005. *Prev Chronic Dis*, 8(5):A106. PMID:21843409

Chung E-K, Shin J-A, Lee B-K, Kwon J, Lee N, Chung K-J, et al. (2010). Characteristics of occupational exposure to benzene during turnaround in the petrochemical industries. *Saf Health Work*, 1(1):51–60. doi:10.5491/SHAW.2010.1.1.51 PMID:22953163

Clavel J, Conso F, Limasset JC, Mandereau L, Roche P, Flandrin G, et al. (1996). Hairy cell leukaemia and occupational exposure to benzene. *Occup Environ Med*, 53(8):533–9. doi:10.1136/oem.53.8.533 PMID:8983464

Cocco P, t'Mannetje A, Fadda D, Melis M, Becker N, de Sanjosé S, et al. (2010). Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. *Occup Environ Med*, 67(5):341–7. 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(5):277–88. doi:10.1007/BF00409412 PMID:8832292

Collins JJ, Anteau SE, Swaen GM, Bodner KM, Bodnar CM (2015). Lymphatic and hematopoietic cancers among benzene-exposed workers. *J Occup Environ Med*, 57(2):159–63. doi:10.1097/JOM.0000000000000324 PMID:25654516

Collins JJ, Ireland B, Buckley CF, Shepperly D (2003). Lymphohaematopoeitic cancer mortality among workers with benzene exposure. *Occup Environ Med*, 60(9):676–9. doi:10.1136/oem.60.9.676 PMID:12937190

Consonni D, Pesatori AC, Tironi A, Bernucci I, Zocchetti C, Bertazzi PA (1999). Mortality study in an Italian oil refinery: extension of the follow-up. *Am J Ind Med*, 35(3):287–94. 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, Kriebel D, Tumino R, Ramazzotti V, 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(11):803–11. doi:10.1002/ajim.20592 PMID:18651579

Crosignani P, Tittarelli A, Borgini A, Codazzi T, Rovelli A, Porro E, et al. (2004). Childhood leukemia and road traffic: a population-based case-control study. *Int J Cancer*, 108(4):596–9. doi:10.1002/ijc.11597 PMID:14696126

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(2):219–42. doi:10.1080/15287399409531875 PMID:8207757

Cuzick J, De Stavola B (1988). Multiple myeloma–a case-control study. *Br J Cancer*, 57(5):516–20. doi:10.1038/bjc.1988.118 PMID:3395559

Dagg TG, Satin KP, Bailey WJ, Wong O, Harmon LL, Swencicki RE (1992). An updated cause specific mortality study of petroleum refinery workers. *Br J Ind Med*, 49(3):203–12. PMID:1554618

Danysh HE, Mitchell LE, Zhang K, Scheurer ME, Lupo PJ (2015). Traffic-related air pollution and the incidence of childhood central nervous system tumors: Texas, 2001-2009. *Pediatr Blood Cancer*, 62(9):1572–8. doi:10.1002/pbc.25549 PMID:25962758

Decouflé P, Blattner WA, Blair A (1983). Mortality among chemical workers exposed to benzene and other agents. *Environ Res*, 30(1):16–25. doi:10.1016/0013-9351(83)90161-5 PMID:6832104

Divine BJ, Hartman CM (2000). Update of a study of crude oil production workers 1946-94. *Occup Environ Med*, 57(6):411–7. doi:10.1136/oem.57.6.411 PMID:10810131

Divine BJ, Hartman CM, Wendt JK (1999a). Update of the Texaco mortality study 1947-93: Part I. Analysis of overall patterns of mortality among refining, research, and petrochemical workers. *Occup Environ Med*, 56(3):167–73. doi:10.1136/oem.56.3.167 PMID:10448325

Divine BJ, Hartman CM, Wendt JK (1999b). Update of the Texaco mortality study 1947-93: Part II. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals. *Occup Environ Med*, 56(3):174–80. doi:10.1136/oem.56.3.174 PMID:10448326

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(1):13–21. doi:10.1179/oeh.2004.10.1.13 PMID:15070021

Faisandier L, Bonneterre V, De Gaudemaris R, Bicout DJ (2011). Occupational exposome: a network-based approach for characterizing Occupational Health Problems. *J Biomed Inform*, 44(4):545–52. doi:10.1016/j.jbi.2011.02.010 PMID:21362498

Feingold L, Savitz DA, John EM (1992). Use of a job-exposure matrix to evaluate parental occupation and childhood cancer. *Cancer Causes Control*, 3(2):161–9. doi:10.1007/BF00051656 PMID:1562706

Feychting M, Plato N, Nise G, Ahlbom A (2001). Paternal occupational exposures and childhood cancer. *Environ Health Perspect*, 109(2):193–6. doi:10.1289/ehp.01109193 PMID:11266332

Fritschi L, Benke G, Hughes AM, Kricker A, Vajdic CM, Grulich A, et al. (2005). Risk of non-Hodgkin lymphoma associated with occupational exposure to

solvents, metals, organic dusts and PCBs (Australia). *Cancer Causes Control*, 16(5):599–607. doi:10.1007/s10552-004-7845-0 PMID:15986116

Fu H, Demers PA, Costantini AS, Winter P, Colin D, Kogevinas M, et al. (1996). Cancer mortality among shoe manufacturing workers: an analysis of two cohorts. *Occup Environ Med*, 53(6):394–8. doi:10.1136/oem.53.6.394 PMID:8758034

Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health*, 14(1):14. doi:10.1186/1476-069X-14-14 PMID:25636809

García-Pérez J, López-Abente G, Gómez-Barroso D, Morales-Piga A, Romaguera EP, Tamayo I, et al. (2015). Childhood leukemia and residential proximity to industrial and urban sites. *Environ Res*, 140:542–53. doi:10.1016/j.envres.2015.05.014 PMID:26025512

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(2):144–56. 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, Gibbons C, Sim MR, Fritschi L, et al. (2003). Leukemia risk associated with low-level benzene exposure. *Epidemiology*, 14(5):569–77. doi:10.1097/01.ede.0000082001.05563.e0 PMID:14501272

Glass DC, Schnatter AR, Tang G, Irons RD, Rushton L (2014). Risk of myeloproliferative disease and chronic myeloid leukaemia following exposure to low-level benzene in a nested case-control study of petroleum workers. *Occup Environ Med*, 71(4):266–74. doi:10.1136/oemed-2013-101664 PMID:24532441

Greenland S, Salvan A, Wegman DH, Hallock MF, Smith TJ (1994). A case-control study of cancer mortality at a transformer-assembly facility. *Int Arch Occup Environ Health*, 66(1):49–54. doi:10.1007/BF00386579 PMID:7927843

Guberan E, Raymond L (1985). Mortality and cancer incidence in the perfumery and flavour industry of Geneva. *Br J Ind Med*, 42(4):240–5. PMID:3978043

Gudzenko N, Hatch M, Bazyka D, Dyagil I, Reiss RF, Brenner A, et al. (2015). Non-radiation risk factors for leukemia: A case-control study among chornobyl cleanup workers in Ukraine. *Environ Res*, 142:72–6. doi:10.1016/j.envres.2015.06.019 PMID:26117815

Guénel P, Imbernon E, Chevalier A, Crinquand-Calastreng A, Goldberg M (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(2):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(7):476–81. doi:10.1136/oem.2005.023796 PMID:16698808

Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Chow WH, et al. (1996). Mortality among benzene-exposed workers in China. *Environ Health Perspect*, 104(Suppl 6):1349–52. doi:10.1289/ehp.961041349 PMID:9118919

Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, 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(14):1065–71. doi:10.1093/jnci/89.14.1065 PMID:9230889

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. *Environ Res*, 127:1–6. doi:10.1016/j.envres.2013.09.002 PMID:24139061

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B (2014). Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. *Int J Hyg Environ Health*, 217(6):662–8. doi:10.1016/j.ijheh.2013.12.003 PMID:24472648

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B (2015). Retinoblastoma and ambient exposure to air toxics in the perinatal period. *J Expo Sci Environ Epidemiol*, 25(2):182–6. doi:10.1038/jes.2013.84 PMID:24280682

Honda Y, Delzell E, Cole P (1995). An updated study of mortality among workers at a petroleum manufacturing plant. *J Occup Environ Med*, 37(2):194–200. doi:10.1097/00043764-199502000-00020 PMID:7655961

Houot J, Marquant F, Goujon S, Faure L, Honoré C, Roth MH, et al. (2015). Residential proximity to heavy-traffic roads, benzene exposure, and childhood leukemia – the GEOCAP study, 2002-2007. *Am J Epidemiol*, 182(8):685–93. doi:10.1093/aje/kwv111 PMID:26377958

Huebner WW, Wojcik NC, Rosamilia K, Jorgensen G, Milano CA (2004). Mortality updates (1970-1997) of two refinery/petrochemical plant cohorts at Baton Rouge, Louisiana, and Baytown, Texas. *J Occup Environ Med*, 46(12):1229–45. PMID:15591975

IARC (1982). Some industrial chemicals and dyestuffs. *IARC Monogr Eval Carcinog Risk Chem Hum*, 29:1––398. Available from: http://publications.iarc.fr/47 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. Available from: http://publications.iarc.fr/139 PMID:3482203

IARC (2012a). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F:1–599. Available from: http://publications.iarc.fr/123 PMID:23189753

IARC (2012b). Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum*, 100E:1–575. Available from: http://publications.iarc.fr/122 PMID:23193840

IARC (2014). Report of the IARC Advisory Group to Recommend on Quantitative Risk Characterization (IARC Internal Report 14/001). Available from: https://monographs.iarc.fr/wp-content/uploads/2018/06/14-001.pdf.

Infante PF, Rinsky RA, Wagoner JK, Young RJ (1977). Leukaemia in benzene workers. *Lancet*, 2(8028):76–8. doi:10.1016/S0140-6736(77)90074-5 PMID:69157

Infante-Rivard C, Siemiatycki J, Lakhani R, Nadon L (2005). Maternal exposure to occupational solvents and childhood leukemia. *Environ Health Perspect*, 113(6):787–92. doi:10.1289/ehp.7707 PMID:15929905

Ireland B, Collins JJ, Buckley CF, Riordan SG (1997). Cancer mortality among workers with benzene exposure. *Epidemiology*, 8(3):318–20. doi:10.1097/00001648-199705000-00016 PMID:9115030

Janitz AE, Campbell JE, Magzamen S, Pate A, Stoner JA, Peck JD (2017). Benzene and childhood acute leukemia in Oklahoma. *Environ Res*, 158:167–73. doi:10.1016/j.envres.2017.06.015 PMID:28645022

Järvholm B, Mellblom B, Norrman R, Nilsson R, Nordlinder R (1997). Cancer incidence of workers in the Swedish petroleum industry. *Occup Environ Med*, 54(9):686–91. doi:10.1136/oem.54.9.686 PMID:9423584

Jiang WC, Wu SY, Ke YB (2016). [Association of exposure to environmental chemicals with risk of childhood acute lymphocytic leukemia]. *Zhonghua Yu Fang Yi Xue Za Zhi*, 50(10):893–9. [Chinese] PMID:27686768

Jiao J, Zheng T, Lan Q, Chen Y, Deng Q, Bi X, et al. (2012). Occupational solvent exposure, genetic variation of DNA repair genes, and the risk of non-Hodgkin's lymphoma. *Eur J Cancer Prev*, 21(6):580–4. doi:10.1097/CEJ.0b013e328351c762 PMID:22430443

Kaletsch U, Meinert R, Miesner A, Hoisl M, Kaatsch P, Michaelis J (1997). Epidemiologische studien zum Auftreten von Leukämieerkrankungen bei Kindern in Deutschland, Schriftenreihe Reaktorsicherheit und Strahlen schutz, Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit BMU 1997-489. Dossenheim: GFM. [German]

Kato I, Koenig KL, Watanabe-Meserve H, Baptiste MS, Lillquist PP, Frizzera G, et al. (2005). Personal and occupational exposure to organic solvents and risk of non-Hodgkin's lymphoma (NHL) in women (United States). *Cancer Causes Control*, 16(10):1215–24. doi:10.1007/s10552-005-0385-4 PMID:16215872

Kaufman DW, Anderson TE, Issaragrisil S (2009). Risk factors for leukemia in Thailand. *Ann Hematol*, 88(11):1079–88. doi:10.1007/s00277-009-0731-9 PMID:19294385

Kauppinen T, Pukkala E, Saalo A, Sasco AJ (2003). Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. *Am J Ind Med*, 44(4):343–50. doi:10.1002/ajim.10278 PMID:14502761

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(1):13–23. doi:10.1007/s10552-007-9065-x PMID:17906934

Koh DH, Chung EK, Jang JK, Lee HE, Ryu HW, Yoo KM, et al. (2014). Cancer incidence and mortality among temporary maintenance workers in a refinery/petrochemical complex in Korea. *Int J Occup Environ Health*, 20(2):141–5. doi:10.1179/2049396714Y.0000000059 PMID:24999849

Koh DH, Kim TW, Yoon YH, Shin KS, Yoo SW (2011). Lymphohematopoietic cancer mortality and morbidity of workers in a refinery/petrochemical complex in Korea. *Saf Health Work*, 2(1):26–33. doi:10.5491/SHAW.2011.2.1.26 PMID:22953184

La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1989). Occupation and lymphoid neoplasms. *Br J Cancer*, 60(3):385–8. doi:10.1038/bjc.1989.290 PMID:2789947

Lagorio S, Forastiere F, Iavarone I, Rapiti E, Vanacore N, Perucci CA, et al. (1994). Mortality of filling station attendants. *Scand J Work Environ Health*, 20(5):331–8. doi:10.5271/sjweh.1389 PMID:7863296

Lewis RJ, Schnatter AR, Drummond I, Murray N, Thompson FS, Katz AM, et al. (2003). Mortality and cancer morbidity in a cohort of Canadian petroleum workers. *Occup Environ Med*, 60(12):918–28. doi:10.1136/oem.60.12.918 PMID:14634182

Linet MS, Harlow SD, McLaughlin JK (1987). A case-control study of multiple myeloma in whites: chronic antigenic stimulation, occupation, and drug use. *Cancer Res*, 47(11):2978–81. PMID:3567914

Linet MS, Yin SN, Gilbert ES, Dores GM, Hayes RB, Vermeulen R, et al.; Chinese Center for Disease Control and Prevention-U.S. National Cancer Institute Benzene Study Group (2015). A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers. *Int J Cancer*, 137(9):2184–97. doi:10.1002/ijc.29591 PMID:25944549

Lundberg I, Milatou-Smith R (1998). Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. *Scand J Work Environ Health*, 24(4):270–5. doi:10.5271/sjweh.320 PMID:9754858

Lynge E, Andersen A, Nilsson R, Barlow L, Pukkala E, Nordlinder R, et al. (1997). Risk of cancer and exposure to gasoline vapors. *Am J Epidemiol*, 145(5):449–58. doi:10.1093/oxfordjournals.aje.a009127 PMID:9048519

Mao Y, Hu J, Ugnat AM, White K; Canadian Cancer Registries Epidemiology Research Group (2000). Non-Hodgkin's lymphoma and occupational exposure to chemicals in Canada. *Ann Oncol*, 11(Suppl 1):69–73. doi:10.1093/annonc/11.suppl_1.S69 PMID:10707783

McCraw DS, Joyner RE, Cole P (1985). Excess leukemia in a refinery population. *J Occup Med*, 27(3):220–2. PMID:3856637

McKinney PA, Alexander FE, Cartwright RA, Parker L (1991). Parental occupations of children with leukaemia in west Cumbria, north Humberside, and Gateshead. *BMJ*, 302(6778):681–7. doi:10.1136/bmj.302.6778.681 PMID:2021741

Merlo DF, Stagi E, Fontana V, Consonni D, Gozza C, Garrone E, et al. (2010). A historical mortality study among bus drivers and bus maintenance workers exposed to urban air pollutants in the city of Genoa, Italy. *Occup Environ Med*, 67(9):611–9. doi:10.1136/oem.2009.050377 PMID:20576925

Micheli A, Meneghini E, Mariottini M, Baldini M, Baili P, Di Salvo F, et al. (2014). Risk of death for hematological malignancies for residents close to an Italian petrochemical refinery: a population-based case-control study. *Cancer Causes Control*, 25(12):1635–44. doi:10.1007/s10552-014-0468-1 PMID:25281327

Miligi L, Costantini AS, Benvenuti A, Kriebel D, Bolejack V, Tumino R, et al. (2006). Occupational exposure to solvents and the risk of lymphomas. *Epidemiology*, 17(5):552–61. doi:10.1097/01.ede.0000231279.30988.4d PMID:16878041

National Cancer Institute (2015). Benzene. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/benzene, accessed 21 September 2018.

Nilsson RI, Nordlinder R, Hörte LG, Järvholm B (1998). Leukaemia, lymphoma, and multiple myeloma in seamen on tankers. *Occup Environ Med*, 55(8):517–21. doi:10.1136/oem.55.8.517 PMID:9849537

Orsi L, Monnereau A, Dananche B, Berthou C, Fenaux P, Marit G, et al. (2010). Occupational exposure to organic solvents and lymphoid neoplasms in men: results of a French case-control study. *Occup Environ Med*, 67(10):664–72. doi:10.1136/oem.2009.049460 PMID:20837648

Ott MG, Townsend JC, Fishbeck WA, Langner RA (1978). Mortality among individuals occupationally exposed to benzene. *Arch Environ Health*, 33(1):3–10. doi:10.1080/00039896.1978.10667299 PMID:629594

Persson B, Fredrikson M (1999). Some risk factors for non-Hodgkin's lymphoma. *Int J Occup Med Environ Health*, 12(2):135–42. PMID:10465904

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W (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(6):1014–24. doi:10.1093/ije/29.6.1014 PMID:11101542

Peters S, Glass DC, Greenop KR, Armstrong BK, Kirby M, Milne E, et al. (2014). Childhood brain tumours: associations with parental occupational exposure to solvents. *Br J Cancer*, 111(5):998–1003. doi:10.1038/bjc.2014.358 PMID:24960405

Poynter JN, Richardson M, Roesler M, Blair CK, Hirsch B, Nguyen P, et al. (2017). Chemical exposures and risk of acute myeloid leukemia and myelodysplastic syndromes in a population-based study. *Int J Cancer*, 140(1):23–33. doi:10.1002/ijc.30420 PMID:27603749

Pukkala E (1998). Cancer incidence among Finnish oil refinery workers, 1971-1994. *J Occup Environ Med*, 40(8):675–9. doi:10.1097/00043764-199808000-00003 PMID:9729749

Punjindasup A, Sangrajrang S, Ekpanyaskul C (2015). Occupational risk factors of lymphohematopoietic cancer in Rayong Province, Thailand. *J Med Assoc Thai*, 98(Suppl 10):S13–22. PMID:27276828

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(5):433–43. doi:10.1093/aje/153.5.433 PMID:11226975

Raaschou-Nielsen O, Ketzel M, Harbo Poulsen A, Sørensen M (2016). Traffic-related air pollution and risk for leukaemia of an adult population. *Int J Cancer*, 138(5):1111–7. doi:10.1002/ijc.29867 PMID:26415047

Rhomberg L, Goodman J, Tao G, Zu K, Chandalia J, Williams PR, et al. (2016). Evaluation of acute nonlymphocytic leukemia and its subtypes with updated benzene exposure and mortality estimates: a lifetable analysis of the Pliofilm cohort. *J Occup Environ Med*, 58(4):414–20. doi:10.1097/JOM.0000000000000689 PMID:27058483

Richardson DB (2009). Multistage modeling of leukemia in benzene workers: a simple approach to fitting the 2-stage clonal expansion model. *Am J Epidemiol*, 169(1):78–85. doi:10.1093/aje/kwn284 PMID:18996834

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(6):474–80. doi:10.1002/ajim.10138 PMID:12439870

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, et al. (1987). Benzene and leukemia. An epidemiologic risk assessment. *N Engl J Med*, 316(17):1044–50. doi:10.1056/NEJM198704233161702 PMID:3561457

Rinsky RA, Young RJ, Smith AB (1981). Leukemia in benzene workers. *Am J Ind Med*, 2(3):217–45. doi:10.1002/ajim.4700020305 PMID:7345926

Ruckart PZ, Bove FJ, Maslia M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case-control

study. *Environ Health*, 12(1):104. doi:10.1186/1476-069X-12-104 PMID:24304547

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 6):77–84. 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(3):152–66. doi:10.1136/oem.54.3.152 PMID:9155776

Rushton L, Schnatter AR, Tang G, Glass DC (2014). Acute myeloid and chronic lymphoid leukaemias and exposure to low-level benzene among petroleum workers. *Br J Cancer*, 110(3):783–7. doi:10.1038/bjc.2013.780 PMID:24357793

Saberi Hosnijeh F, Christopher Y, Peeters P, Romieu I, Xun W, Riboli E, et al. (2013). Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Occup Environ Med*, 70(7):464–70. doi:10.1136/oemed-2012-101135 PMID:23576671

Satin KP, Wong O, Yuan LA, Bailey WJ, Newton KL, Wen CP, et al. (1996). A 50-year mortality follow-up of a large cohort of oil refinery workers in Texas. *J Occup Environ Med*, 38(5):492–506. doi:10.1097/00043764-199605000-00010 PMID:8733641

Scherr PA, Hutchison GB, Neiman RS (1992). Non-Hodgkin's lymphoma and occupational exposure. *Cancer Res*, 52(19 Suppl):5503s–9s. PMID:1394164

Schnatter AR, Armstrong TW, Nicolich MJ, Thompson FS, Katz AM, Huebner WW, et al. (1996). Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup Environ Med*, 53(11):773–81. doi:10.1136/oem.53.11.773 PMID:9038803

Schnatter AR, Glass DC, Tang G, Irons RD, Rushton L (2012). Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis. *J Natl Cancer Inst*, 104(22):1724–37. doi:10.1093/jnci/djs411 PMID:23111193

Schnatter AR, Katz AM, Nicolich MJ, Thériault G (1993). A retrospective mortality study among Canadian petroleum marketing and distribution workers. *Environ Health Perspect*, 101(Suppl 6):85–99. doi:10.1289/ehp.93101s685 PMID:8020452

Seidler A, Möhner M, Berger J, Mester B, Deeg E, Elsner G, et al. (2007). Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. *J Occup Med Toxicol*, 2(1):2. doi:10.1186/1745-6673-2-2 PMID:17407545

Senkayi SN, Sattler ML, Rowe N, Chen VCP (2014). Investigation of an association between childhood leukemia incidences and airports in Texas. *Atmos Pollut Res*, 5(2):189–95. doi:10.5094/APR.2014.023

Shaw G, Lavey R, Jackson R, Austin D (1984). Association of childhood leukemia with maternal age, birth order, and paternal occupation. A case-control study. *Am J Epidemiol*, 119(5):788–95. doi:10.1093/oxfordjournals.aje.a113799 PMID:6720675

Shrestha A, Ritz B, Wilhelm M, Qiu J, Cockburn M, Heck JE (2014). Prenatal exposure to air toxics and risk of Wilms' tumor in 0- to 5-year-old children. *J Occup Environ Med*, 56(6):573–8. doi:10.1097/JOM.0000000000000167 PMID:24854250

Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W, et al. (1988). A population-based case-control study of childhood leukemia in Shanghai. *Cancer*, 62(3):635–44. doi:10.1002/1097-0142(19880801)62:3<635::AID-CNCR2820620332>3.0.CO;2-3 PMID:3164642

Shu XO, Stewart P, Wen WQ, Han D, Potter JD, Buckley JD, et al. (1999). Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. *Cancer Epidemiol Biomarkers Prev*, 8(9):783–91. PMID:10498397

Sorahan T, Kinlen LJ, Doll R (2005). Cancer risks in a historical UK cohort of benzene exposed workers. *Occup Environ Med*, 62(4):231–6. doi:10.1136/oem.2004.015628 PMID:15778255

Sorahan T, Nichols L, Harrington JM (2002). Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-1998. *Occup Med (Lond)*, 52(6):333–9. doi:10.1093/occmed/52.6.333 PMID:12361995

Spycher BD, Lupatsch JE, Huss A, Rischewski J, Schindera C, Spoerri A, et al.; Swiss Paediatric Oncology Group; Swiss National Cohort Study Group (2017). Parental occupational exposure to benzene and the risk of childhood cancer: A census-based cohort study. *Environ Int*, 108:84–91. doi:10.1016/j.envint.2017.07.022 PMID:28802171

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte A, et al. (2004). Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. *Occup Environ Med*, 61(9):773–8. doi:10.1136/oem.2003.010868 PMID:15317919

Steinsvåg K, Bråtveit M, Moen BE (2007). Exposure to carcinogens for defined job categories in Norway's offshore petroleum industry, 1970 to 2005. *Occup Environ Med*, 64(4):250–8. doi:10.1136/oem.2006.028225 PMID:17043075

Stenehjem JS, Kjærheim K, Bråtveit M, Samuelsen SO, Barone-Adesi F, Rothman N, et al. (2015). Benzene exposure and risk of lymphohaematopoietic cancers in 25 000 offshore oil industry workers. *Br J Cancer*, 112(9):1603–12. doi:10.1038/bjc.2015.108 PMID:25867262

Stenehjem JS, Kjærheim K, Rabanal KS, Grimsrud TK (2014). Cancer incidence among 41,000 offshore oil industry workers. *Occup Med (Lond)*, 64(7):539–45. doi:10.1093/occmed/kqu111 PMID:25082833

Stenehjem JS, Robsahm TE, Bråtveit M, Samuelsen SO, Kirkeleit J, Grimsrud TK (2017). Aromatic hydrocarbons and risk of skin cancer by anatomical site in 25 000 male offshore petroleum workers. *Am J Ind Med*, 60(8):679–88. doi:10.1002/ajim.22741 PMID:28692192

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. (2017). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th Edition, Volume 2 of IARC WHO Classification of Tumours Series. Lyon, France: International Agency for Research on Cancer.

Symanski E, Tee Lewis PG, Chen TY, Chan W, Lai D, Ma X (2016). Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. *Environ Health*, 15(1):70. doi:10.1186/s12940-016-0154-8 PMID:27301866

Talbott EO, Xu X, Youk AO, Rager JR, Stragand JA, Malek AM (2011). Risk of leukemia as a result of community exposure to gasoline vapors: a follow-up study. *Environ Res*, 111(4):597–602. doi:10.1016/j.envres.2011.03.009 PMID:21453914

Talibov M, Lehtinen-Jacks S, Martinsen JI, Kjærheim K, Lynge E, Sparén P, et al. (2014). Occupational exposure to solvents and acute myeloid leukemia: a population-based, case-control study in four Nordic countries. *Scand J Work Environ Health*, 40(5):511–7. doi:10.5271/sjweh.3436 PMID:24840289

Tsai SP, Gilstrap EL, Cowles SR, Snyder PJ, Ross CE (1993). A cohort mortality study of two California refinery and petrochemical plants. *J Occup Med*, 35(4):415–21. PMID:8487121

Tsai SP, Gilstrap EL, Cowles SR, Snyder PJ, Ross CE (1996). Long-term follow-up mortality study of petroleum refinery and chemical plant employees. *Am J Ind Med*, 29(1):75–87. doi:10.1002/(SICI)1097-0274(199601)29:1<75::AID-AJIM10>3.0.CO;2-X PMID:8808045

Tsai SP, Wen CP, Weiss NS, Wong O, McClellan WA, Gibson RL (1983). Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. *J Occup Med*, 25(9):685–92. doi:10.1097/00043764-198309000-00018 PMID:6631569

Tsai SP, Wendt JK, Cardarelli KM, Fraser AE (2003). A mortality and morbidity study of refinery and petrochemical employees in Louisiana. *Occup Environ Med*, 60(9):627–33. doi:10.1136/oem.60.9.627 PMID:12937182

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(2):216–24. doi:10.1093/oxfordjournals.aje.a113992 PMID:3860001

Viechtbauer W (2010). Conducting meta-analyses in R with the metafor package. *J Stat Softw*, 36(3):1–48. doi:10.18637/jss.v036.i03

Villeneuve PJ, Jerrett M, Brenner D, Su J, Chen H, McLaughlin JR (2014). A case-control study of long-term exposure to ambient volatile organic compounds and lung cancer in Toronto, Ontario, Canada. *Am J Epidemiol*, 179(4):443–51. doi:10.1093/aje/kwt289 PMID:24287467

Vinceti M, Rothman KJ, Crespi CM, Sterni A, Cherubini A, Guerra L, et al. (2012). Leukemia risk in children exposed to benzene and PM10 from vehicular traffic: a case-control study in an Italian population. *Eur J Epidemiol*, 27(10):781–90. doi:10.1007/s10654-012-9727-1 PMID:22892901

Vineis P, Miligi L, Costantini AS (2007). Exposure to solvents and risk of non-Hodgkin lymphoma: clues on putative mechanisms. *Cancer Epidemiol Biomarkers Prev*, 16(3):381–4. doi:10.1158/1055-9965.EPI-07-0124 PMID:17337640

Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R (2011). Occupational benzene exposure and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. *Environ Health Perspect*, 119(2):159–67. doi:10.1289/ehp.1002318 PMID:20880796

Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R (2012). Occupational benzene exposure and the risk of chronic myeloid leukemia: a meta-analysis of cohort studies incorporating study quality dimensions. *Am J Ind Med*, 55(9):779–85. doi:10.1002/ajim.22087 PMID:22729623

Vlaanderen J, Portengen L, Rothman N, Lan Q, Kromhout H, Vermeulen R (2010). Flexible meta-regression to assess the shape of the benzene-leukemia exposure-response curve. *Environ Health Perspect*, 118(4):526–32. doi:10.1289/ehp.0901127 PMID:20064779

Von Behren J, Reynolds P, Gunier RB, Rull RP, Hertz A, Urayama KY, et al. (2008). Residential traffic density and childhood leukemia risk. *Cancer Epidemiol Biomarkers Prev*, 17(9):2298–301. doi:10.1158/1055-9965.EPI-08-0338 PMID:18768496

von Ehrenstein OS, Heck JE, Park AS, Cockburn M, Escobedo L, Ritz B (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. *Environ Health Perspect*, 124(7):1093–9. PMID:26505805

Walker JT, Bloom TF, Stern FB, Okun AH, Fingerhut MA, Halperin WE (1993). Mortality of workers employed in shoe manufacturing. *Scand J Work Environ Health*, 19(2):89–95. doi:10.5271/sjweh.1492 PMID:8316784

Wang R, Zhang Y, Lan Q, Holford TR, Leaderer B, Zahm SH, et al. (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut

women. *Am J Epidemiol*, 169(2):176–85. doi:10.1093/aje/kwn300 PMID:19056833

Whitworth KW, Symanski E, Coker AL (2008). Childhood lymphohematopoietic cancer incidence and hazardous air pollutants in southeast Texas, 1995-2004. *Environ Health Perspect*, 116(11):1576–80. doi:10.1289/ehp.11593 PMID:19057714

Wilcosky TC, Checkoway H, Marshall EG, Tyroler HA (1984). Cancer mortality and solvent exposures in the rubber industry. *Am Ind Hyg Assoc J*, 45(12):809–11. doi:10.1080/15298668491400683 PMID:6549104

Williams PR, Paustenbach DJ (2003). Reconstruction of benzene exposure for the Pliofilm cohort (1936-1976) using Monte Carlo techniques. *J Toxicol Environ Health A*, 66(8):677–781. doi:10.1080/15287390306379 PMID:12746133

Wong O (1987a). An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. *Br J Ind Med*, 44(6):365–81. PMID:3606966

Wong O (1987b). An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. *Br J Ind Med*, 44(6):382–95. PMID:3606967

Wong O (1995). Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med*, 52(6):380–4. doi:10.1136/oem.52.6.380 PMID:7627314

Wong O, Harris F, Armstrong TW, Hua F (2010a). A hospital-based case-control study of acute myeloid leukemia in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem Biol Interact*, 184(1–2):112–28. doi:10.1016/j.cbi.2009.10.017 PMID:19900423

Wong O, Harris F, Armstrong TW, Hua F (2010b). A hospital-based case-control study of non-Hodgkin lymphoid neoplasms in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem Biol Interact*, 184(1–2):129–46. doi:10.1016/j.cbi.2009.10.016 PMID:19900422

Wong O, Harris F, Rosamilia K, Raabe GK (2001a). An updated mortality study of workers at a petroleum refinery in Beaumont, Texas, 1945 to 1996. *J Occup Environ Med*, 43(4):384–401. doi:10.1097/00043764-200104000-00017 PMID:11322100

Wong O, Harris F, Rosamilia K, Raabe GK (2001b). Updated mortality study of workers at a petroleum refinery in Torrance, California, 1959 to 1997. *J Occup Environ Med*, 43(12):1089–102. doi:10.1097/00043764-200112000-00011 PMID:11765680

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 6):63–76. doi:10.1289/ehp.93101s663 PMID:8020450

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(2):188–99. doi:10.1006/rtph.1997.1162 PMID:9356282

Wong O, Trent L, Harris F (1999). Nested case-control study of leukaemia, multiple myeloma, and kidney cancer in a cohort of petroleum workers exposed to gasoline. *Occup Environ Med*, 56(4):217–21. doi:10.1136/oem.56.4.217 PMID:10450237

Xu CG, Zheng SP, Huang J, Wu JX (2003). [A case-control study for assessing the relation between the incidence of malignant lymphomas and environmental factors in Sichuan province]. *Zhonghua Liu Xing Bing Xue Za Zhi*, 24(10):875–8. [Chinese] PMID:14575598

Yin SN, Hayes RB, Linet MS, Li GL, Dosemeci M, Travis LB, et al. (1996a). A cohort study of cancer among benzene-exposed workers in China: overall results. *Am J Ind Med*, 29(3):227–35. doi:10.1002/(SICI)1097-0274(199603)29:3<227::AID-AJIM2>3.0.CO;2-N PMID:8833775

Yin SN, Hayes RB, Linet MS, Li GL, Dosemeci M, Travis LB, et al.; Benzene Study Group (1996b). An expanded cohort study of cancer among benzene-exposed workers in China. *Environ Health Perspect*, 104(Suppl 6):1339–41. PMID:9118917

Yuan JM, Butler LM, Gao YT, Murphy SE, Carmella SG, Wang R, et al. (2014). Urinary metabolites of a polycyclic aromatic hydrocarbon and volatile organic compounds in relation to lung cancer development in lifelong never smokers in the Shanghai Cohort Study. *Carcinogenesis*, 35(2):339–45. doi:10.1093/carcin/bgt352 PMID:24148823