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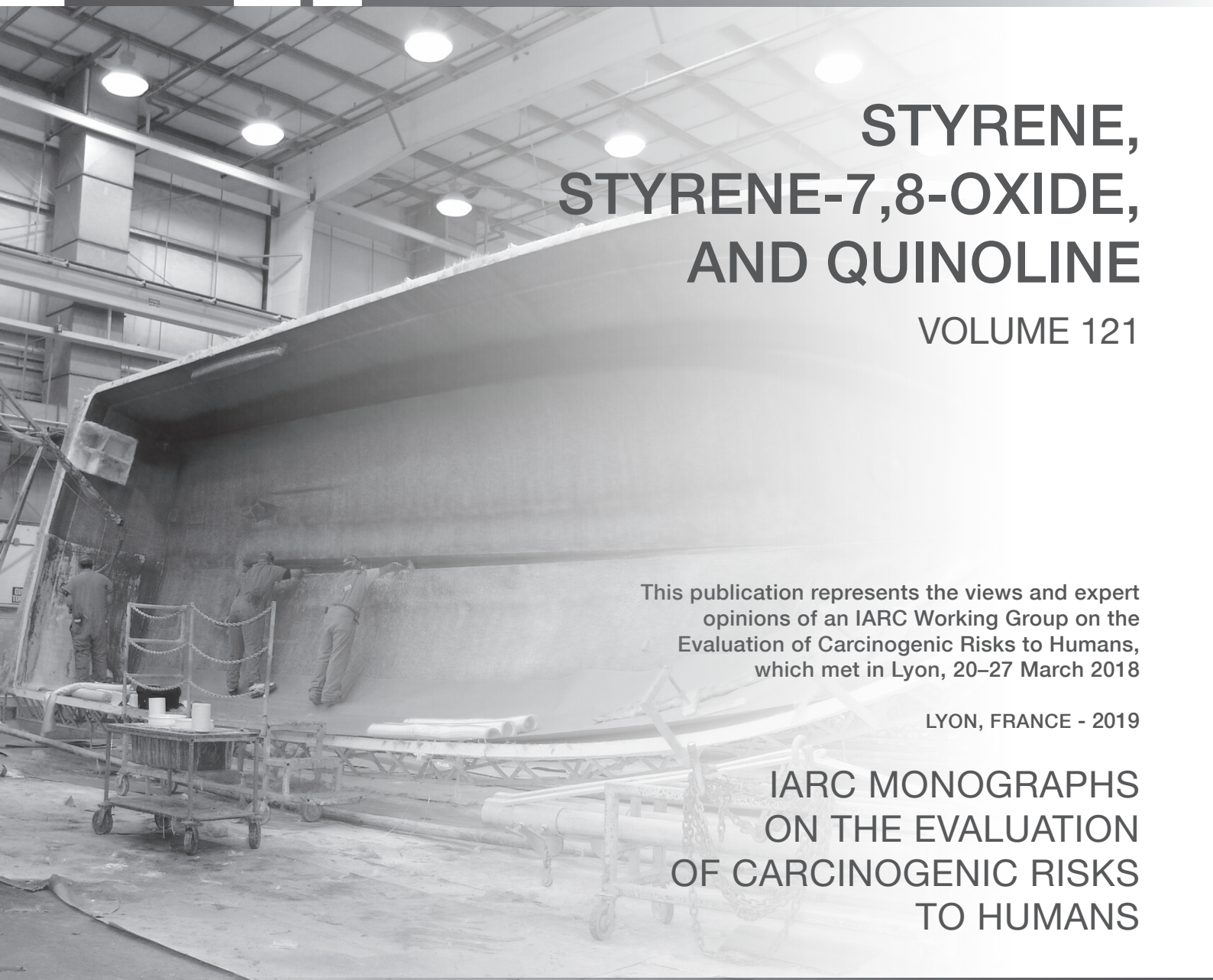

STYRENE, STYRENE-7,8-OXIDE, AND QUINOLINE

VOLUME 121

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(e) Appropriateness of exposure metrics

Identifying the so-called ideal exposure metric (or summary measure of exposure) for carcinogenicity studies of styrene requires knowledge, or a strong assumption, of the pathophysiological mechanism (Kriebel et al., 2007). The best metric might even differ from one cancer site to another because of internal dose dynamics. Despite this uncertainty about the ideal form, occupational cancer epidemiology has often used cumulative exposure and its components (average exposure intensity and duration) as exposure metrics. There is good empirical evidence that these are often proportional to risk of cancer when applied to the data for known carcinogens such as asbestos and silica (IARC, 2012a). It is important to stress that no one standard summary measure of exposure can be said a priori to be closer to the so-called ideal metric for a particular chemical and target organ; it is therefore reasonable to fit models with several of these metrics.

Another well-recognized consideration in evaluating summary measures of exposure is that cancers typically develop after long periods of latency; it is therefore important to evaluate associations between exposures and their effect by evaluating exposures occurring at different time periods before the onset of disease. The only key epidemiological study to investigate multiple quantitative summary measures of exposure (cumulative exposure, average intensity, average probability, and duration) in time windows of exposure was that of Christensen et al. (2018). Several others (Collins et al., 2013; Sathiakumar et al., 2015; Loomis et al., 2019) used a simpler approach, such as setting a minimum latency that each exposed worker had to achieve before at-risk follow-up time began accruing, or the use of exposure lagging.

1.6.4 Overall summary of exposure assessment in key epidemiological studies

Analyses of the exposure assessments for the key epidemiological studies indicate that two of the cohort studies (Christensen et al., 2018; Loomis et al., 2019) are likely to be more informative than others for two reasons: the substantial exposure experience of cohort members (duration and intensity of exposure to styrene) and the use of high-quality, well-documented exposure assessment methods. Other good-quality exposure data are found in Collins et al. (2013) and Coggon et al. (2015). Several case–control studies (Scélo et al., 2004; Seidler et al., 2007; Cocco et al., 2010) were of relatively high quality in terms of assessment methods; however, the prevalence of styrene exposure and estimated average levels of exposure were considerably lower in these general-population studies than for the cohort studies, limiting their informativeness.

2. Cancer in Humans

2.1 Introduction

Styrene is an important industrial chemical and a major intermediate in the manufacture of both synthetic rubber and certain plastics. Epidemiological studies covering the working populations in all major industries using styrene have been conducted. Industry-based cohorts have evaluated the exposure to styrene of workers in the reinforced plastics, synthetic rubber, and styrene monomer and polymers industries. General-population studies include case–control studies in adults and children.

Early research in occupational cohorts focused mainly on the potential associations between exposure to styrene and leukaemia and lymphomas, whereas more recent analyses have also evaluated several other outcomes,

including cancer of the lung, kidney, breast, and oesophagus. Available studies involved mostly men, examined incidence and/or mortality, and were conducted in North America and western Europe even though styrene is produced and used in many more countries. The Working Group excluded studies without an assessment of styrene exposure. No attempt was made by the Working Group to take account of co-exposures to styrene-7,8-oxide. Such exposures were considered likely, but to be at very low concentrations relative to that of styrene.

In examining the epidemiological evidence, several factors need to be considered (see Section 1.6): the size of the study and, in particular, the number of subjects exposed; the potential for confounding by other chemicals in the work environment and also by lifestyle or social factors; uncertainty in exposure levels and exposure contrasts, exposure misclassification and, related to this, the exposure metric(s) used; outcome misclassification; and, finally, selection bias, which may be of importance in some studies due to the high turnover of the workforce.

The accuracy and precision of the effect estimates are dependent upon the size of the study, the proportion of exposed subjects, and also the frequency of the outcome of interest. There are several large industry-based studies of tens of thousands of workers and, for most outcomes of interest, the size of the study is therefore not a major issue. However, for general-population studies (mainly case–control studies) size may be a serious issue because exposure to styrene is not common; only about 1–2% of the population may have been exposed to styrene and, if exposed, usually not to high concentrations. This is not a problem which is specific to styrene exposure, but is present in many general-population studies regarding exposure to occupational carcinogens.

Confounding has been discussed extensively in some of the industry-based studies concerning co-exposure to other chemicals in the workplace. This is particularly an issue in the synthetic rubber industry, mainly due to the high correlation (correlation coefficient, ~0.7) between exposure to styrene and exposure to 1,3-butadiene, which is an identified human carcinogen (IARC Group 1). Although the main study in synthetic rubber production provides effect estimates adjusted for this co-exposure, this still remains an issue of concern because of the high exposure correlation and the likely misclassification of styrene for 1,3-butadiene, and vice versa. Exposure to benzene and other chemicals also occurs in styrene production and polymerization and, as a consequence, potential confounding by these chemicals may have an impact on effect estimates in those studies.

Studies in the reinforced plastics industry do not appear to be particularly affected by potential confounding due to other co-exposures. Conversely, confounding from lifestyle and socioeconomic factors may be an issue in the reinforced plastics industry because of the high proportion of short-term workers who may have different lifestyle patterns and exposures from other jobs than workers with more stable work histories. However, nearly all major studies in this industry have conducted internal comparisons that, to some extent, take into account confounding by lifestyle factors. Although this selection out of employment may be adjusted for through appropriate statistical analysis, it may still complicate interpretation and affect exposure indices based on duration of exposure.

The concentrations of styrene exposure were up to 1–2 orders of magnitude higher in studies in the reinforced plastics industry compared with those in the synthetic rubber industry, in the styrene monomer and polymers industries, and in the general-population studies. As a consequence, the studies in reinforced plastics are the most informative for hazard identification purposes. Exposure misclassification is probably a more important problem in general-population studies, although several of these have

applied elaborate exposure assessment protocols including job-exposure matrices (JEMs) and expert assessment.

In the cohort studies, workplace styrene exposure was measured extensively in the later periods of work history coverage, and less exposure information was available for earlier periods of employment, potentially affecting the validity of exposure assessment estimates. However, as described in Section 1.6, exposure and work history information was not collected in recent years and was assumed to be constant. However, many of the large cohorts have extensive data on workplace exposures; although exposure misclassification is certainly an issue, it is very unlikely that this has had a considerable effect on the main exposure subgroups evaluated, particularly in the reinforced plastics industry. The exposure metric used varied between studies, for example, peaks of exposure, average exposure levels (intensity), and cumulative exposure (which combines average intensity with duration). Results from some of the larger studies appear to vary depending on the exposure metric used; there is no way through statistical analysis to identify which metric is the most appropriate, since this is essentially an issue related to biological mechanisms.

Outcome misclassification is a less important issue for most cancers but may have affected some analyses, particularly of leukaemia and lymphomas. Studies conducted in earlier periods (corresponding roughly to before the year 2000) examined phenotypes of leukaemia and lymphomas that were shown later to be heterogeneous concerning etiology and prognosis. This may have resulted in an underestimation of exposure–disease associations. In addition, changes in disease definitions for leukaemia and lymphomas over time complicate the comparison of results between studies conducted over different periods. Another concern regarding outcome definition is that most of the cohort studies have used cancer mortality, rather than cancer incidence, data for neoplasms that have relatively good prognosis, such as cancer of the prostate or chronic lymphocytic leukaemia (CLL). In some circumstances, this may result in bias due to different characteristics of incidence versus mortality data, as the mortality data may include a lower proportion of cases with a good prognosis. This factor mostly results in a loss of precision, because not all subjects with a diagnosis of disease will be identified in mortality studies. Poorer cancer prognosis may also be related to reduced access to health care and lower socioeconomic status, so that deaths in mortality studies may overrepresent workers with lower socioeconomic status compared with cancer cases in incidence studies.

Finally, selection bias in the context of industry-based studies has usually been discussed in relation to the healthy worker effect. This is undoubtedly an issue in the styrene cohorts, and would probably tend to underestimate exposure–disease associations when mortality is compared with that of the general population. Many of the larger cohorts have conducted internal analyses that would minimize the potential problem of the healthy worker effect, a type of confounding, and have also incorporated time-related variables in the analysis. As mentioned earlier in this introduction, the relatively high proportion of short-term workers in the reinforced plastics industry is of particular concern.

Two reviews of the epidemiology of styrene exposure and cancer have been published in the last decade (Boffetta et al., 2009; Collins & Delzell, 2018). The Working Group noted that several human studies considered in this *Monograph* were published after the more recent of the two reviews (Bertke et al., 2018; Christensen et al., 2018; Loomis et al., 2019; Nissen et al., 2018).

Overall, the available epidemiological studies have many strengths and, notwithstanding the potential limitations present in industrial cohort and population-based studies, provide a solid base for the evaluation of the association

between exposure to styrene and risk of cancer in human populations. A careful evaluation of the strengths and limitations of the different study designs and the industries examined is included to summarize the evidence in an informative way.

2.2 Cohort studies

2.2.1 Occupational cohort studies

(a) Reinforced plastics industry

See Table 2.1.

In the reinforced plastics industry, boats, tanks, containers, car parts, and other goods are produced from unsaturated polyester resin by hand and spray lamination in open moulds, by vacuum moulding, or by other closed or semi-closed processes (IARC, 2002). The *IARC Monographs* Volume 82 (IARC, 2002) included results on cancer incidence or mortality from five reinforced plastics industry cohorts from Europe (Kogevinas et al., 1993, 1994), Denmark (Kolstad et al., 1993, 1994, 1995), the United Kingdom (Coggon et al., 1987), the USA (Wong, 1990; Wong et al., 1994), and Washington State (Okun et al., 1985). Since then, the Danish (Christensen et al., 2017, 2018; Nissen et al., 2018), United Kingdom (Coggon et al., 2015), United States (Collins et al., 2013), and Washington State (Ruder et al., 2016; Ruder & Bertke, 2017; Bertke et al., 2018) cohorts have all been updated with extended follow-up and the European cohort reanalysed (Loomis et al., 2019). No additional reinforced plastics industry cohorts are included in the current *Monograph*. A succinct summary of the evaluated cohorts is provided in Supplemental Table S1.

Styrene is the dominant exposure; average workplace air concentrations of 100–200 ppm were measured in the 1960s and 1970s, and have significantly declined since then. According to the information provided in the publications, workers may also have been exposed to fibreglass and acetone, and, in some jobs, to glycols, anhydrides, methyl ethyl ketone peroxide, benzoyl peroxide, paints, or wood dust, but encountered no or minimal exposure to benzene or 1,3-butadiene.

Collins et al. (2013) reported cancer mortality for 1948–2008 among 15 826 workers employed at 30 United States reinforced plastics plants during 1948–1977. Wong (1990) and Wong et al. (1994) had previously followed this population from 1948 to 1977 and from 1948 to 1989, respectively. The study population comprised workers who had worked for at least 6 months in an area with potential exposure to styrene.

Styrene exposure estimates were constructed from production characteristics obtained from all companies about 1980 and routine exposure monitoring. A total of 43% of the study population had been directly exposed to styrene (Wong, 1990). The average styrene exposure level was 35 ppm during the 1960s and 25 ppm in 1977 (Collins et al., 2013).

Standard SMR analyses and internal Cox regression models analysed hazard ratios (HRs) by cumulative styrene exposure. Wong (1990) also estimated the association between exposure to styrene and mortality from cancer of the respiratory system among 40 cases and 102 controls nested within the study population; 83% of 63 controls reported ever smoking (Wong, 1990).

For all workers, increased standardized mortality ratios for all cancers (SMR, 1.12; 95% confidence interval (CI), 1.05–1.18) and cancer of the lung (SMR, 1.34; 95% CI, 1.23–1.46) were observed. Standardized mortality ratios greater than 1.10 were observed for cancer of the buccal cavity and pharynx (SMR, 1.16; 95% CI, 0.78–1.66), kidney (SMR, 1.18; 95% CI, 0.83–1.62), and urinary bladder (SMR, 1.25; 95% CI, 0.87–1.74), chronic myeloid leukaemia (CML) (SMR, 1.17; 95% CI, 0.43–2.55), all other myeloid leukaemia (SMR, 1.50; 95% CI, 0.18–5.41), all other cancers of the lymphopoietic tissue

Table 2.1 Occupational cohort studies of exposure to styrene in the reinforced plastics industry

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. (2013) USA 1948–2008 Cohort	15 826 (11 958 men and 3868 women) at 30 United States plants; previous update of this study followed vital status to 31 December 1989 and reduced the number of study participants to 15 826 workers by eliminating 30 duplicate records and removing 52 workers exposed to styrene for < 6 mo Exposure assessment method: expert judgement; employment records available at each plant combined with industrial hygiene assessment of styrene levels about 1980	Lymphatic and haematopoietic (all)	Cumulative exposure to styrene (ppm-mo)			Sex, age, year of hire	Strengths: long follow-up and high number of cancer cases; exposure to styrene at high concentrations; limited competing risk factors in the reinforced plastics industry Limitations: limited information on the quantitative exposure assessment
			0.0–149.9	26	0.85 (0.56–1.25)		
			150.0–399.9	23	0.80 (0.51–1.21)		
			400.0–1199.9	29	0.90 (0.60–1.29)		
			≥ 1200	28	0.80 (0.53–1.16)		
			Trend test *P* value, 0.819				
		HL	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	2	1.07 (0.13–3.88)		
			150.0–399.9	1	0.60 (0.02–3.33)		
			400.0–1199.9	1	0.59 (0.02–3.27)		
			≥ 1200	1	0.65 (0.02–3.60)		
			Trend test *P* value, 0.827				
		NHL	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	13	1.08 (0.58–1.85)		
			150.0–399.9	2	0.17 (0.02–0.64)		
			400.0–1199.9	12	0.94 (0.49–1.64)		
			≥ 1200	9	0.65 (0.30–1.23)		
			Trend test *P* value, 0.766				
		Leukaemia	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	7	0.61 (0.25–1.26)		
			150.0–399.9	14	1.30 (0.71–2.18)		
			400.0–1199.9	8	0.66 (0.28–1.30)		
			≥ 1200	11	0.83 (0.42–1.49)		
			Trend test *P* value, 0.908				
		Leukaemia (lymphoid)	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	1	0.35 (0.09–1.97)		
			150.0–399.9	3	1.14 (0.23–3.32)		
			400.0–1199.9	1	0.33 (0.08–1.83)		
			≥ 1200	3	0.87 (0.18–2.54)		
			Trend test *P* value, 0.681				

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. (2013) (cont.)		Leukaemia (myeloid)	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	5	0.90 (0.29–2.10)		
			150.0–399.9	5	0.96 (0.31–2.23)		
			400.0–1199.9	4	0.69 (0.19–1.77)		
			≥ 1200	8	1.27 (0.55–2.50)		
			Trend test *P* value, 0.432				
		All other lymphopoietic tissue (including multiple myeloma)	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	4	0.79 (0.22–2.02)		
			150.0–399.9	6	1.24 (0.46–2.70)		
			400.0–1199.9	8	1.43 (0.62–2.81)		
			≥ 1200	7	1.11 (0.45–2.29)		
			Trend test *P* value, 0.912				
		Pancreas	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	14	0.90 (0.49–1.51)		
			150.0–399.9	17	1.15 (0.67–1.84)		
			400.0–1199.9	9	0.53 (0.24–1.01)		
			≥ 1200	23	1.24 (0.78–1.86)		
			Trend test *P* value, 0.274				
		Lung	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	157	1.60 (1.36–1.87)		
			150.0–399.9	131	1.41 (1.18–1.67)		
			400.0–1199.9	138	1.31 (1.10–1.55)		
			≥ 1200	130	1.10 (0.92–1.31)		
			Trend test *P* value, 0.003				
		Kidney	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	6	0.76 (0.28–1.66)		
			150.0–399.9	8	1.09 (0.47–2.15)		
			400.0–1199.9	8	0.98 (0.42–1.94)		
			≥ 1200	16	1.79 (1.02–2.91)		
			Trend test *P* value, 0.045				

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. (2013) (cont.)		Urinary bladder	Cumulative exposure to styrene (ppm-mo)				
			0.0–149.9	7	1.09 (0.44–2.25)		
			150.0–399.9	11	1.82 (0.91–3.26)		
			400.0–1199.9	11	1.53 (0.77–2.74)		
			≥ 1200	6	0.72 (0.26–1.57)		
			Trend test *P* value, 0.137				
		Lymphatic and haematopoietic (all combined)	No. days at peak exposure				
			0	57	0.79 (0.59–1.02)		
			1–179	30	0.93 (0.63–1.33)		
			720–1799	9	0.81 (0.37–1.54)		
			≥ 1800	10	0.97 (0.47–1.78)		
			Trend test *P* value, 0.601				
		HL	No. days at peak exposure				
			0	4	1.06 (0.29–2.71)		
			1–179	1	0.51 (0.01–2.81)		
			720–1799	0	0 (0–0)		
			≥ 1800	0	0 (0–0)		
			Trend test *P* value, 0.157				
		NHL	No. days at peak exposure				
			0	20	0.70 (0.43–1.08)		
			1–179	9	0.70 (0.32–1.33)		
			720–1799	5	1.12 (0.37–2.63)		
			≥ 1800	2	0.49 (0.06–1.76)		
			Trend test *P* value, 0.868				
		Leukaemia	No. days at peak exposure				
			0	21	0.76 (0.47–1.17)		
			1–179	12	0.99 (0.51–1.74)		
			720–1799	3	0.72 (0.15–2.09)		
			≥ 1800	4	1.03 (0.28–2.63)		
			Trend test *P* value, 0.691				

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. (2013) (cont.)		Leukaemia (lymphoid)	No. days at peak exposure				
			0	4	0.57 (0.16–1.47)		
			1–179	2	0.68 (0.08–2.46)		
			720–1799	0	0 (0–3.52)		
			≥ 1800	2	1.95 (0.24–7.03)		
			Trend test *P* value, 0.177				
		Leukaemia (myeloid)	No. days at peak exposure				
			0	11	0.86 (0.43–1.53)		
			1–179	7	1.15 (0.46–2.38)		
			720–1799	2	0.96 (0.12–3.48)		
			≥ 1800	2	1.07 (0.13–3.86)		
			Trend test *P* value, 0.835				
		All other lymphopoietic tissue (including MM)	No. days at peak exposure				
			0	4	0.79 (0.22–2.02)		
			1–179	6	1.24 (0.46–2.70)		
			720–1799	8	1.43 (0.62–2.81)		
			≥ 1800	7	1.11 (0.45–2.29)		
			Trend test *P* value, 0.835				
		Pancreas	No. days at peak exposure				
			0	32	0.84 (0.58–1.19)		
			1–179	20	1.21 (0.74–1.87)		
			720–1799	3	0.52 (0.11–1.51)		
			≥ 1800	8	1.45 (0.63–2.85)		
			Trend test *P* value, 0.337				
		Lung	No. days at peak exposure				
			0	314	1.32 (1.18–1.47)		
			1–179	154	1.50 (1.28–1.76)		
			720–1799	49	1.34 (1.00–1.77)		
			≥ 1800	39	1.06 (0.76–1.46)		
			Trend test *P* value, 0.201				

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. (2013) (cont.)		Kidney	No. days at peak exposure				
			0	16	0.88 (0.50–1.42)		
			1–179	9	1.08 (0.49–2.04)		
			720–1799	8	2.73 (1.17–5.38)		
			≥ 1800	5	1.82 (0.59–4.24)		
			Trend test *P* value, 0.054				
		Urinary bladder	No. days at peak exposure				
			0	22	1.31 (0.82–1.98)		
			1–179	7	1.12 (0.45–2.31)		
			720–1799	0	0 (0–1.54)		
			≥ 1800	6	2.35 (0.87–5.13)		
			Trend test *P* value, 0.337				
		Lymphatic and haematopoietic (all)	Cumulative exposure to styrene (ppm-mo)			Sex, year of hire, year of birth, age	
			Continuous	NR	0.994 (0.983–1.006)		
		HL	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	0.957 (0.843–1.086)		
		NHL	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	0.994 (0.976–1.013)		
		Leukaemia	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	0.996 (0.979–1.014)		
		Leukaemia (lymphoid)	All workers: continuous	NR	1.010 (0.994–1.027)		
		Leukaemia (myeloid)	All workers: continuous	NR	0.991 (0.962–1.019)		
		Other: all other leukaemia	All workers: continuous	NR	0.900 (0.767–1.056)		
		Lymphatic and haematopoietic: all other including MM	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	0.994 (0.972–1.017)		

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. (2013) (cont.)		Pancreas	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	1.008 (1.002–1.015)		
		Lung	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	0.997 (0.993–1.002)		
		Kidney	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	1.009 (1.000–1.017)		
		Urinary bladder	Cumulative exposure to styrene (ppm-mo)				
			Continuous	NR	1.004 (0.992–1.016)		
		All cancers combined	All workers: reinforced plastic	1431	1.12 (1.05–1.18)	Sex, age, calendar period	
		Lymphatic and haematopoietic (all combined)	All workers: reinforced plastic	106	0.84 (0.69–1.02)		
		Leukaemia (ALL)	All workers: reinforced plastic	2	0.75 (0.09–2.71)		
		NHL (CLL)	All workers: reinforced plastic	6	0.71 (0.26–1.55)		
		Leukaemia	All workers: reinforced plastic	40	0.84 (0.60–1.14)		
		Leukaemia (lymphoid)	All workers: reinforced plastic	8	0.67 (0.29–1.32)		
		Leukaemia (myeloid)	All workers: reinforced plastic	22	0.96 (0.60–1.46)		
		Leukaemia (AML)	All workers: reinforced plastic	14	0.85 (0.47–1.43)		

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. (2013) (cont.)		NHL	All workers: reinforced plastic	36	0.72 (0.50–1.00)		
		HL	All workers: reinforced plastic	5	0.74 (0.24–1.72)		
		Leukaemia (CML)	All workers: reinforced plastic	6	1.17 (0.43–2.55)		
		MM: all and other lymphopoietic tissue (except HL, NHL, leukaemia)	All workers: reinforced plastic	25	1.15 (0.74–1.69)		
		All other leukaemia	All workers: reinforced plastic	9	0.79 (0.36–1.49)		
		All other myeloid leukaemia	All workers: reinforced plastic	2	1.50 (0.18–5.41)		
		Pancreas	All workers: reinforced plastic	63	0.96 (0.73–1.22)		
		Lung	All workers: reinforced plastic	556	1.34 (1.23–1.46)		
		Breast	All workers: reinforced plastic	55	0.88 (0.66–1.15)		
		Prostate	All workers: reinforced plastic	68	1.03 (0.8–1.31)		

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. (2013) (cont.)		Kidney	All workers: reinforced plastic	38	1.18 (0.83–1.62)		
		Urinary bladder	All workers: reinforced plastic	35	1.25 (0.87–1.74)		
		Buccal cavity and larynx	All workers: reinforced plastic	29	1.16 (0.78–1.66)		
Kogevinas et al. (1994) Denmark (1970–1990); Finland (1958–1989); Italy (Liguria, 1969–1991; Emilia Romagna, 1956–1989); Norway (1956–1991); Sweden (1955–1987); United Kingdom (1, 1945–1990; 2, 1961–1988) Cohort	40 688 (34 560 men and 6128 women); ~60% of the total population had been employed in the industry for < 2 yr; proportion of short-term workers varied among countries from 9% (Finland) to 81% (Denmark); ~50% of the cohort was first employed at age < 25 yr, similar proportion was first employed after 1975 Exposure assessment method: records; employment histories combined with an exposure matrix constructed from 16 500 personal workroom air styrene measurements and 18 500 urinary styrene metabolites	Lymphatic and haematopoietic neoplasms: ICD-8 (code 200–208)	Cumulative exposure to styrene (ppm-yr)			Age, sex, country, calendar period, time since first exposure	Strengths: large international study population characterized by quantitative measures of styrene exposure Limitations: short duration of follow-up (average 13 yr); no smoking information
			< 75	20	1		
			75–199	8	0.98 (0.43–2.26)		
			200–499	10	1.24 (0.57–2.72)		
			≥ 500	9	0.84 (0.35–2.02)		
			Trend test *P* value, 0.65				
		Leukaemia: ICD-8 (code 204–208)	Cumulative exposure to styrene (ppm-yr)				
			< 75	11	1		
			75–199	2	0.46 (0.10–2.09)		
			200–499	3	0.69 (0.19–2.53)		
			≥ 500	5	0.86 (0.26–2.83)		
			Trend test *P* value, > 0.52				
		Malignant lymphomas: ICD-8 (code 200–202); lymphomas and HL	Cumulative exposure to styrene (ppm-yr)				
			< 75	5	1		
			75–199	5	2.63 (0.74–9.32)		
			200–499	5	2.99 (0.82–10.91)		
			≥ 500	3	1.64 (0.34–7.82)		
			Trend test *P* value, 0.52				

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
Kogevinas et al. (1994) (cont.)		Oesophagus	Cumulative exposure to styrene (ppm-yr)				
			< 75	5	1		
			75–199	2	1.01 (0.20–5.23)		
			200–499	3	1.67 (0.39–7.18)		
			≥ 500	4	1.76 (0.42–7.30)		
			Trend test *P* value, 0.31				
		Pancreas	Cumulative exposure to styrene (ppm-yr)				
			< 75	9	1		
			75–199	5	1.44 (0.48–4.34)		
			200–499	6	1.90 (0.65–5.53)		
			≥ 500	10	2.56 (0.90–7.31)		
			Trend test *P* value, 0.068				
		Lung	Cumulative exposure to styrene (ppm-yr)				
			< 75	73	1		
			75–199	25	0.75 (0.47–1.19)		
			200–499	26	0.74 (0.47–1.16)		
			≥ 500	37	0.90 (0.58–1.38)		
			Trend test *P* value, < 0.43				
		Kidney	Cumulative exposure to styrene (ppm-yr)				
			< 75	2	1		
			75–199	3	4.40 (0.71–27.15)		
			200–499	2	3.30 (0.42–25.60)		
			≥ 500	3	6.04 (0.74–49.45)		
			Trend test *P* value, 0.12				
		All cancers combined	All workers: reinforced plastic	686	0.87 (0.81–0.94)		
		All lympho-haematopoietic	All workers: reinforced plastic	60	0.93 (0.71–1.20)		

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
Kogevinas et al. (1994) (cont.)		Leukaemia (myeloid)	All workers: reinforced plastic	16	1.10 (0.63–1.79)		
		Leukaemia	All workers: reinforced plastic	28	1.04 (0.69–1.50)		
		NHL	All workers: reinforced plastic	15	0.77 (0.43–1.28)		
		HL	All workers: reinforced plastic	7	0.90 (0.36–1.84)		
		MM	All workers: reinforced plastic	10	0.99 (0.48–1.83)		
		Buccal cavity and pharynx	All workers: reinforced plastic	5	0.33 (0.11–0.77)		
		Oesophagus	All workers: reinforced plastic	17	0.82 (0.47–1.31)		
		Rectum	All workers: reinforced plastic	21	0.62 (0.38–0.95)		
		Pancreas	All workers: reinforced plastic	37	1.00 (0.71–1.38)		
		Larynx	All workers: reinforced plastic	10	1.11 (0.53–2.05)		
		Lung	All workers: reinforced plastic	235	0.99 (0.87–1.13)		

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
Kogevinas et al. (1994) (cont.)		Lung	Laminators: reinforced plastic	60	1.06 (0.81–1.36)		
		Breast	All workers: reinforced plastic	13	0.52 (0.28–0.89)		
		Prostate	All workers: reinforced plastic	41	1.02 (0.74–1.39)		
		Urinary bladder	All workers: reinforced plastic	25	0.95 (0.61–1.40)		
		Brain	All workers: reinforced plastic	18	0.62 (0.37–0.98)		
Coggon et al. (2015) England 1946–1984, followed up until 2012 Cohort	7970 (6650 men and 1320 women); all employed during specified periods at eight reinforced plastics companies in England using styrene Exposure assessment method: records; from employment histories, participants were classified into four levels of potential for styrene exposure; exposure to styrene at 40–100 ppm was estimated for the high-exposure category between 1975 and 1984	Leukaemia	Background	10	1.15 (0.55–2.12)	Age, sex, calendar period	Strengths: expected exposure to styrene at high concentrations; limited exposure to other suspected occupational carcinogens; long follow-up Limitations: no styrene exposure information since 1984; no smoking information; 11.5% lost from follow-up
			Low/moderate	6	0.86 (0.31–1.87)		
			High for < 1 yr	4	0.72 (0.20–1.84)		
			High for ≥ 1 yr	3	0.76 (0.16–2.22)		
		NHL (including CLL)	Background	10	1.20 (0.58–2.21)		
			Low/moderate	3	0.44 (0.09–1.28)		
			High for < 1 yr	6	1.04 (0.38–2.26)		
			High for ≥ 1 yr	5	1.22 (0.40–2.85)		
		Lymphatic and haematopoietic (all combined)	Background	43	1	Age, sex, calendar period, factory	
			Low/moderate	28	0.73 (0.40–1.33)		
			High for < 1 yr	31	0.81 (0.47–1.41)		
			High for ≥ 1 yr	20	0.76 (0.40–1.44)		

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
Coggon et al. (2015) (cont.)		NHL (including CLL)	Background	26	1		
			Low/moderate	14	0.53 (0.24–1.15)		
			High for < 1 yr	18	0.61 (0.30–1.25)		
			High for ≥ 1 yr	11	0.54 (0.23–1.27)		
		HL	Background	3	1		
			Low/moderate	2	1.05 (0.17–13.56)		
			High for < 1 yr	1	0.39 (0.03–5.09)		
			High for ≥ 1 yr	1	0.74 (0.06–9.94)		
		MM	Background	6	1		
			Low/moderate	7	2.15 (0.51–9.12)		
			High for < 1 yr	6	2.66 (0.67–10.64)		
			High for ≥ 1 yr	5	2.66 (0.62–11.35)		
		Leukaemia: all other	Background	8	1		
			Low/moderate	5	0.60 (0.13–2.79)		
			High for < 1 yr	6	0.84 (0.23–3.02)		
			High for ≥ 1 yr	3	0.62 (0.13–3.03)		
		Oesophagus	Background	12	0.86 (0.45–1.51)	Age, sex, calendar period	
			Low/moderate	13	1.02 (0.54–1.74)		
			High for < 1 yr	12	1.18 (0.61–2.06)		
			High for ≥ 1 yr	10	1.41 (0.68–2.60)		
		Pancreas	Background	21	1.41 (0.87–2.15)		
			Low/moderate	11	0.95 (0.47–1.70)		
			High for < 1 yr	10	1.11 (0.53–2.03)		
			High for ≥ 1 yr	6	0.89 (0.33–1.95)		
		Lung	Background	100	1.07 (0.87–1.30)		
			Low/moderate	98	1.20 (0.98–1.47)		
			High for < 1 yr	68	1.22 (0.95–1.55)		
			High for ≥ 1 yr	60	1.44 (1.10–1.86)		

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
Coggon et al. (2015) (cont.)		Prostate	Background	19	0.85 (0.51–1.33)		
			Low/moderate	20	0.79 (0.48–1.22)		
			High for < 1 yr	15	1.03 (0.58–1.70)		
			High for ≥ 1 yr	9	0.86 (0.39–1.63)		
		Kidney	Background	10	1.49 (0.72–2.75)		
			Low/moderate	7	1.18 (0.47–2.43)		
			High for < 1 yr	7	1.43 (0.58–2.95)		
			High for ≥ 1 yr	4	1.17 (0.32–30.0)		
		Urinary bladder	Background	10	0.90 (0.43–1.65)		
			Low/moderate	16	1.58 (0.90–2.57)		
			High for < 1 yr	8	1.23 (0.53–2.43)		
			High for ≥ 1 yr	3	0.62 (0.13–1.81)		
		Leukaemia	All workers: reinforced plastic	23	0.91 (0.58–1.36)	Age, sex, calendar period	
		NHL	All workers: reinforced plastic	24	0.95 (0.61–1.42)		
		HL	All workers: reinforced plastic	2	0.49 (0.06–1.77)		
		MM	All workers: reinforced plastic	13	0.94 (0.50–1.60)		
		Lymphatic and haematopoietic	All workers: reinforced plastic	62	0.89 (0.68–1.14)		
		Pharynx	All workers: reinforced plastic	9	1.34 (0.61–2.54)		

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
Coggon et al. (2015) (cont.)		Oesophagus	All workers: reinforced plastic	47	1.06 (0.78–1.41)		
		Pancreas	All workers: reinforced plastic	48	1.13 (0.83–1.50)		
		Larynx	All workers: reinforced plastic	13	1.70 (1.91–2.91)		
		Lung	All workers: reinforced plastic	329	1.20 (1.08–1.34)		
		Breast	All workers: reinforced plastic	24	0.77 (0.49–1.15)		
		Prostate	All workers: reinforced plastic	63	0.86 (0.66–1.10)		
		Kidney	All workers: reinforced plastic	28	1.33 (0.88–1.92)		
		Urinary bladder	All workers: reinforced plastic	38	1.16 (0.82–1.59)		

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
Christensen et al. (2017) Denmark Enrolment 1964–2007/ follow-up 1968–2012 Cohort	72 292 (60 478 men and 11 774 women) workers employed in 443 small- and medium-sized companies producing reinforced plastics Exposure assessment method: records; annual employment information from national register; expert assessment; worker survey	Leukaemia (lymphoid)	All workers: reinforced plastic	123	0.96 (0.79–1.14)	Age, sex, calendar period	Strengths: large population of workers of small- and medium-sized companies with expected homogeneous and high-concentration styrene exposure and a long and almost complete follow-up Limitations: no use of quantitative estimates of styrene exposure or smoking information
		Lymphatic and haematopoietic	All workers: reinforced plastic	661	0.97 (0.90–1.04)		
		Leukaemia (myeloid)	All workers: reinforced plastic	101	1.06 (0.86–1.28)		
		MM (Multiple myeloma)	All workers: reinforced plastic	90	[0.79 (0.64–0.97)]		
		NHL	All workers: reinforced plastic	270	0.97 (0.86–1.10)		
		HL	All workers: reinforced plastic	64	1.21 (0.93–1.54)		
		Monocytic leukaemia	All workers: reinforced plastic	< 4	0.77 (0.15–2.25)		
		Other and unspecified leukaemia	All workers: reinforced plastic	10	1.05 (0.50–1.94)		
		Pharynx	All workers: reinforced plastic	170	1.21 (1.03–1.40)		
		Buccal activity and pharynx	All workers: reinforced plastic	398	1.20 (1.08–1.32)		
		Oesophagus	All workers: reinforced plastic	160	1.05 (0.89–1.22)		

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
Christensen et al. (2017) (cont.)		Stomach/gastric cancer	All workers: reinforced plastic	237	1.11 (0.97–1.26)		
		Pancreas	All workers: reinforced plastic	247	1.04 (0.91–1.18)		
		Nasal cavity and sinuses	All workers: reinforced plastic	40	1.62 (1.16–2.21)		
		Larynx	All workers: reinforced plastic	176	1.34 (1.15–1.55)		
		Lung	All workers: reinforced plastic	1638	1.28 (1.22–1.34)		
		Breast	All workers: reinforced plastic	432	0.95 (0.86–1.05)		
		Prostate	All workers: reinforced plastic	1025	0.88 (0.83–0.94)		
		Kidney	All workers: reinforced plastic	247	1.12 (0.98–1.27)		
		Urinary bladder	All workers: reinforced plastic	675	1.06 (0.98–1.14)		

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
Kolstad et al. (1994) Denmark 1964–1988 Cohort	53 720 workers (36 525 male employees of 386 companies producing reinforced plastics and 14 254 employees not exposed to styrene of similar industries) included in historical cohort study; observed numbers of newly diagnosed cases of lymphohaematopoietic malignancies in the study population compared with expected numbers based on the national rates; study conducted in the Danish reinforced plastics industry, in which exposure to high concentrations of styrene occurs frequently in an environment free of most other suspected carcinogens Exposure assessment method: semiquantitative: cumulated styrene exposure scores modelled from job title, styrene exposure probability, styrene exposure levels since the early 1970s, and duration of employment	Leukaemia	Exposed jobs vs unexposed jobs: time since first employment; time window (1964–1970)			Age, sex, year of diagnosis	Strengths: large study population of workers exposed to high concentration of styrene; semiquantitative exposure characterization; long follow-up; high number of incident and specific lymphohaematopoietic malignancies; analyses of exposure time windows Limitations: lack of individual work histories
			< 10 yr since first employment	5	1.06 (0.35–2.48)		
			≥ 10 yr since first employment	25	1.69 (1.09–2.49)		
			Total	30	1.54 (1.04–2.19)		

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
Kolstad et al. (1996) Denmark 1970–1990 Nested case–control	12 cases; 19 identified with myeloid leukaemia in the Danish cohort (see Christensen et al. 2017, 2018) diagnosed between 1970 and 1991, 12 of which showed clonal chromosome aberrations Controls: 57 Exposure assessment method: semiquantitative: cumulated styrene exposure scores modelled from job title, styrene exposure probability, styrene exposure levels since the early 1970s, and duration of employment	Leukaemia (AML)	Cumulative exposure to styrene ((mg/m³)-yr) Any exposed vs unexposed Cumulative exposure to styrene ((mg/m³)-yr) Low High Cumulative exposure to styrene ((mg/m³)-yr): year of first employment Later than 1970 Before 1970 Cumulative exposure to styrene ((mg/m³)-yr): length of exposed employment < 1 yr ≥ 1 yr	 11 8 3 4 7 8 3	 2.5 (0.2–25.0) 3.0 (0.3–32.2) 1.6 (0.1–22.0) 2.3 (0.2–26.2) 5.9 (0.6–57.8) 5.9 (0.5–74.3) 1.1 (0.1–15.3)	Calendar year, time since first employment, year of first employment, age	Strengths: may indicate that chromosome aberrations might be part of the disease process in relation to styrene exposure and myeloid carcinoma Limitations: results are only preliminary because of the few observations, the lack of specific exposure data, and the incomplete case ascertainment
Wong (1990) USA 1948–1977 Nested case–control	Cases: 40 deaths from respiratory cancer Controls: 102; for each case, a maximum of 3 controls were selected from deceased members of the cohort, matched with respect to plant, age at death (within 5 yr), year of death (within 5 yr), sex, and race (from death certificates) Exposure assessment method: other	Respiratory tract	Direct exposure to styrene Exposed Trend test *P* value, 0.29	 15	 0.63	Calendar year, time since first employment, year of first employment, age	Cohort nested in the population described in Collins et al. (2013)

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
Ruder & Bertke (2017) Washington, USA 1991–2007 Cohort	3704 employees of two reinforced plastics facilities during1959–1978 and living in Washington State by 1991 Exposure assessment method: records; exposure assessment identical to that of the Ruder et al. (2016) study	Lymphatic and haematopoietic	All workers	47	1.03 (0.77–1.35)	Age, sex, calendar period, race	Strengths: incidence data Limitations: only 71.2% of the original study population of 5203 workers included
			Low exposure	35	1.05 (0.73–1.46)		
			High exposure	18	0.99 (0.59–1.57)		
		Lung	All workers	87	1.11 (0.89–1.37)		
			Low exposure	50	0.96 (0.71–1.27)		
			High exposure	37	1.42 (1.00–1.95)		
		Breast	All workers	21	0.81 (0.50–1.23)		
			Low exposure	6	0.67 (0.25–1.46)		
			High exposure	15	0.88 (0.49–1.45)		
		Prostate	All workers	140	0.82 (0.69–0.97)		
			Low exposure	89	0.74 (0.60–0.91)		
			High exposure	51	1.02 (0.76–1.34)		
		Urinary organ	All workers	51	1.00 (0.75–1.32)		
			Low exposure	32	0.93 (0.63–1.31)		
			High exposure	19	1.17 (0.70–1.82)		

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
Christensen et al. (2018) Denmark 1968–2011 Cohort	73 036 male and female workers of 456 small- and medium-sized companies producing reinforced plastics Exposure assessment method: semiquantitative: cumulated styrene exposure scores modelled from job title, styrene exposure probability, styrene exposure levels since the early 1970s, and duration of employment	Leukaemia (AML)	Cumulative exposure score: complete work history ((mg/m³)-yr)			Age, sex, calendar period	Results for additional subcategories of lymphohaematopoietic cancers are reported Strengths: large study population of workers exposed to high concentrations of styrene; semiquantitative exposure characterization; long and almost complete follow-up; high number of incident and specific lymphohaematopoietic malignancies; and analyses of exposure time windows Limitations: exposure characterization included an element of probability
			1–17	12	1		
			18–70	12	0.77 (0.34–1.74)		
			> 70	26	1.35 (0.65–2.80)		
			Trend test *P* value, 0.28				
			Cumulative exposure score: previous < 15 yr ((mg/m³)-yr)				
			0	28	1		
			1–28	10	1.01 (0.46–2.20)		
			> 28	12	0.81 (0.38–1.73)		
			Trend test *P* value, 0.60				
			Cumulative exposure score: previous 15–29 yr ((mg/m³)-yr)				
			0	18	1		
			1–45	10	1.34 (0.60–2.97)		
			> 45	22	2.35 (1.21–4.57)		
			Trend test *P* value, 0.01				
			Cumulative exposure score: previous ≥ 30 yr ((mg/m³)-yr)				
			0	37	1		
			1–45	7	2.12 (0.82–5.48)		
			> 45	6	1.55 (0.57–4.26)		
			Trend test *P* value, 0.28				
		HL	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	16	1		
			18–70	16	1.04 (0.51–2.13)		
			> 70	25	1.60 (0.81–2.16)		
			Trend test *P* value, 0.15				

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
Christensen et al. (2018) (cont.)		HL	Cumulative exposure score: previous < 15 yr ((mg/m³)-yr)				
			0	20	1		
			1–28	16	1.17 (0.55–2.48)		
			> 28	21	1.72 (0.79–3.75)		
			Trend test *P* value, 0.17				
			Cumulative exposure score: previous 15–29 yr ((mg/m³)-yr)				
			0	38	1		
			1–45	12	1.17 (0.59–2.34)		
			> 45	7	0.61 (0.26–1.43)		
			Trend test *P* value, 0.36				
			Cumulative exposure score: previous ≥ 30 yr ((mg/m³)-yr)				
			0	44	1		
			1–45	7	2.25 (0.86–5.88)		
			> 45	6	1.71 (0.62–4.74)		
			Trend test *P* value, 0.21				
		Lymphatic and haematopoietic (all combined)	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	182	1		
			18–70	220	0.92 (0.76–1.13)		
			> 70	263	0.92 (0.76–1.13)		
			Trend test *P* value, 0.042				
		Leukaemia (CML)	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	6	1		
			18–70	7	0.74 (0.24–2.22)		
			> 70	11	0.94 (0.34–2.63)		
			Trend test *P* value, 0.99				

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
Christensen et al. (2018) (cont.)		NHL (all combined)	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	67	1		
			18–70	80	0.94 (0.68–1.32)		
			> 70	89	0.91 (0.65–1.27)		
			Trend test *P* value, 0.58				
		NHL (B-cell lymphoma)	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	49	1		
			18–70	62	1.00 (0.68–1.46)		
			> 70	63	0.87 (0.59–1.29)		
			Trend test *P* value, 0.46				
		MM	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	19	1		
			18–70	20	0.77 (0.40–1.46)		
			> 70	30	0.93 (0.51–1.70)		
			Trend test *P* value, 0.91				
		Leukaemia (lymphoid) (all combined)	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	29	1		
			18–70	40	0.94 (0.58–1.53)		
			> 70	33	0.60 (0.36–1.02)		
			Trend test *P* value, 0.04				
		NHL (T-cell lymphoma)	Cumulative exposure score: complete work history ((mg/m³)-yr)				
			1–17	NR	1		
			18–70	NR	1.14 (0.25–5.15)		
			> 70	NR	3.21 (0.87–11.77)		
			Trend test *P* value, 0.04				

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
Christensen et al. (2018) (cont.)			Cumulative exposure score: previous < 15 yr ((mg/m³)-yr)				
			0	NR	1		
			1–28	NR	0.56 (0.14–2.28)		
			> 28	NR	0.18 (0.02–1.52)		
			Trend test *P* value, 0.09				
			Cumulative exposure score: previous 15–29 yr ((mg/m³)-yr)				
			0	NR	1		
			1–45	NR	0.85 (0.22–3.28)		
			> 45	NR	2.04 (0.75–5.52)		
			Trend test *P* value, 0.17				
			Cumulative exposure score: previous ≥ 30 yr ((mg/m³)-yr)				
			0	NR	1		
			1–45	NR	2.78 (0.80–9.60)		
			> 45	NR	2.40 (0.68–8.46)		
			Trend test *P* value, 0.15				

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
Nissen et al. (2018) Denmark 1968–2011 Nested case–control	Cases: 9 adenocarcinomas, 15 squamous cell carcinomas, 13 other subtypes, 73 092 reinforced plastics workers Controls: 90, 150, 130, none Exposure assessment method: semiquantitative: cumulated styrene exposure scores modelled from job title, styrene exposure probability, styrene exposure levels since the early 1970s, and duration of employment	Nasal cavity and sinuses: adenocarcinoma	Complete work history: ≥ 37 (mg/m³)-yr	9	5.11 (0.58–45.12)	Age, sex, employment in a reinforced plastics company producing boats or in the wood industry	Strengths: large study population of workers exposed to high concentrations of styrene; semiquantitative exposure characterization; long follow-up; information on specific and incident histological subtypes Limitations: exposure characterization included an element of probability
			Per 100 (mg/m³)-yr	9	1.08 (0.96–1.21)		
		Nasal cavity and sinuses: squamous cell carcinoma	Complete work history: ≥ 37 (mg/m³)-yr	15	1.15 (0.34–3.89)		
			Per 100 (mg/m³)-yr	15	1.02 (0.83–1.25)		
		Nasal cavity and sinuses: other histological subtypes	Complete work history: ≥ 37 (mg/m³)-yr	13	0.74 (0.22–2.42)		
			Per 100 mg/m³-yr	13	0.75 (0.46–1.23)		
Loomis et al. (2019) International cohort 1945–1991 Cohort	40 668 (34 560 men and 6128 women) workers enrolled from eight centres from more than 600 plants Exposure assessment method: quantitative measurements	NHL	Mean styrene exposure (ppm)			Sex, age, and calendar decade	Strengths: large international study population characterized by quantitative measures of styrene exposure; internal analysis Limitations: short duration of follow-up (average 13 yr); no sampling information
			0 yr lag	NR	2.31 (1.29–4.12)		
			5 yr lag	NR	2.29 (1.33–3.93)		
			10 yr lag	NR	1.78 (1.05–3.02)		
		MM	Mean styrene exposure (ppm)				
			0 yr lag	NR	1.86 (0.71–4.86)		
			5 yr lag	NR	2.25 (0.92–5.48)		
			10 yr lag	NR	1.31 (0.48–3.58)		
		Leukaemia (myeloid, acute and chronic combined)	Mean styrene exposure (ppm)				
			0 yr lag	NR	0.92 (0.37–2.32)		
			5 yr lag	NR	1.34 (0.61–2.94)		
			10 yr lag	NR	1.50 (0.71–3.17)		

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
Loomis et al. (2019) (cont.)		Oesophagus	Mean styrene exposure (ppm)			Age	
			0 yr lag	NR	2.44 (1.11–5.36)		
			10 yr lag	NR	2.53 (1.30–4.90)		
			20 yr lag	NR	3.36 (1.74–6.49)		
		Pancreas	Mean styrene exposure (ppm)				
			0 yr lag	NR	1.89 (1.17–3.06)		
			10 yr lag	NR	1.31 (0.82–2.10)		
			20 yr lag	NR	1.14 (0.57–2.28)		
		Lung	Mean styrene exposure (ppm)			Sex, age, country	
			0 yr lag	NR	0.98 (0.79–1.22)		
			10 yr lag	NR	0.97 (0.80–1.18)		
			20 yr lag	NR	0.81 (0.59–1.12)		
		Prostate	Mean styrene exposure (ppm)			Age, country	
			0 yr lag	NR	1.26 (0.76–2.11)		
			10 yr lag	NR	1.03 (0.64–1.68)		
			20 yr lag	NR	1.07 (0.55–2.10)		
		NHL	Exposed jobs vs unexposed jobs			Age, country, calendar decade, sex	
			All exposed	22	1.01 (0.37–2.74)		
		MM	Exposed jobs vs unexposed jobs				
			All exposed	8	1.05 (0.20–5.37)		
		Leukaemia (myeloid, acute and chronic combined)	Exposed jobs vs unexposed jobs				
			All exposed	12	0.57 (0.09–3.49)		
		Oesophagus	Exposed jobs vs unexposed jobs			Age	
			All exposed	15	3.50 (0.46–26.82)		
		Pancreas	Exposed jobs vs unexposed jobs				
			All exposed	27	1.06 (0.46–2.46)		
		Lung	Exposed jobs vs unexposed jobs			Age, country, calendar decade, sex	
			All exposed	159	0.85 (0.57–1.19)		

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
Loomis et al. (2019) (cont.)		Prostate	Exposed jobs vs unexposed jobs			Age, country	
			All exposed	27	1.85 (0.64–5.36)		
		Kidney	Exposed jobs vs unexposed jobs			Age, country, calendar decade, sex	
			All exposed	9	0.83 (0.18–3.99)		
		Urinary bladder	Exposed jobs vs unexposed jobs				
			All exposed	21	0.92 (0.22–3.80)		
Bertke et al. (2018) Washington, USA 1959–1978/1 January 1960–31 December 2016 Cohort	5201 workers employed in two Washington boatbuilding facilities Exposure assessment method: records; work history information was used to construct an exposure index based on exposure duration and exposure potential (from industrial hygiene surveys conducted at each plant)	NHL	Person-time employed: external comparison (yr)			Regressions matched on attained age, sex, race, calendar period	Supersedes Ruder et al. (2016) Strengths: exposure to high concentrations of styrene; few competing risk factors; long follow-up Limitations: the lack of quantitative styrene exposure and smoking information
			≥ 1	5	0.60 (0.19–1.40)		
		Leukaemia	Person-time employed: external comparison (yr)				
			≥ 1	7	0.88 (0.35–1.81)		
		MM	Person-time employed: external comparison (yr)				
			≥ 1	6	1.50 (0.55–3.25)		
		Lymphatic and haematopoietic (all combined)	Person-time employed: external comparison (yr)				
			≥ 1	18	0.85 (0.51–1.35)		
		Buccal cavity and pharynx	Person-time employed: external comparison (yr)				
			≥ 1	< 5	0.49 (0.06–1.78)		
		Oesophagus	Person-time employed: external comparison (yr)				
			≥ 1	7	1.06 (0.43–2.19)		
		Pancreas	Person-time employed: external comparison (yr)				
			≥ 1	13	1.11 (0.59–1.90)		
		Larynx	Person-time employed: external comparison (yr)				
			≥ 1	< 5	0.61 (0.02–3.39)		
		Lung: trachea, bronchus, and lung (162)	Person-time employed: external comparison (yr)				
			≥ 1	76	1.20 (0.95–1.51)		
		Breast	Person-time employed: external comparison (yr)				
			≥ 1	5	0.97 (0.32–2.26)		
		Prostate	Person-time employed: external comparison (yr)				
			≥ 1	23	1.38 (0.87–2.07)		

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
Bertke et al. (2018) (cont.)		Kidney	Person-time employed: external comparison (yr)				
			≥ 1	9	1.66 (0.76–3.16)		
		Urinary bladder	Person-time employed: external comparison (yr)				
			≥ 1	8	1.34 (0.58–2.65)		
		Lymphatic and haematopoietic	Duration employed as continuous			Regressions matched on attained age, sex, race, calendar period, employment duration of < or > 1 yr	
			Log-linear per 1 yr employment	49	1.2 (1.0–1.3)		
		NHL	Duration employed as continuous				
			Log-linear per 1 yr employment	18	0.9 (0.2–1.4)		
		MM	Duration employed as continuous				
			Log-linear per 1 yr employment	11	1.1 (0.6–1.5)		
		Leukaemia	Duration employed as continuous				
			Log-linear per 1 yr employment	18	1.3 (1.0–1.5)		
		Oesophagus	Duration employed as continuous				
			Log-linear per 1 yr employment	21	1.2 (0.8–1.6)		
		Pancreas	Duration employed as continuous				
			Log-linear per 1 yr employment	38	1.0 (0.6–1.2)		
		Respiratory tract: trachea, bronchus, and lung (162)	Duration employed as continuous				
			Log-linear per 1 yr employment	204	0.9 (0.7–1.0)		

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
Bertke et al. (2018) (cont.)		Breast	Duration employed as continuous				
			Log-linear per 1 yr employment	6	0.3 (0.0–0.69)		
		Prostate	Duration employed as continuous				
			Log-linear per 1 yr employment	44	1.2 (1.0–1.4)		
		Kidney	Duration employed as continuous				
			Log-linear per 1 yr employment	15	1.1 (0.7–1.3)		
		Urinary bladder	Duration employed as continuous				
			Log-linear per 1 yr employment	15	1.2 (0.8–1.5)		

ALL, acute lymphoblastic/lymphocytic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; ICD, International Classification of Diseases; MM, multiple myeloma; mo, month(s); NHL, non-Hodgkin lymphoma; NR, not reported; ppm, parts per million; RR, relative risk; vs, versus; yr, year(s).

including multiple myeloma (SMR, 1.15; 95% CI, 0.74–1.69), and myelodysplasia (SMR, 1.73; 95% CI, 0.70–3.57), but not for cancer of the prostate, pancreas, or breast or for Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), acute lymphoblastic/lymphocytic leukaemia (ALL), CLL, or acute myeloid leukaemia (AML).

Internal Cox analyses showed increasing trends by cumulative styrene exposure of statistical significance for cancer of the pancreas (HR, 1.008; 95% CI, 1.002–1.015) and kidney (HR, 1.009; 95% CI, 1.000–1.017) per 100 ppm-months. A decreasing trend of borderline significance was seen for cancer of the lung (HR, 0.997; 95% CI, 0.993–1.002). No significant trends were apparent for cancer of the bladder, all cancers of the lymphoid and haematopoietic tissues, NHL, HL, lymphoid or myeloid leukaemia, or all other cancers of the lymphopoietic tissue including multiple myeloma (MM). Increased standardized mortality ratios were seen for myeloid leukaemia (SMR, 1.27; 95% CI, 0.55–2.50) and cancer of the kidney (SMR, 1.79; 95% CI, 1.02–2.91) in the category of highest exposure (≥ 1200 ppm-months).

Analyses of days with peak exposure (> 100 ppm for 15 minutes of the working day) showed increased point estimates in the category of highest exposure (≥ 1800 days with peaks) for lymphoid leukaemia (SMR, 1.95; 95% CI, 0.24–7.03), other lymphatic cancers (SMR, 2.13; 95% CI, 0.58–5.45), and cancer of the pancreas (SMR, 1.45; 95% CI, 0.63–2.85), kidney (SMR, 1.82; 95% CI, 0.59–4.24), and bladder (SMR, 2.35; 95% CI, 0.87–5.13). The nested case–control study within this cohort showed no association between styrene exposure and cancer of the respiratory system (Wong, 1990). [The Working Group noted that the strengths of this study were the long follow-up, the high number of cases, the high concentrations of styrene exposure, and the lack of known carcinogenic occupational co-exposures within the industry. Quantitative styrene exposure metrics were applied but information on the exposure assessment was sparse; no styrene intensity information was apparently available for a substantial part of the exposure period, namely between 1948 and 1976, and 27% of the cohort was missing exposure data after 1977.]

Bertke et al. (2018) reported cancer mortality from 1959 to 2016 for 5201 workers employed in two reinforced plastics boatbuilding facilities in Washington State between 1959 and 1978. This was an update of the same population or subsets thereof previously followed up until 1978 (Okun et al., 1985), 1998 (Ruder et al., 2004), and 2011 (Ruder et al., 2016). Full-shift average concentrations of styrene exposure of 42.5 ppm and 71.7 ppm were reported for exposed workers between 1978 and 1979. In the most recent follow-up (Bertke et al., 2018), for those with more than 1 year of employment, many cancer sites showed increased standardized mortality ratios when compared with Washington State expected values, including cancer of the lung (SMR, 1.20; 95% CI, 0.95–1.51) but not cancer of the buccal cavity and pharynx (SMR, 0.49; 95% CI, 0.06–1.78) or breast (SMR, 0.97; 95% CI, 0.32–2.26), lymphatic and haematopoietic malignancies (SMR, 0.85; 95% CI, 0.51–1.35), NHL (SMR, 0.60; 95% CI, 0.19–1.40), or leukaemia (SMR, 0.88; 95% CI, 0.35–1.81).

In internal Cox regression analyses, leukaemia showed increasing mortality with duration of employment in an employment category of high concentration of exposure with a relative risk (RR) estimate of 1.3 (95% CI, 1.0–1.5) per year. Results were also provided for cancers of the lymphoid and haemopoietic tissues (RR, 1.2; 95% CI, 1.0–1.3), NHL (RR, 0.9; 95% CI, 0.2–1.4), and MM (RR, 1.1; 95% CI, 0.6–1.5). Decreasing mortality with duration was observed for cancer of the lung (RR, 0.9; 95% CI, 0.7–1.0), but not for cancer of the kidney (RR, 1.1; 95% CI, 0.7–1.3). [The strengths of this study were the high concentrations of styrene exposure, the few competing risk factors, and the long follow-up. Limitations

were the lack of quantitative styrene exposure and information on smoking.]

Ruder & Bertke (2017) studied the incidence of cancer during 1991–2007 among 3704 workers of the Washington cohort who were living in Washington State by 1991, with no restriction on duration of employment, using data from the Washington State cancer registry and applying statistical methods as for the mortality analyses (Ruder et al., 2016). Elevated standardized incidence ratios (SIRs) for lung cancer were observed for the total population (SIR, 1.11; 95% CI, 0.89–1.37) and for workers potentially exposed to high concentrations of styrene (SIR, 1.42; 95% CI, 1.00–1.95). For all workers and for those exposed to styrene at high concentrations, standardized incidence ratios for cancers of the lymphoid and haematopoietic tissues were 1.03 (95% CI, 0.77–1.35) and 0.99 (95% CI, 0.59–1.57); for cancer of the urinary organ, 1.00 (95% CI, 0.75–1.32) and 1.17 (95% CI, 0.70–1.82); and for cancer of the breast, 0.81 (95% CI, 0.50–1.23) and 0.88 (95% CI, 0.49–1.45), respectively. [The Working Group noted that the cancer incidence data were a strength, and the limited time period coverage of this outcome information was a limitation. Other quality aspects were as for Bertke et al. (2018).]

Kogevinas et al. (1994) reported cancer mortality among 40 688 employees of 660 plants in Denmark (15 867), Finland (2085), Italy (7256), Norway (2035), Sweden (3667), and the United Kingdom (9778). Cancer mortality of the United Kingdom subset followed up until 2012 was also reported by Coggon et al. (2015), and cancer incidence for the Danish subset until 2012 was also reported by Christensen et al. (2017, 2018) and Nissen et al. (2018). The follow-up periods started between 1945 (UK) and 1970 (Denmark) and ended between 1987 (Sweden) and 1991 (Norway).

From job titles recorded on individual payroll records, the pooled population was categorized as laminators (n = 10 629), workers with unspecified tasks (n = 19 408), other exposed workers with bystander exposure (n = 5406), workers not exposed to styrene (n = 4044), and workers with unknown job titles (n = 1201) (Kogevinas et al., 1994). An exposure matrix was constructed from 16 500 personal styrene measurements obtained between 1955 and 1990, and from 18 500 measurements of styrene metabolites in urine sampled in the 1980s. Styrene exposure levels recorded among laminators declined from about 200 ppm before 1965 to less than 80 ppm in the 1980s.

Among all workers, the overall cancer mortality (SMR, 0.87; 95% CI, 0.81–0.94) was lower than that for the European reference population. Standardized mortality ratios of 1.0 or more were observed for cancer of the larynx (SMR, 1.11; 95% CI, 0.53–2.05) and myeloid leukaemia (SMR, 1.10; 95% CI, 0.63–1.79). No increased mortality was observed for other cancer sites of primary interest.

In internal analyses, no increasing mortality with increasing cumulative styrene exposure was observed for cancer of the lung, all lymphohaematopoietic malignancies, or leukaemia. Relative risks of between 1.64 (95% CI, 0.34–7.82) and 2.99 (95% CI, 0.82–10.91) were seen for HL and NHL combined, but there was no linear trend (P value, 0.52). Mortality increased with increasing latency; for 20 years or more since first exposure, the relative risk for lymphohaematopoietic malignancies was 3.97 (95% CI, 1.30–12.13; P value for trend, 0.012), for leukaemia was 3.71 (95% CI, 0.70–20.59; P value for trend, 0.094), and for HL and NHL combined was 5.16 (95% CI, 0.90–29.47; P value for trend, 0.072). Mortality increased statistically significantly with increasing average styrene exposure for lymphohaematopoietic malignancies (P value for trend, 0.019) and for HL and NHL combined (P value for trend, 0.52), but not for leukaemia (P value for trend, 0.47). For average styrene exposure at 200 ppm or more, the relative risk for all lymphohaematopoietic malignancies was 3.59 (95% CI, 0.98–13.14), for HL and NHL combined

was 4.40 (95% CI, 0.42–45.99), and for leukaemia was 2.16 (95% CI, 0.29–16.24; *P* value for trend, 0.47). Increasing mortality by cumulative styrene exposure was suggested for cumulative exposure of 500 ppm-years or more for cancer of the pancreas (RR, 2.56; 95% CI, 0.90–7.31; *P* value for trend, 0.068) and kidney (RR, 6.04; 95% CI, 0.74–49.45; *P* value for trend, 0.12). No significant trend was seen for cancer of the oesophagus or lung. [The Working Group noted that the large European study population, characterized by quantitative measures of styrene exposure, was a strength of this study. The study was limited by the short follow-up (average, 13 years) and lack of smoking information.]

Loomis et al. (2019) reanalysed the European cohort (Kogevinas et al., 1994) with no additional follow-up, while also excluding data from Norway due to new national privacy protection legislation. Lymphomas and leukaemias were regrouped to approximate current World Health Organization classification. Lymphosarcoma and reticulosarcoma (ICD-8, ICD-9 codes 200), other malignant neoplasms of lymphoid and histiocytic tissue (202), CLL (204.1), and MM (203) were aggregated under the heading of NHL. Internal adjusted analyses showed a relative risk of 2.31 (95% CI, 1.29–4.12) per 100 ppm mean styrene exposure for NHL with a zero lag, but not with cumulative exposure. For AML and CML combined, the relative risk was 1.50 (95% CI, 0.71–3.17) when a 10-year lag was applied. An association between mean styrene exposure as well as cumulative exposure, lagged by 20 years, and cancer of the oesophagus was reported. [The Working Group noted that a strength of this study was the internal analyses by quantitative measures of styrene exposure. Other quality aspects were as for Kogevinas et al. (1994).]

Coggon et al. (2015) studied cancer mortality of 7970 workers employed in eight reinforced plastics companies in the United Kingdom between 1946 and 1984, and followed up until 2012. This was an update of an original study of 7949 workers employed in the same companies during 1947–1984 and followed up until 1984 (Coggon et al., 1987). Follow-up of this population until 1990 was included in the study by Kogevinas et al. (1994).

From personnel records, workers were classified into four concentrations of styrene exposure: high (laminators, 44%); moderate (regular bystander exposure, 7%); low (occasional bystander exposure, 17%); or background exposure (all other jobs, including employment for which job title was missing, 32%) (Coggon et al., 1987, 2015). Based on measurements conducted at five of the companies during 1975–1984, the authors estimated that hand laminators were exposed to styrene at 8-hour time-weighted average concentrations of 40–100 ppm, but this information was not used to classify workers in the statistical analyses.

Among all workers, increased standardized mortality ratios of note were reported for cancer of the lung (SMR, 1.20; 95% CI, 1.08–1.34), pharynx (SMR, 1.34; 95% CI, 0.61–2.54), larynx (SMR, 1.70; 95% CI, 0.91–2.91), bladder (SMR, 1.16; 95% CI, 0.82–1.59), and kidney (SMR, 1.33; 95% CI, 0.88–1.92). Subgroup analyses for cancer of the lung yielded a standardized mortality ratio of 1.44 (95% CI, 1.10–1.86) for a category defined by 1 year or more of employment with exposure to a high concentration of styrene.

Internal analyses of a case–control study nested within the study population defining cases by underlying and contributing causes of death and cancer registrations showed doubled odds ratios (OR) for MM, including one of 2.66 (95% CI, 0.62–11.35) for a category defined by 1 year or more of employment with exposure to a high concentration of styrene. No increased occurrence was indicated for HL, NHL including CLL, or leukaemia in the total population or the internal analyses. [The Working Group noted that exposure to a high concentration of styrene, limited exposure to other suspected carcinogens, and the long follow-up were the strengths of this

study. However, the study was limited by a lack of styrene exposure information since 1984, quantitative styrene exposure, or smoking information, and by the high loss to follow-up (11.5%).]

Christensen et al. (2017) studied cancer incidence in 72 292 workers employed during 1964–2007 in 443 small- and medium-sized companies producing reinforced plastics, followed up until 1968–2012. Kolstad et al. (1993) previously studied the incidence of cancer during 1970–1990 for about 64 000 workers of 552 companies with an assumed relevant production and 36 500 male workers of 386 companies with confirmed relevant production (Kolstad et al., 1994, 1995). The workers ever employed in these companies during 1964–2007 were identified in a national pension fund register. Based on a survey conducted in 2013 of current and former employees, the proportion of workers exposed to styrene in each company was computed and workers were classified into four categories of probability of styrene exposure. Sixteen per cent of all person-years at risk was observed in workers employed in companies with a probability of exposure to styrene of 75–100%. A smoking survey showed a slightly lower ever-smoking prevalence with longer duration of employment. The concentrations of exposure to styrene, measured mainly during lamination work, were 180 ppm during 1964–1970, 88 ppm during 1971–1975, and 43 ppm during 1976–1988, corresponding to an annual decline of 7% (Kolstad et al., 1994).

Among all workers in the study by Christensen et al. (2017), estimates of standardized incidence ratios of greater than 1.1 were observed for cancer of the pharynx (SIR, 1.21; 95% CI, 1.03–1.40), oesophagus (SIR, 1.05; 95% CI, 0.89–1.22), nasal cavities (SIR, 1.62; 95% CI, 1.16–2.21), lung (SIR, 1.28; 95% CI, 1.22–1.34), and kidney (SIR, 1.12; 95% CI, 0.98–1.27), and for HL (SIR, 1.21; 95% CI, 0.93–1.54). A decreased risk was observed for cancer of the prostate (SIR, 0.88; 95% CI, 0.83–0.94). The standardized incidence ratios for the other cancer types of priority were not increased.

Subgroup analyses showed lower standardized incidence ratios for cancer of the lung with a longer duration of employment. Standardized incidence ratios for HL and cancer of the sinonasal cavities were higher with one or more of the following factors: longer duration of employment, earlier year of first employment, and higher probability of exposure to styrene. The risks of myeloid leukaemia and cancer of the kidney were higher with longer duration of employment and higher probability of exposure to styrene. A standardized incidence ratio of 1.69 (95% CI, 1.09–2.49) for all leukaemia was observed for those first employed during early years; workers were followed up until 1989 (Kolstad et al., 1994). [The Working Group noted that the strengths of this study were the large study population of workers of small- and medium-sized companies, with expected homogeneous and high-concentration exposure to styrene, and a long and almost complete follow-up. The limitations were the lack of quantitative estimates of exposure to styrene or any information on the prevalence of smoking.]

In a case–control study nested within the cohort, Kolstad et al. (1996) studied the association between exposure to styrene and myeloid leukaemia with clonal chromosome aberrations. The study was based on 12 cases with an identifiable chromosomal analysis (out of 34 cases of myeloid leukaemia in the total study population) and 57 incidence density sampled controls. The classification of exposure was based upon information in Kolstad et al. (1994, 1995). An increased risk (OR, 2.5; 95% CI, 0.2–25.0) was observed for any employment with exposure to styrene; however, the association was stronger for workers employed for less than 1 year (OR, 5.9; 95% CI, 0.5–74.3) than for workers employed for 1 year or longer (OR, 1.1; 95% CI, 0.1–15.3). [The Working Group noted the very small numbers of cases and controls but, considered with the

positive findings for AML in other analyses, this study was found to be relevant for the current evaluation.]

Christensen et al. (2018) analysed the exposure–response relation between cumulative styrene exposure scores and the incidence of 21 different lymphohaematopoietic malignancies and their combinations in an internal analysis of the Danish reinforced plastics industry during 1968–2011. The study population was principally the same as for Christensen et al. (2017), but included an additional 744 workers from 13 companies. Cumulative styrene exposure scores were modelled from 1122 historical measurements of personal styrene exposure intensity, job title, survey data of 11 264 current and former workers, and duration of employment during styrene production. Data were analysed using a discrete time hazard model and spline regression.

The authors observed 50 cases of AML and an increasing risk with increasing cumulative exposure to styrene experienced during the prior 15–29 years (*P* value for trend, 0.01); the adjusted incidence rate ratio was 2.35 (95% CI, 1.21–4.57) for the highest compared with the lowest exposure tertile. Increased incidence was also suggested after styrene exposure experienced at least 30 years earlier, whereas no increased incidence was observed after exposure within the previous 15 years. Increasing incidence with increasing cumulative styrene exposure accrued during the full work history were seen for T-cell lymphoma (*P* value for trend, 0.04); the adjusted incidence rate ratio was 3.21 (95% CI, 0.87–11.77) for the highest compared with the lowest exposure tertile. Increasing incidence with increasing cumulative styrene exposure was also indicated for HL (*P* value for trend, 0.15); the adjusted incidence rate ratio was 1.60 (95% CI, 0.81–2.16) for the highest compared with the lowest exposure tertile. However, the incidence patterns for T-cell lymphoma and HL were inconsistent across the previous 1–14 years, 15–29 years, and 30 years or more exposure windows. No increasing incidences with cumulative exposure were seen for other lymphohaematopoietic malignancies. [The strengths of this study were the large study population of workers from small- and medium-sized companies exposed to high concentrations of styrene, the semiquantitative measures of styrene exposure, the long and almost complete follow-up, the high number of incident cases of 21 different lymphohaematopoietic malignancies, and the analyses of exposure time windows.]

Nissen et al. (2018) analysed the association between exposure to styrene and adenocarcinoma, squamous cell carcinoma, and a category of other histological subtypes of sinonasal cancers in a case–control study nested within the Danish reinforced plastics industry cohort. The study population and assessment of exposure corresponded to that of Christensen et al. (2018). The authors observed 9 cases of sinonasal adenocarcinoma, corresponding to a 5-fold increase in odds ratio, adjusted for age, sex, and whether employed in the wood industry, for high versus low cumulative styrene exposure (OR, 5.11; 95% CI, 0.58–45.12). The increased incidence was confined to exposure during the previous 15 years. No association was seen for the other histological subtypes. [The main strength of this analysis was the specific histological information; however, the study was limited by the small number of cases due to the rarity of the disease and possible residual confounding from exposure to wood dust.]

(b) Synthetic rubber industry

See Table 2.2.

All of the information on workers in the synthetic rubber industry is from cohort studies of the mortality of North American workers in the styrene–butadiene rubber (SBR) industry. According to Matanoski et al. (1990), there were initially 15 plants built in the USA and 1 in Canada in the early 1940s; an additional plant was built in the USA in the 1950s. As of 1977, there were only 10 of these 17 plants still in

Table 2.2 Occupational cohort studies on exposure to styrene in the synthetic rubber industry

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sathiakumar et al. (2005) North America 1944–1998	17 924 men who worked for at least 1 yr before 1 January 1992 in one of eight synthetic rubber plants. Exposure assessment method: records; job/ employment histories	Leukaemia	Employment type			Age, race, calendar period	Strengths: large cohort with long follow-up Limitations: 21% of the cohort were actively employed in 1991, and their exposure estimates would therefore be incomplete after the date; styrene exposure strongly correlated with 1,3-butadiene exposure; no control for smoking Results by job title are also reported for HL, MM, and NHL
			Hourly	63	1.23 (0.94–1.57)		
		NHL	Employment type				
			Hourly	49	1.11 (0.82–1.47)		
		MM	Employment type				
			Hourly	20	0.86 (0.53–1.33)		
		HL	Employment type				
			Hourly	7	0.77 (0.31–1.58)		
		Leukaemia (ALL)	Job title				
			Coagulation	10	2.31 (1.11–4.25)		
			Job title				
			Polymerization	18	2.04 (1.21–3.22)		
			Job title				
			Laboratory jobs	14	3.26 (1.78–5.46)		
			Job title				
			Maintenance labour	15	2.03 (1.14–3.35)		
		All cancers combined	Full cohort	1608	0.92 (0.88–0.97)		
		Lymphatic and haematopoietic	Full cohort	162	1.06 (0.90–1.23)		
		Leukaemia	Full cohort	71	1.16 (0.91–1.47)		
		Pharynx	Full cohort	22	0.47 (0.29–0.71)		
		Oesophagus	Full cohort	44	0.94 (0.68–1.26)		
		Pancreas	Full cohort	76	0.87 (0.68–1.08)		
		Stomach	Full cohort	64	0.85 (0.65–1.08)		
		Larynx	Full cohort	17	0.71 (0.41–1.13)		
		Lung	Full cohort	563	0.91 (0.84–0.99)		
		Prostate	Full cohort	154	1.04 (0.88–1.21)		
		Kidney	Full cohort	39	0.96 (0.68–1.31)		
		Urinary bladder	Full cohort	37	0.90 (0.64–1.25)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Graff et al. (2005) North America 1943–1998	16 579 men who had worked at any of the six study plants for at least 1 yr by the end of 1991 and who were actively working as of a calendar year that varied by plant from 1943 to 1950 Exposure assessment method: expert judgement; quantitative estimates of exposure to styrene, 1,3-butadiene, and DMDTC were developed by identifying, for each work area/job group at each plant, its component tasks and historical changes in tasks; mathematical models were used to calculate job- and time-period-specific exposure estimates to create a JEM that was linked to subjects' work history	NHL (CLL)	Cumulative exposure (ppm-yr)			Age, years since hire	Strengths: large cohort with long follow-up; internal comparisons by exposure level; results attempted to control for confounding by 1,3-butadiene and DMDTC Limitations: styrene exposure strongly correlated with 1,3-butadiene exposure (Spearman rank correlation of 0.79)
			0 to < 8.3	7	1		
			8.3 to < 61.1	11	1.7 (0.7–4.4)		
			≥ 61.1	7	2.6 (0.9–7.3)		
			Cumulative exposure (ppm-yr)			Age, years since hire, 1,3-butadiene, DMDTC	
			0 to < 8.3	7	1		
			8.3 to < 61.1	11	1.2 (0.4–3.7)		
			≥ 61.1	7	0.9 (0.2–3.7)		
		Leukaemia (CML)	Cumulative exposure (ppm-yr)			Age, years since hire	
			0 to < 8.3	4	1		
			8.3 to < 61.1	8	2.1 (0.6–7.1)		
			≥ 61.1	4	2.7 (0.7–10.9)		
			Cumulative exposure (ppm-yr)			Age, years since hire, 1,3-butadiene, DMDTC	
			0 to < 8.3	4	1		
			8.3 to < 61.1	8	1.0 (0.2–4.1)		
			≥ 61.1	4	0.6 (0.1–3.5)		
		Leukaemia (AML)	Cumulative exposure (ppm-yr)			Age, years since hire	
			0 to < 8.3	9	1		
			8.3 to < 61.1	14	1.9 (0.8–4.4)		
			≥ 61.1	3	1.0 (0.3–3.9)		
			Cumulative exposure (ppm-yr)			Age, years since hire, 1,3-butadiene, DMDTC	
			0 to < 8.3	9	1		
			8.3 to < 61.1	14	2.1 (0.8–5.8)		
			≥ 61.1	3	1.1 (0.2–5.6)		
		NHL	Cumulative exposure (ppm-yr)			Age, years since hire	
			0	6	1		
			> 0 to < 8.3	16	1.4 (0.5–3.6)		
			8.3 to < 31.8	11	1.1 (0.4–2.9)		
			31.8 to < 61.1	9	1.5 (0.5–4.2)		
			≥ 61.1	16	2.3 (0.9–5.9)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Graff et al. (2005) (cont.)		NHL	Cumulative exposure (ppm-yr)			Age, years since hire, DMDTC	
			0	6	1		
			> 0 to < 8.3	16	1.4 (0.4–4.9)		
			8.3 to < 31.8	11	1.3 (0.3–5.2)		
			31.8 to < 61.1	9	1.7 (0.4–7.0)		
			≥ 61.1	16	2.3 (0.6–9.2)		
		MM	Cumulative exposure (ppm-yr)			Age, years since hire	
			0	4	1		
			> 0 to < 8.3	10	1.4 (0.4–4.4)		
			8.3 to < 31.8	3	0.5 (0.1–2.1)		
			31.8 to < 61.1	2	0.6 (0.1–3.3)		
			≥ 61.1	8	2.0 (0.6–6.6)		
		MM	Cumulative exposure (ppm-yr)			Age, years since hire, 1,3-butadiene, DMDTC	
			0	4	1		
			> 0 to < 8.3	10	0.8 (0.1–4.6)		
			8.3 to < 31.8	3	0.2 (0.0–1.7)		
			31.8 to < 61.1	2	0.3 (0.0–2.5)		
			≥ 61.1	8	0.8 (0.1–5.7)		
		Leukaemia	Cumulative exposure (ppm-yr)			Age, years since hire	
			0	7	1		
			> 0 to < 8.3	18	1.3 (0.6–3.2)		
			8.3 to < 31.8	19	1.6 (0.7–3.9)		
			31.8 to < 61.1	18	3.0 (1.2–7.1)		
			≥ 61.1	19	2.7 (1.1–6.4)		
			Cumulative exposure (ppm-yr)			Age, years since hire, 1,3-butadiene	
			0	7	1		
			> 0 to < 8.3	18	1.2 (0.4–3.7)		
			8.3 to < 31.8	19	1.4 (0.4–4.5)		
			31.8 to < 61.1	18	1.9 (0.6–6.5)		
			≥ 61.1	19	1.3 (0.4–4.3)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Graff et al. (2005) (cont.)			Cumulative exposure (ppm-yr)			Age, years since hire, 1,3-butadiene, DMDTC	
			0	7	1		
			> 0 to < 8.3	18	0.6 (0.2–2.2)		
			8.3 to < 31.8	19	0.7 (0.2–2.5)		
			31.8 to < 61.1	18	0.8 (0.2–3.1)		
			≥ 61.1	19	0.5 (0.1–2.0)		
Sathiakumar & Delzell (2009) USA and Canada 1943–2002	4863 women who were employed for at least 1 d before the close of cohort ascertainment for the study of male synthetic rubber workers at the same plants (31 December 1991), who had been at work during the period when her plant systematically retained the personnel records of former workers and who had personnel records providing identifying and work history information Exposure assessment method: as for Graff et al. (2005)	All cancers combined	All workers: synthetic rubber	374	0.92 (0.83–1.02)	Race, age, calendar period	Limitations: few exposed women (31%) with lower levels of exposure compared with men (exposed men had 7.6× higher median styrene exposure); styrene exposure strongly correlated with 1,3-butadine exposure; no smoking information
			Ever hourly: synthetic rubber	139	1.01 (0.85–1.19)	As above	
		MM	All workers: synthetic rubber	7	0.89 (0.36–1.83)	As above	
			Ever hourly: synthetic rubber	3	0.91 (0.19–2.67)	As above	
		NHL	All workers: synthetic rubber	15	1.05 (0.59–1.73)	As above	
			Ever hourly: synthetic rubber	7	1.54 (0.62–3.17)	As above	
		Leukaemia	All workers: synthetic rubber	10	0.78 (0.38–1.44)	As above	
			Ever hourly: synthetic rubber	2	0.46 (0.06–1.64)	As above	

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sathiakumar & Delzell (2009) (cont.)		HL	All workers: synthetic rubber	1	0.63 (0.02–3.49)	As above	
			Ever hourly: synthetic rubber	0	0 (0–0)	Not applicable	
		Lymphatic and haematopoietic (all combined)	All workers: synthetic rubber	34	0.95 (0.66–1.33)	Race, age, calendar period	
			Ever hourly: synthetic rubber	12	0.99 (0.51–1.74)	As above	
		Oesophagus	All workers: synthetic rubber	3	0.70 (0.14–2.04)	As above	
			Ever hourly: synthetic rubber	0	0 (0–0)	Not applicable	
		Pancreas	All workers: synthetic rubber	14	0.69 (0.38–1.15)	Race, age, calendar period	
			Ever hourly: synthetic rubber	6	0.80 (0.29–1.73)	As above	
		Larynx	All workers: synthetic rubber	0	0 (0–0)	Not applicable	
			Ever hourly: synthetic rubber	0	0 (0–0)	Not applicable	
		Lung	All workers: synthetic rubber	106	1.14 (0.93–1.38)	Race, age, calendar period	
			Ever hourly: synthetic rubber	47	1.59 (1.17–2.11)	As above	

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sathiakumar & Delzell (2009) (cont.)		Breast	All workers: synthetic rubber	72	0.97 (0.76–1.22)	As above	
			Ever hourly: synthetic rubber	18	0.76 (0.45–1.21)	As above	
		Kidney	All workers: synthetic rubber	2	0.29 (0.04–1.05)	As above	
			Ever hourly: synthetic rubber	0	0 (0–0)	Not applicable	
		Urinary bladder	All workers: synthetic rubber	8	1.74 (0.75–3.43)	Race, age, calendar period	
			Ever hourly: synthetic rubber	6	3.32 (1.22–7.23)	As above	
Sathiakumar et al. (2009) Canada and USA 1943–2002 (women); 1944–1998 (men)	4101 (women) and 15 958 (men); exclusions from the original cohorts were (i) 352 women and 1345 men who worked at two of the eight plants that originally were studied; and (ii) 410 women and 621 men who dropped out of follow-up at ages younger than the youngest lung cancer decedent Exposure assessment method: as for Graff et al. (2005)	Lung	Men ever exposed styrene: synthetic rubber	NR	1.0 (0.76–1.24)	Age, year of birth, race, years since hire, plant, and pay status	Strengths: large cohort and long follow-up; internal comparisons by exposure metrics Limitations: 21% of the cohort were actively employed in 1991 and their exposure estimates would therefore be incomplete after this date; no smoking information; styrene exposure strongly correlated with 1,3-butadiene exposure
		Lung	Women ever exposed styrene: synthetic rubber	NR	1.64 (1.02–2.65)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sathiakumar et al. (2015) North America 1944–2009	16 579 male workers employed before 1 January 1992 for at least 1 yr at any of the six synthetic rubber plants located in Texas, Louisiana, Kentucky, and Canada, and for whom detailed work histories and historical exposure information were available Exposure assessment method: as for Graff et al. (2005)	Leukaemia	0 yr lagged: cumulative exposure to styrene (RR at 25 ppm-yr)			Age, race, year of birth, plant	Strengths: large cohort with long follow-up Limitations: 21% of the cohort were actively employed in 1991, and their exposure estimates would therefore be incomplete after the date; styrene exposure strongly correlated with 1,3-butadiene exposure; no control for smoking
			Log-log at 25 ppm-yr	114	[2.99 (1.46–6.12)]		
			Trend test *P* value, < 0.01				
		NHL	0 yr lagged: cumulative exposure to styrene (RR at 25 ppm-yr)				
			Log-log at 25 yr	89	[1.51 (0.93–2.45)]		
			Trend test *P* value, 0.10				
		MM	0 yr lagged: cumulative exposure to styrene (RR at 25 ppm-yr)				
			at 25 ppm-yr	48	[0.84 (0.66–1.06)]		
			Trend test *P* value, 0.14				

ALL, acute lymphoblastic/lymphocytic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; d, day(s); DMDTC, dimethyldithiocarbamate; HL, Hodgkin lymphoma; JEM, job-exposure matrix; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; ppm, parts per million; RR, relative risk; yr, year(s).

operation. Researchers from the Johns Hopkins School of Hygiene and Public Health established a cohort from eight of these plants (Matanoski & Schwartz, 1987; Matanoski et al., 1990, 1993, 1997; Santos-Burgoa et al., 1992), and researchers from the National Institute for Occupational Safety and Health (NIOSH) established a cohort from the remaining two plants (Meinhardt et al., 1982). In the mid-1990s, researchers from the University of Alabama combined and analysed workers from seven of the eight plants from the Johns Hopkins cohort studies and the two plants from the NIOSH cohort studies (Delzell et al., 1996, 2001; Macaluso et al., 1996; Sathiakumar et al., 1998). The cohort size analysed in these initial studies varied between 13 000 and 17 000, depending on the various inclusion criteria, but all studies were restricted to males employed for at least 1 year in the North American SBR industry between 1943 and 1991, with mortality updated until 1991. More recent studies of this pooled cohort have updated mortality until as late as 2009 (e.g. Sathiakumar et al., 2015), and have begun considering the approximately 5000 women employed for at least 1 day between 1943 and 1991. These more recent studies will be the focus of the remainder of this section.

Macaluso et al. (2004) assigned quantitative estimates of exposure to styrene, as well as the confounder 1,3-butadiene and the stopping agent dimethyldithiocarbamate (DMDTC), by identifying the component tasks, and historical changes in tasks, for each work area and/or job group at each plant. This exposure assessment was restricted to only six of the eight plants since two plants did not contain sufficiently specific work histories; as a result, exposure–response analyses were limited to 16 579 of the original 17 964 men. The results of this exposure assessment estimated that approximately 84% of the male cohort were exposed to styrene with a median exposure of 13 ppm-years and that approximately 77% of the male cohort were exposed to 1,3-butadiene with a median exposure of 54 ppm-years. The correlation coefficient for these two exposures was 0.79 (Graff et al., 2005).

The most recent overall standardized mortality ratio analysis for men (Sathiakumar et al., 2005) contains mortality data until 1998. Although the cohort has been updated until 2009 (Sathiakumar et al., 2015), this later study does not report overall external comparisons (i.e. SMRs) for the full cohort. In the 1998 follow-up of the cohort of 17 924 men, vital status was established for 97% of the cohort and all cancer mortality was lower than expected with 1608 cancer deaths (SMR, 0.92; 95% CI, 0.88–0.97) (Sathiakumar et al., 2005). However, mortality from cancer of the lymphoid and haematopoietic tissues was slightly elevated with 162 deaths (SMR, 1.06; 95% CI, 0.90–1.23), which included 71 leukaemia deaths (SMR, 1.16; 95% CI, 0.91–1.47). Mortality from all leukaemias was significantly elevated among workers who were employed in polymerization (18 deaths; SMR, 2.04; 95% CI, 1.21–3.22), coagulation (10 deaths; SMR, 2.31; 95% CI, 1.11–4.25), maintenance labour (15 deaths; SMR, 2.03; 95% CI, 1.14–3.35), and laboratory jobs (14 deaths; SMR, 3.26; 95% CI, 1.78–5.46), which are jobs the authors note have a high potential for exposure to styrene as well as to 1,3-butadiene. In addition to leukaemia, a slight excess of HL (12 deaths; SMR, 1.11; 95% CI, 0.58–1.95) was observed, whereas mortality from NHL, MM, and cancers of the larynx, oesophagus, stomach, kidney, prostate, pancreas, and bladder was not elevated, with standardized mortality ratios ranging from 0.8 to 1.1. There were significantly fewer deaths from cancer of the lung than expected (563 deaths; SMR, 0.91; 95% CI, 0.84–0.99).

Sathiakumar et al. (2015) updated the mortality of this cohort until 2009 and performed a Cox regression with age as the time scale, and further controlled for race, year of birth, and plant to assess the exposure–response relation between styrene exposure as well as 1,3-butadiene exposure, both as continuous variables, and mortality from leukaemia, NHL, and MM. This study was

restricted to the 16 579 men with calculated individual exposure metrics, and found a significant association between unlagged styrene exposure and risk of mortality from leukaemia (114 cases). [The Working Group used the β coefficients and standard errors reported in the manuscript to calculate a relative risk of 2.99 (95% CI, 1.46–6.12) from exposure to 25 ppm-years compared with 0 ppm-years from the best-fitting model.] A positive relationship was observed between exposure to styrene and risk of mortality from NHL (89 cases). [The Working Group calculated a relative risk of 1.51 (95% CI, 0.93–2.45) from exposure to 25 ppm-years compared with 0 ppm-years from the best-fitting model.] There did not appear to be a relationship between exposure to styrene and risk of mortality from MM (48 cases). [The Working Group calculated a relative risk of 0.84 (95% CI, 0.66–1.06) from exposure to 25 ppm-years compared with 0 ppm-years from the best-fitting model.] [The Working Group noted that no model considered exposure to both styrene and 1,3-butadiene; the study therefore provides no insight into the effect of exposure to styrene independently of exposure to 1,3-butadiene.]

In an earlier publication on this cohort, Graff et al. (2005) modelled exposure to styrene while also controlling for exposure to 1,3-butadiene as well as to DMDTC. This study additionally considered mortality from various subtypes of leukaemia. This earlier report followed up workers until 1998 and performed a Poisson regression, controlling for age and number of years since hire date. This study showed a positive relationship between unlagged styrene exposure and mortality from leukaemia (81 cases); however, this trend decreased when 1,3-butadiene was also added to the model. The increased relative risks for leukaemia without controlling for 1,3-butadiene were 1.0 (referent), 1.3 (95% CI, 0.6–3.2), 1.6 (95% CI, 0.7–3.9), 3.0 (95% CI, 1.2–7.1), and 2.7 (95% CI, 1.1–6.4) at cumulative styrene exposure levels of 0, more than 0 to less than 8.3, 8.3 to less than 31.8, 31.8 to less than 61.1, and 61.1 ppm-years or more, respectively. These relative risks decreased to 1.0 (referent), 1.2 (95% CI, 0.4–3.7), 1.4 (95% CI, 0.4–4.5), 1.9 (95% CI, 0.6–6.5), and 1.3 (95% CI, 0.4–4.3) when cumulative 1,3-butadiene exposure was included in the model. The association between exposure and response effectively disappeared when exposure to DMDTC was also included in the model. The subtypes of leukaemia considered in this study were CLL, AML, and CML. For cumulative styrene exposures of less than 8.3 ppm-years, 8.3 to less than 61.1 ppm-years, and 61.1 ppm-years or more, the relative risks for these analyses, without controlling for 1,3-butadiene or DMDTC, were: 1.0 (reference), 1.7 (95% CI, 0.7–4.4), and 2.6 (95% CI, 0.9–7.3) for CLL; 1.0 (referent), 1.9 (95% CI, 0.8–4.4), and 1.0 (95% CI, 0.3–3.9) for AML; and 1.0 (referent), 2.1 (95% CI, 0.6–7.1), and 2.7 (95% CI, 0.7–10.9) for CML, respectively. Again, with the exception of AML, the relative risks decreased dramatically when models controlled for 1,3-butadiene and DMDTC; the results for AML were largely unchanged after this adjustment, yielding relative risks of 1.0 (referent), 2.1 (95% CI, 0.8–5.8), and 1.1 (95% CI, 0.2–5.6). [For the leukaemia subtype analyses, the only adjusted models presented controlled for DMDTC. The Working Group put more emphasis on the results adjusted for 1,3-butadiene rather than those adjusted for DMDTC. The models that controlled for DMDTC, hypothesized to affect metabolism, may have been overadjusted due to a lack of evidence of the carcinogenicity of DMDTC.]

Sathiakumar & Delzell (2009) were the first to investigate women from this cohort, and considered 4863 women who had worked at a synthetic rubber plant for at least 1 day between 1943 and 1991. Mortality was updated for these women until 2002. Women in this cohort tended to be exposed to styrene at lower concentrations than men, with a median cumulative exposure of 1.9 ppm-years (Sathiakumar et al., 2009). Deaths

from any cancer were lower than expected, with 374 deaths (SMR, 0.92; 95% CI, 0.83–1.02). There was no elevation in overall cancer of the lymphoid and haematopoietic tissues, or for NHL, HL, leukaemia, or MM. The authors noted that those workers ever employed with an hourly payroll designation were most likely to have been exposed to higher concentrations of styrene; among this subcohort, there was a non-significant elevation of NHL with 7 deaths (SMR, 1.54; 95% CI, 0.62–3.17), a significant elevation of cancer of the lung with 47 deaths (SMR, 1.59; 95% CI, 1.17–2.11), and a significant elevation of cancer of the bladder with 6 deaths (SMR, 3.32; 95% CI, 1.22–7.23).

Sathiakumar et al. (2009) further investigated the elevation of risk of cancer of the lung found among women by fitting an exposure–response Cox regression model. The study also extended the analysis of mortality from cancer of the lung to men. Men did not show evidence of an association between exposure to styrene and mortality from cancer of the lung; comparing person-time ever exposed to styrene versus never exposed to styrene provided a relative risk of 1.0 (95% CI, 0.76–1.24). In contrast, women did show an increased risk of cancer of the lung associated with styrene exposure; a comparison of person-time ever exposed to styrene versus never exposed to styrene yielded a relative risk of 1.64 (95% CI, 1.02–2.65). [A limitation of this analysis was the lack of information on smoking as a possible confounder. In addition, the Working Group noted that the different inclusion criteria could have explained the discrepancy in results between men and women. Overall, the strengths of the analyses of this cohort were its size and long follow-up time. A major limitation was the high correlation of exposure to styrene with other confounding exposures, namely 1,3-butadiene, which is classified as Group 1 (*carcinogenic to humans*) as a risk factor for cancers of the haematolymphatic organs. Further, 21% of the cohort were employed at the time of records collection in 1991, with incomplete information on exposure after this date.]

(c) Styrene monomer and polymers industry

See Table 2.3.

Four cohort studies of workers in the styrene monomer and polymers industry were identified. This industry is known to incur exposures to lower concentrations of styrene and has a more stable workforce than for the reinforced plastics industry, which has a high proportion of short-term workers. Three of these studies only resulted in a single publication each with no follow-up papers; the fourth study resulted in an initial paper (Ott et al., 1980) and a later follow-up (Bond et al., 1992). The most recent paper was published 25 years ago, and no new papers have been published since styrene was first considered by an IARC Working Group. All of the papers, except for the Nicholson et al. (1978) paper, were included in the previous *IARC Monograph* published in 2002.

The most informative cohort study was the largest, which comprised 2904 male workers who were employed for at least 1 year at one of four plants in the USA where styrene-based products were being developed and produced. The cohort members were identified from census lists of employees starting work from 1937, and mortality was followed up from 1940 to 1 January 1976 (Ott et al., 1980). Bond et al. (1992) extended the follow-up of this cohort by 11 years to the end of 1986, by which time the average follow-up was 31 years. The level of exposure to styrene varied by process; an industrial hygienist assigned all manufacturing jobs an exposure intensity with respect to five chemical exposures (e.g. styrene, 1–4 ppm or ≥ 5 pm). Other chemicals that workers were exposed to at the plants included benzene, acrylonitrile, 1,3-butadiene, ethylbenzene, dyes, and pigments.

Bond et al. (1992) found that overall mortality from cancer for the whole cohort was significantly reduced (162 observed deaths; SMR, 0.81;

Table 2.3 Occupational cohort studies on exposure to styrene in the styrene monomer and polymers industries

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bond et al. (1992) USA 1937–1986	2904 male workers who were potentially exposed to styrene and related materials for 1 yr or more during 1937–1971 Exposure assessment method: records	Leukaemia	All workers: styrene production	9	1.18 (0.54–2.24)	Age, calendar year	Strengths: long follow-up Limitations: small number of deaths; multiple exposures
		Lymphatic and haematopoietic (all)	All workers: styrene production	28	1.44 (0.95–2.08)		
		HL	All workers: styrene production	5	2.22 (0.71–5.18)		
		MM	All workers: styrene production	7	1.84 (0.74–3.80)		
		NHL	All workers: styrene production	7	1.17 (0.47–2.40)		
		Lymphoma (type not specified)	All workers: styrene monomer and finishing	5	1.28		
			Polymerization, colouring, and extrusion	16	1.72		
		Oesophagus	All workers: styrene production	3	0.63 (0.13–1.85)		
		Stomach	All workers: styrene production	11	1.27 (0.64–2.28)		
		Pancreas	All workers: styrene production	5	0.49 (0.16–1.13)		
		Larynx	All workers: styrene production	1	NR		
		Lung	All workers: styrene production	56	0.81 (0.61–1.05)		
		Prostate	All workers: styrene production	10	0.85 (0.41–1.57)		
		Kidney	All workers: styrene production	5	0.98 (0.32–2.30)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bond et al. (1992) (cont.)		Urinary bladder	All workers: styrene production	2	NR		
		Lymphatic and haematopoietic (all)	Relative to unexposed workers from non-styrene plant: styrene production	28	1.39 (0.92–2.08)	Age, interval since entry, pay status	
		HL	Relative to unexposed workers from non-styrene plant: styrene production	5	2.43 (0.94–6.28)		
		NHL	Relative to unexposed workers from non-styrene plant: styrene production	7	1.09 (0.48–2.49)		
		MM	Relative to unexposed workers from non-styrene plant: styrene production	7	2.45 (1.07–5.65)		
		Leukaemia	Relative to unexposed workers from non-styrene plant: styrene production	9	1.18 (0.58–2.39)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hodgson & Jones (1985) England 1945–1974	622 men; 131 exposed to styrene among others chemicals in laboratories and 491 with mixed chemical exposures and a specific potential exposure to styrene in the production, polymerization, and manufacture of products Exposure assessment method: records	All cancers combined	All workers: styrene production	10	0.9	Age, calendar year, duration of exposure	No relationship between length of employment in jobs with exposure to styrene and risk of cancer Limitations: small cohort; mixed exposures; no information on smoking status
		Lymphoma (type not specified)	All workers: styrene production	3	[5.40 (1.10–16.0)]	Age, time since first exposure, duration of exposure	
		Lymphohaematopoietic	All workers: styrene production	4	[2.50 (0.67–6.40)]		
		Larynx	All workers: styrene production	3	[6.0 (1.20–1.80)]		
		Lung	All workers: styrene production	5	[1.20 (0.39–2.80)]		
Nicholson et al. (1978) USA 1960–1975	560 male workers employed for > 5 yr were considered for inclusion in a cohort in which each individual would be followed prospectively from 1 May 1960 or upon attaining his 10th anniversary of employment Exposure assessment method: records	Leukaemia	All workers: styrene production	1	[1.26 (0.03–7.05)]	Age, years since hire	Limitations: small cohort with short follow-up; complex mix of exposures; potential for confounding from co-exposures
		Lung	All workers: styrene production	6	[0.86 (0.32–1.87)]		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Frentzel-Beyme et al. (1978) Germany 1931–1976	1960 workers in styrene and polystyrene manufacture facility; employed for > 1 mo during 1931–1976 Exposure assessment method: records	All cancers combined	All workers: styrene production	12	–	Age, duration of exposure	Strengths: long follow-up Limitations: follow-up incomplete for non-German workers; low statistical power; no individual exposure data; potential for confounding by co-exposures to known carcinogens
		Pancreas	All workers: styrene production	2	–		
		Lung	All workers: styrene production	3	–		

CI, confidence interval; HL, Hodgkin lymphoma; MM, multiple myeloma; mo, month(s); NHL, non-Hodgkin lymphoma; NR, not reported; yr, year(s).

95% CI, 0.69–0.95). An increased, but not statistically significant, standardized mortality ratio was observed for all deaths from cancer of the lymphoid and haematopoietic tissues (28 deaths; SMR, 1.44; 95% CI, 0.95–2.08). This was contributed to by small to moderate non-significant excesses across all types of cancer of the lymphoid and haematopoietic tissues, with the highest for HL (SMR, 2.22; 95% CI, 0.71–5.18), but this was based on only 5 deaths. There were 7 deaths from NHL (SMR, 1.17; 95% CI, 0.47–2.40), 7 deaths from MM (SMR, 1.84; 95% CI, 0.74–3.80), and 9 deaths from leukaemia and aleukaemia (SMR, 1.18; 95% CI, 0.54–2.24). A similar pattern of small to moderate non-statistically significant excesses of deaths from cancer of the lymphoid and haematopoietic tissues was seen for workers with the job titles of "polymerization, colouring, and extrusion" and "styrene monomer and finishing". Further analyses of the deaths from cancer of the lymphoid and haematopoietic tissues by duration of exposure, exposure intensity, and lag periods revealed no clear patterns. [These analyses were limited by the small numbers.]

When unexposed workers from another non-styrene plant were used as the reference group, a statistically significant increase in risk for MM (RR, 2.45; 95% CI, 1.07–5.65) was observed, as well as a small non-significant increase in risk of death from cancer of the lymphoid and haematopoietic tissues (RR, 1.39; 95% CI, 0.92–2.08) and a moderate non-significant increase in risk of death from HL (RR, 2.43; 95% CI, 0.94–6.28). [No analyses were adjusted for other known lymphohaematopoietic carcinogens at these plants, implying that confounding cannot be ruled out as an explanation for the mortality results from cancer of the lymphoid and haematopoietic tissues.]

Cancer of the stomach was the only other cancer type to have an excess of deaths (11) with a standardized mortality ratio of 1.27 (95% CI, 0.64–2.28). No elevated risk was observed for cancer of the lung (56 deaths; SMR, 0.81; 95% CI, 0.61–1.05), kidney (5 deaths; SMR, 0.98; 95% CI, 0.32–2.30), oesophagus (3 deaths; SMR, 0.63; 95% CI, 0.13–1.85), prostate (10 deaths; SMR, 0.85; 95% CI, 0.41–1.57), and pancreas (5 deaths; SMR, 0.49; 95% CI, 0.16–1.13). There were only 2 deaths from cancer of the bladder (no SMR was estimated).

Nicholson et al. (1978) conducted a mortality study of 560 workers who had been employed at a styrene monomer and polymerization plant in the USA for at least 5 years. Workers were followed from 1 May 1960 or from the 10th anniversary of their employment to the end of December 1975. NIOSH measurements in 1974 showed exposure to styrene at concentrations of less than 1 ppm in low-concentration areas and at 5–20 ppm in the high-concentration areas. Workers were also exposed to other chemicals at the plant, including ethylbenzene, toluene, xylene, and benzene; benzene was produced at the plant from 1943 to 1962 to form ethylbenzene, resulting in potentially significant exposure to benzene for longer-term workers in the cohort.

Seventeen deaths from cancer were observed in the cohort during the follow-up period, less than the 21 expected. The numbers of observed (expected) deaths were 6 (6.99) from cancer of the lung, 1 (0.79) from leukaemia, and 1 (1.25) from lymphoma. An analysis by type of employment found that the number of observed cancer deaths was half that of the expected number (4 vs 8.17) for production and polymerization workers in the plant. No analyses were conducted for specific types of cancer death, as numbers were too small. [The Working Group noted that this study had too few cancer deaths to be informative for overall cancer deaths or for deaths from any specific cancer type. There was also potential for confounding by co-exposures to known carcinogens in the plants.]

Frentzel-Beyme et al. (1978) studied 1960 workers engaged in the manufacture of styrene and polystyrene polymers in Germany for longer

than 1 month between 1931 and the end of 1975. The percentage of those workers who were followed up was much lower for non-German workers (29%) than for German workers (93%); however, non-German workers tended to be shorter-term workers, with almost half of them exposed for less than 6 months. Workers were exposed to styrene at concentrations that were generally less than 1 ppm, according to measurements in 1975 and 1976. However, higher concentrations were occasionally recorded and no information was available on concentrations of exposure in earlier years when open systems were used (Thiess & Friedheim, 1978).

A total of 12 deaths from cancer were observed. A higher than expected number of deaths from cancer of the pancreas was observed, but the numbers were small (2 observed vs 0.72 expected) and the excess was not statistically significant. Deaths from cancer of the lung were lower than expected (3 observed vs 5.4 expected). Other analyses by exposure duration and age groups involved too few numbers to be informative. [This study had too few cancer deaths to be informative for overall cancer deaths or for deaths from any specific cancer type. There was also a potential for confounding by co-exposures to known carcinogens in the plants.]

Hodgson & Jones (1985) reported on the mortality of a cohort of 622 men who had worked for at least 1 year in the production, polymerization, and processing of styrene at a chemical site in England between 1945 and 1974. The workers were followed up until the end of 1978. A cohort of 3072 male workers who worked at the same site but were not exposed to styrene was used as a reference group. No concentrations of styrene exposure were available, but the authors stated that the styrene process was enclosed and they believed that the concentrations of exposure were well below 100 ppm, the hygiene standard at the time. Other chemicals that the workers were possibly exposed to at the plant included 1,3-butadiene, acrylonitrile, benzene, dyes, and ethylene oxide.

Ten cancer deaths were observed (10.9 expected) among the workers exposed to styrene (SMR, 0.90; no 95% CI provided). A statistically significant excess of deaths from lymphoma was observed (3 vs 0.56 expected). [Although the standardized mortality ratio was not provided in the Hodgson & Jones (1985) paper, this was calculated for the previous *IARC Monograph* in 2002 as 5.40 (95% CI, 1.10–16.0).]

An analysis of cancer registrations for this cohort until the end of 1981 showed no overall excess of the incidence of cancer, with 22 observed versus 23.7 expected. A total of 4 incident cases of cancer of the lymphoid and haematopoietic tissues was found, with a standardized incidence ratio (calculated for the 2002 *IARC Monograph*) of 2.50 (95% CI, 0.67–6.40). Three of these cases were from lymphoma, which was significantly more than expected (SIR, 3.75; *P* value for trend, 0.047). In addition, 3 incident cases of cancer of the larynx were observed, which was significantly higher than the number expected (SIR, 6.0; 95% CI, 1.20–18.0) (calculated for the 2002 *IARC Monograph*). [This study had too few cancer deaths and cases to be informative for overall cancer or any specific cancer site. There was also a potential for confounding by co-exposures to known carcinogens in the plants.]

2.2.2 General-population cohort studies

There were no population-based cohort studies with information on styrene exposure available to the Working Group.

2.3 Case–control studies

See Table 2.4.

Several case–control studies have investigated the association between workplace exposure to styrene and the risk of various cancers. Cancers of the lymphoid and haematopoietic

Table 2.4 General-population case–control studies on exposure to styrene

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Flodin et al. (1986) Sweden 1977–1982	Cases: 59 incident from medical clinics and a hospital cytology department Controls: 354 from general-population register, matched by sex, age, and parish (n = 236) or randomly selected (n = 118) Exposure assessment method: expert judgement; mailed questionnaire eliciting leisure and occupational activities (17 questions); quantitative assessment (five categories) based on judgement; nine exposures evaluated	Leukaemia (AML, ICD 1965 205.00)	Ever exposed	3	18.9 (1.9–357.0)	Time of diagnosis or selection	Men and women aged 20–70 yr; 0.3% of controls exposed to styrene Limitations: few exposed subjects; low response rate among cases (~50%); eligible patients too ill to participate or deceased excluded (no proxies); self-reported nature of exposure circumstances
Cantor et al. (1995) USA (24 states) 1984–1989	Cases: 29 397 White women and 4112 Black women; from death certificates Controls: 102 955 White women and 14 839 Black women; from death certificates (excluding cancers) Exposure assessment method: records; usual occupation and industry from death certificate; population JEM to assign probability (0–4) and level (0–3) of exposure; JEM constructed from professional judgment based on literature (NIOSH JEM, IMIS-OSHA)	Breast (ICD 174)	White women: probability of exposure			Age, SES (based on occupation on death certificate)	Similar findings for level of exposure after excluding subjects with low probability of exposure; among controls, 4.9% of White women and 2.6% of Black women were exposed to styrene Strengths: large sample Limitations: no adjustment for known breast cancer risk factors; use of death certificates as primary source of information; use of usual occupation; later jobs held may be in higher SES levels; no information on duration and latency
			1	804	1.13 (1.00–1.20)		
			2	527	1.18 (1.10–1.30)		
			3	64	1.38 (1.00–1.90)		
			4	4	NR		
			White women: level of exposure				
			1	807	1.16 (1.10–1.30)		
			2	522	1.13 (1.00–1.30)		
			3	70	1.19 (0.90–1.60)		
			Black women: probability of exposure				
			1	80	1.49 (1.10–2.00)		
			2	61	1.52 (1.10–2.10)		
			3	7	1.32 (0.50–3.30)		
			4	2	NR		
			Black women: level of exposure				
			1	87	1.59 (1.20–2.10)		
			2	63	1.41 (1.00–1.90)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gérin et al. (1998) Montreal, Canada 1979–1986	Cases: 3730 incident cases (15 types), ascertained across hospitals Controls: 1066: 533 population controls from electoral lists and 533 other cancers (excluding lung) Exposure assessment method: expert judgement; lifetime job history from interview; expert-based assessment assigning frequency and intensity of exposure categorized as low, medium, or high exposure (converted to 1, 4, 9 scores); cumulative exposure (product of intensity, frequency, and duration) was expressed as low, medium, and high, defined by cut-points at the 70th and 90th percentile of the distribution among exposed; 294 agents evaluated	NHL (ICD9 200, 202)	Ever exposed	8	2.0 (0.8–4.8)	Age, family income, ethnic group, cigarette smoking, proxy status	Men aged 35–70 yr; other cancers included oesophagus, stomach, pancreas, kidney, melanoma, HL, and lung oat-cell and adenocarcinoma subtypes (< 5 exposed cases); lifetime prevalence of exposure to styrene was 2% with 45% of exposures in the high confidence level Strengths: expert-based assessment; adjustment for several potential confounders Limitations: few exposed subjects
		Colon (ICD9 153) Rectum (ICD9 154)	Ever exposed	11	1.2 (0.6–2.5)	Age, family income, ethnic group, cigarette smoking, proxy status	
			Cumulative exposure				
			Low	4	1.0 (0.3–2.9)		
			Medium/high	5	5.1 (1.4–19.4)		
		Lung (ICD9 162)	Cumulative exposure				
			Low	5	0.3 (0.1–0.9)		
			Medium/high	5	0.9 (0.2–3.3)		
		Lung (SCC)	Ever exposed	6	0.7 (0.3–1.9)	Age, family income, ethnic group, cigarette smoking, proxy status, exposure to arsenic, asbestos, chromium VI, nickel, crystalline silica, beryllium, cadmium, and PAHs	
		Prostate (ICD9 185)	Cumulative exposure			Age, family income, ethnic group, cigarette smoking, proxy status	
			Low	5	1.0 (0.4–2.9)		
			Medium/high	7	5.5 (1.4–21.8)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gérin et al. (1998) (cont.)		Urinary bladder (ICD9 188)	Cumulative exposure Low Medium/high	 9 3	 1.0 (0.4–2.4) 0.7 (0.2–2.6)	Age, family income, ethnic group, cigarette smoking, proxy status, exposure to aromatic amines	
Dumas et al. (2000) Montreal, Canada 1979–1986	Cases: 257 incident cases ascertained across hospitals Controls: 1295 other cancers, excluding lung and adjacent intestinal sites Exposure assessment method: expert judgement; interview with lifetime job history; exposure assessment assigning frequency and intensity of exposure categorized as low, medium, or high exposure; substantial cumulative exposure defined as > 5 yr exposure at medium or high concentration and frequency; 294 agents evaluated	Rectum (ICD9 154)	Cumulative exposure Any level Substantial level	 6 5	 1.7 (0.7–4.5) 3.9 (1.2–12.9)	Age, education, respondent status, cigarette smoking, beer consumption, BMI	Expansion of Gérin et al. (1998) and Siemiatycki (1991); men aged 35–70 yr; results shown are based on cancer controls; analyses were also conducted using a population control series (n = 533); unexposed subjects included possible exposures and exposures only in recent 5 yr; 5-yr lag applied Strengths: expert-based assessment; adjustment for several potential confounders Limitations: few exposed subjects; no information on diet

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Scélo et al. (2004) Europe (Czechia, Hungary, Poland, Romania, Russian Federation, Slovakia, United Kingdom) 1998–2002	Cases: 2861 incident from hospitals and a dispensary Controls: 3118 from hospitals (excluding cancers and tobacco-related diseases) and from population registers (2 centres) Exposure assessment method: expert judgement; lifetime job history (≥1 yr) from interview; expert-based exposure assessment to assign confidence (low, medium, high), intensity (< 5 ppm, 5–50 ppm, > 50 ppm for styrene), and frequency (1–5%, > 5–30%, > 30%); 70 agents evaluated	Lung (NR)	Ever exposed Duration (yr) 1–6 7–14 > 14 Weighted duration (yr) 0.01–0.50 0.51–3.00 > 3.00 Cumulative exposure (ppm-yr) 0.01–2.75 2.76–12.50 > 12.50	51 13 19 19 13 21 17 22 9 20	0.70 (0.42–1.18) 0.98 (0.37–2.61) 0.72 (0.33–1.59) 0.59 (0.26–1.34) 0.67 (0.28–1.56) 1.19 (0.52–2.73) 0.38 (0.13–1.03) 1.15 (0.55–2.41) 0.37 (0.13–1.08) 0.53 (0.20–1.43)	Centre, sex, age, tobacco consumption, vinyl chloride, acrylonitrile, formaldehyde, inorganic pigments in dust	Men (75%) and women (25%); the proportion of ever-exposed controls was 1.5% Strengths: expert-based assessment; high response rates; ability to control for smoking and other potential confounders; several sensitivity analyses (20-yr lag, restricting to exposures with high confidence level) Limitations: few exposed subjects

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Miligi et al. (2006) Italy 1991–1993	Cases: 1135 incident from hospitals or cancer registry Controls: 1246 from general-population demographic or health services files, frequency matched by sex, age group, and area Exposure assessment method: expert judgement; detailed occupational history; assigned probability (low, medium, high) and intensity (very low, low, medium, high) of exposure	NHL (NR)	Intensity			Sex, age, area, education	Men (52%) and women (48%) aged 20–74 yr; subjects with low probability of exposure were excluded; reference category were unexposed to any solvent; duration of exposure also analysed; DLBCL also included (3 exposed cases); associations between styrene exposure and Hodgkin disease not reported; the prevalence of exposure to styrene among controls (NHL series) was 2.2% Strengths: expert-based assessment; relatively high response rates; use of pathologic classification; 20% of cases and uncertain cases reviewed by pathologists for consistency Limitations: few exposed subjects
			Very low/low	9	0.7 (0.3–1.6)		
			Medium/high	14	1.3 (0.6–2.9)		
		NHL (NR)	Duration at medium/high level (yr)				
			≤ 15	9	1.3 (0.5–3.7)		
			> 15	4	NR		
		NHL (SLL/CLL)	Intensity				
			Medium/high	5	1.6 (0.5–5.1)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cocco et al. (2010) Europe (Czech Republic, France, Germany, Ireland, Italy, Spain) 1998–2004	Cases: 2348 incident recruited from hospitals Controls: 2462 from hospitals (excluding cancers and infectious or immunodeficient diseases) except in two countries in which general-population controls used (matched by sex, age group, residence area) Exposure assessment method: expert judgement; lifetime job history (≥1 yr) from interview; expert-based exposure assessment assigning confidence (based on probability of exposure and proportion of exposed workers), intensity (low, medium, high), and frequency (1–5%, > 5–30%, > 30%); 43 agents evaluated	NHL (B-cell lymphoma)	Ever exposed	66	1.6 (1.1–2.3)	Age, sex, education, centre	Epilymph study; men (55%) and women (45%); reference category were unexposed to any solvent; Bonferroni adjustment of estimates for cumulative exposure; duration also analysed; NHL (T-cell) also ascertained (2 exposed cases); prevalence of exposure to styrene in the study population: 2–3% Strengths: expert-based assessment; up-to-date pathological definitions; 20% of cases per centre reviewed by panel of pathologists for consistency; consideration of multiple comparisons Limitations: few exposed subjects; lower response rate (52%) among population controls; Bonferroni adjustment probably too conservative
			Cumulative exposure				
			Low	19	1.3 (0.7–2.4)		
			Medium	30	3.1 (1.6–5.9)		
			High	17	1.0 (0.5–1.9)		
			Trend test *P* value, 0.04				
		HL (NR)	Ever exposed	10	1.1 (0.5–2.3)		
			Cumulative exposure				
			Low	5	0.9 (0.3–2.6)		
			Medium	4	2.1 (0.6–7.0)		
			High	1	0.6 (0.1–4.4)		
			Trend test *P* value, 0.90				
		NHL (DLBCL)	Ever exposed	20	1.5 (0.9–2.5)		
			Cumulative exposure				
			Low	2	0.4 (0.1–1.6)		
			Medium	11	3.5 (1.5–7.8)		
			High	7	1.4 (0.6–3.4)		
			Trend test *P* value, 0.06				
		NHL (follicular)	Ever exposed	11	2.6 (1.3–5.2)		
			Cumulative exposure				
			Low	4	2.5 (0.8–7.7)		
			Medium	5	4.8 (1.7–13.9)		
			High	2	1.2 (0.3–5.3)		
			Trend test *P* value, 0.04				
		NHL (CLL)	Ever exposed	10	1.2 (0.6–2.5)		
			Cumulative exposure				
			Low	2	0.8 (0.2–3.3)		
			Medium	5	2.9 (1.0–8.5)		
			High	3	0.8 (0.2–2.7)		
			Trend test *P* value, 0.65				
		MM (NR)	Ever exposed	6	0.9 (0.4–2.2)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Karami et al. (2011) Central and eastern Europe (Czechia, Poland, Romania, Russian Federation) 1999–2003	Cases: 1097 incident from hospitals Controls: 1476 hospital controls (excluding conditions associated with smoking or genitourinary disorders) Exposure assessment method: expert judgement; lifetime job history (≥1 yr) from interview; expert-based assessment assigning confidence (< 40%, 40–90%, > 90% probability), intensity (low, medium, high), and frequency (1–5%, 5–30%, > 30%); 72 agents evaluated	Kidney (RCC, ICD C64)	Ever exposed Cumulative exposure < median ≥ median	17 NR NR	1.7 (0.8–3.6) 0.6 (0.2–1.7) 6.7 (1.8–24.3)	Age, sex, study centre, BMI, self-reported hypertension, smoking status, family history of cancer	Central and eastern European RCC study; men (62%) and women (38%) aged 20–88 yr; no association with duration or average exposure (not shown) or modification by genetic polymorphisms; 1.2% of controls were ever exposed to styrene Strengths: expert-based assessment; high response rates; ability to control for several potential confounders; several sensitivity analyses including 20-yr lag and restricting to exposures assessed with high confidence Limitations: few exposed subjects; hospital controls may be less representative of the general population

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Heck et al. (2013) California, USA 1990–2007	Cases: 75 incident, children aged < 6 yr from cancer registry Controls: 14 602 population controls from birth records, frequency matched to cases by birth year Exposure assessment method: quantitative measurements; ambient air monitoring stations (n = 39); average exposure levels during pregnancy assigned to subjects living within a 5 km radius of home address or zip code listed on birth certificates; mean styrene exposure, 0.16 (SD, 0.12) ppbV; interquartile range, 0.14 ppbV	Brain: neuroblastoma (ICCC-3 041)	Per interquartile range increase			Birth year, mother's age and race/ethnicity, payment method for prenatal care (as proxy for SES and family income)	Air Pollution and Childhood Cancer study; matching rate of cases to birth registry to obtain address and other variables: 89%; analyses also considered other radii; maternal education and neighbourhood socioeconomic index had little influence on risk estimates Strengths: use of measurements and registry; no recall or selection bias; ability to study associations at several time points Limitations: limited number of cases; no individual exposure estimates; no information on other sources of exposure or on smoking; using home address does not take into account other locations; did not consider moves; use of zip code centroid for some subjects
			Entire pregnancy	48	1.22 (0.84–1.78)		
			First trimester	48	1.05 (0.76–1.43)		
			Second trimester	48	1.10 (0.83–1.47)		
			Third trimester	48	1.10 (0.96–1.26)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Heck et al. (2014) California, USA 1990–2007	Cases: 69 ALL and 46 AML incident children aged < 6 yr from cancer registry Controls: 2994 and 19 209 population controls from birth records, frequency matched to cases by birth year Exposure assessment method: quantitative measurements as in Heck et al. (2013); estimates assigned to subjects living within a 2 km (for ALL) or 6 km (for AML) radius from station	Leukaemia (ALL)	Per interquartile range increase			Birth year; maternal race/ ethnicity, birthplace, and parity; neighbourhood socioeconomic index	Matching rate of cases to birth registry to obtain address and other variables: 89%; sex, urban/ rural area of residence, maternal age, education, and payment method for prenatal care had little influence on risk estimates Strengths: as for Heck et al. (2013) Limitations: as for Heck et al. (2013)
			Entire pregnancy	46	0.87 (0.58–1.32)		
			First trimester	46	0.85 (0.60–1.19)		
			Second trimester	46	0.89 (0.65–1.22)		
			Third trimester	46	1.01 (0.83–1.23)		
			First year of life	36	0.97 (0.57–1.66)		
		Leukaemia (AML)	Per interquartile range increase				
			Entire pregnancy	36	1.38 (0.94–2.03)		
			First trimester	36	1.27 (0.92–1.75)		
			Second trimester	36	1.20 (0.86–1.68)		
			Third trimester	36	1.08 (0.92–1.27)		
			First year of life	21	1.63 (0.93–2.83)		
Heck et al. (2015) California, USA 1990–2007	Cases: 103 incident; children aged < 6 yr from cancer registry Controls: 30 601 population controls from birth records, frequency matched to cases by birth year Exposure assessment method: quantitative measurements as in Heck et al. (2013); estimates assigned to subjects living within a 5-mile radius from station	Eye: retinoblastoma (ICCC3 050)	Per interquartile range increase			Birth year, paternal age, maternal race and birthplace, payment method for prenatal care (as proxy for SES and family income)	Matching rate of cases to birth registry: 89% Strengths: as for Heck et al. (2013) Limitations: as for Heck et al. (2013)
			Entire pregnancy: all tumours	69	1.28 (0.96–1.69)		
			Unilateral tumours	51	1.35 (0.98–1.85)		
			Bilateral tumours	18	1.07 (0.59–1.93)		
			First year of life: all tumours	31	1.64 (1.12–2.39)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
von Ehrenstein et al. (2016) California, USA 1990–2007	Cases: 34 medulloblastoma, 43 PNET, 106 astrocytoma; incident; children aged < 6 yr from cancer registry Controls: 30 569 population controls from birth records, frequency matched to cases by birth year Exposure assessment method: quantitative measurements as in Heck et al. (2013); estimates assigned to subjects living within a 5-mile radius from station	Brain (childhood cancer: PNET, ICD-O 9473)	Per interquartile range increase			Birth year, maternal age, race/ethnicity, education, and birthplace	Matching rate of cases to birth registry: 89%; type of insurance (proxy for SES), rural/urban residence, sex, parity and pre-term birth had little influence on risk estimates Strengths: as for Heck et al. (2013) Limitations: as for Heck et al. (2013)
			Entire pregnancy	29	1.31 (0.88–1.94)		
			First trimester	29	1.31 (0.99–1.73)		
			Second trimester	29	1.24 (0.94–1.64)		
			Third trimester	29	0.99 (0.69–1.43)		
			First year of life	21	1.27 (0.72–2.25)		
		Brain (childhood cancer: medulloblastoma, ICD-O 9470)	Entire pregnancy	25	0.95 (0.56–1.62)		
			First year of life	14	0.96 (0.43–2.14)		
		Brain (childhood cancer: astrocytoma, ICCC3 032)	Entire pregnancy	67	0.73 (0.51–1.04)		
			First year of life	47	0.70 (0.42–1.17)		

ALL, acute lymphoblastic/lymphocytic leukaemia; AML, acute myeloid leukaemia; BMI, body mass index; CI, confidence interval; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; ICCC, International Classification of Childhood Cancer; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; IMIS, Integrated Management Information System; JEM, job-exposure matrix; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OSHA, Occupational Safety and Health Administration; PAH, polycyclic aromatic hydrocarbon; PNET, primitive neuroectodermal tumour; ppbV, parts per billion by volume; ppm, parts per million; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SD, standard deviation; SES, socioeconomic status; SLL, small lymphocytic lymphoma; yr, year(s).

tissues, as well as renal cell carcinoma and cancer of the lung, have received particular attention. The Epilymph study, a multicentre case–control study of lymphoma conducted in six European countries (Czechia, France, Germany, Ireland, Italy, and Spain), included 2348 men and women diagnosed during 1998–2004 (Cocco et al., 2010). Controls (n = 2462) were recruited from hospitals (excluding other cancers, infectious diseases, and immune-deficient diseases), except for in Germany and Italy where general-population controls were used, and frequency matched to cases by age, sex, and residence area. Lifetime occupational histories covering all jobs held for at least 1 year were obtained by interviews and from standardized questionnaires. Experts then coded semiquantitative levels of confidence, intensity, and frequency of exposure to 43 agents for each job. Several meetings were held to evaluate and standardize the exposure assessment between centres. A total of 78 cases (3.3%) and 58 controls (2.4%) were considered ever exposed to styrene. Statistical models did not adjust for occupational co-exposures. However, the potential for confounding by other solvents was limited; for instance, only 12% of subjects exposed to styrene were also exposed to benzene, toluene, or xylene. Increased risk of B-cell NHL (OR, 1.6; 95% CI, 1.1–2.3; 66 exposed cases) and follicular lymphoma (OR, 2.6; 95% CI, 1.3–5.2; 11 exposed cases) was observed for ever exposure to styrene. Analyses by categorical cumulative exposure, which applied a Bonferroni adjustment, found increased risks for exposure to medium concentrations for B-cell (OR, 3.1; 95% CI, 1.6–5.9; 30 exposed cases), diffuse large B-cell (OR, 3.5; 95% CI, 1.5–7.8; 11 exposed cases) and follicular (OR, 4.8; 95% CI, 1.7–13.9; 5 exposed cases) lymphomas. Associations between exposure to styrene and T-cell lymphoma were presented, but based on only 2 exposed cases. The German sample of the Epilymph study was the object of an earlier analysis (Seidler et al., 2007), and is reported here as part of the study by Cocco et al. (2010). [The Working Group noted that the strengths of the study included the expert exposure assessment and the attention to the pathological classification of cases. However, the study was limited by the lower participation rate among controls, the high proportion of hospital controls (42%), and the few exposed cases, especially at high concentrations. Co-exposures such as benzene were not adjusted for, although the overlap in exposure with styrene was small. Applying the Bonferroni corrections was probably too stringent. Information provided on occupations exposed to styrene or on benchmark occupations used to assign intensity of exposure was sparse. Finally, the Working Group noted the unusually high prevalence of exposure (24%) among controls in the German study (Seidler et al., 2007).]

The associations between occupational exposure to solvents and lymphohaematopoietic malignancies have been investigated in a multicentre study conducted in Italy during 1991–1993 (Seniori Costantini et al., 2001, 2008; Miligi et al., 2006). Expert judgement was used to assign the probability and intensity of exposure. Among controls for the NHL analysis, the prevalence of exposure was 2.2%. In the analysis of NHL risk (Miligi et al., 2006) based on 1135 cases and 1246 population controls, the odds ratio for very low or low intensity was 0.7 (95% CI, 0.3–1.6; 9 exposed cases) and for medium or high intensity was 1.3 (95% CI, 0.6–2.9; 14 exposed cases). Among subjects exposed for 15 years or less at medium or high intensity, the odds ratio was 1.3 (95% CI, 0.5–3.7; 9 exposed cases). Associations were also reported for small lymphocytic lymphoma and diffuse NHL, but these were based on only 5 and 3 exposed cases, respectively. Because of the small numbers, no associations were reported between exposure to styrene and risk of HL (Miligi et al., 2006) or risk of leukaemia or MM in a related publication (Seniori Costantini et al., 2008). [The Working Group noted that, although exposure assessment was based on a strong protocol and

the cancer outcomes on a detailed pathological evaluation, only a few subjects of the study were exposed to styrene.]

Flodin et al. (1986) conducted a case–control study including 59 cases of AML and 354 controls in Sweden to assess potential risk factors including radiation, medications, and eight occupational exposures. Cases aged 20–70 years were identified at hospitals in Sweden between 1977 and 1982. Two series of controls were drawn from a population register: one was matched to cases for sex, age (within 5 years), and location, and the other was a random population sample. Information on exposure was obtained from a mailed questionnaire. Exposure status was assigned by judgement. An elevated risk was observed from the 3 cases and 1 control who were exposed to styrene (OR, 18.9; 95% CI, 1.9–357.0). [The Working Group noted the small numbers, the low response rates among cases, and the lack of detail on exposure assessment. The prevalence of exposure to styrene among controls (0.3%) was low. There were no cases and only 3 controls exposed to benzene.]

A population-based case–control study including 3730 histologically confirmed cases of cancer at 15 major sites (excluding leukaemia) in men was conducted in Montreal, Canada. Cases were newly diagnosed in 19 major hospitals between 1979 and 1986, and aged 35–70 years. General-population controls (n = 533) were obtained from electoral lists (Siemiatycki, 1991; Gérin et al., 1998). Exposure to 294 occupational agents was assessed by chemists/hygienists based on history of jobs held, and cases of cancer at each site were compared with those in the rest of the study population. Two percent of subjects were classified as having been ever exposed to styrene. Although they did not necessarily entail exposure to styrene at the highest concentrations, the most common occupations assigned exposure to styrene were firefighters, mechanics and repairmen, and painters not working in construction. Cumulative exposures at low, medium, or high concentrations were computed based on the product of duration, frequency, and concentration of exposure. In single-exposure models, elevated odds ratios for exposure to styrene at medium or high concentrations were found for cancers of the prostate (n = 449) (OR, 5.5; 95% CI, 1.4–21.8; 7 exposed cases) and rectum (n = 257) (OR, 5.1; 95% CI, 1.4–19.4; 5 exposed cases). No statistically significant increase in risk emerged for cancer of the lung (n = 857) (OR, 0.3; 95% CI, 0.1–0.9; 5 cases exposed to low concentration; OR, 0.9; 95% CI, 0.2–3.3; 5 cases exposed to medium or high concentration), NHL (n = 215) (OR, 2.0; 95% CI, 0.8–4.8; 8 ever exposed cases), or HL (n = 54) (OR, 2.4; 95% CI, 0.5–11.6; 2 ever exposed cases) (Gérin et al., 1998). Expanded analyses of cancer of the rectum were conducted by Dumas et al. (2000), yielding an odds ratio for ever exposure to styrene of 1.7 (95% CI, 0.7–4.5; 6 exposed cases). Substantial cumulative exposure was defined as exposure to medium or high concentration, at a medium or high frequency, for more than 5 years. For men exposed to styrene at concentrations referred to as "substantial", the odds ratio for cancer of the rectum was 3.9 (95% CI, 1.2–12.9; 5 exposed cases). Other cancers analysed in the study but not presented here, as there were too few exposed cases or too few other studies reporting on these sites, include those of the colon (n = 497), bladder (n = 484), stomach (n = 251), kidney (n = 177), pancreas (n = 116), and oesophagus (n = 99), as well as melanoma (n = 103). [The Working Group noted that the concentrations of exposure among subjects exposed to styrene were probably much lower than those in the cohort studies. The strengths of the study included the exposure assessment and the adjustment for potential confounders, including occupational co-exposures, for some cancer sites. However, analyses were based on only a few subjects exposed to styrene.]

A multicentre case–control study of renal cell carcinoma was conducted in central and eastern Europe (Czechia, Poland, Romania, and the

Russian Federation), including 1097 confirmed incident cases (648 men and 449 women) aged 20–88 years (Karami et al., 2011). Controls (n = 1476) were recruited from the same participating hospitals as cases, and excluded urological diseases and diseases related to smoking. Lifetime occupational history covering each job held for at least 12 months was collected. Experts assessed exposure to 72 agents for each job using semiquantitative ratings of frequency, intensity, and level of confidence. The prevalence of exposure to styrene was 1.2% among controls. Occupational exposure to styrene was assigned primarily to styrene manufacture operators, tank cleaners and tank operators of copolymer manufacturers, auto body repair workers who used polyester resins, and plastic boat manufacturers who processed unsaturated polyesters. Overall, 31 subjects (17 cases and 14 controls) were ever exposed with an odds ratio of 1.7 (95% CI, 0.8–3.6) for the association with renal cell carcinoma. Relative to a reference group who were not exposed to styrene, a positive association was observed for cumulative exposure at or above the median concentration (OR, 6.7; 95% CI, 1.8–24.3) and a reduced risk (OR, 0.6; 95% CI, 0.2–1.7) was reported for a cumulative exposure lower than the median concentration. No association was found for duration or average exposure. [The Working Group noted that the strengths of this study were the exposure assessment, the adjustment for non-occupational confounders, the exceptionally high response rates, and several sensitivity analyses. However, the study included only a few exposed cases and relied on hospital controls, which may be less representative of the general population. In addition, models were not adjusted for potential occupational confounders such as exposure to trichloroethylene, although a low prevalence would have been expected at the population level.]

Scélo et al. (2004) reported on a case–control study of cancer of the lung covering 16 centres in seven countries (Czechia, Hungary, Poland, Romania, the Russian Federation, Slovakia, and the United Kingdom) and including 2861 incident cases (2205 men and 656 women). Controls (n = 3118) were selected from hospitals (excluding cancers and tobacco-related diseases), except for at two centres where population controls were recruited instead. Lifetime occupational histories including every job held for at least 1 year were collected using questionnaires and interviews. Expert assessment was used to assign semiquantitative indices of frequency, intensity (exposure to styrene at < 5 ppm, 5–50 ppm, > 50 ppm), and confidence of exposure to 70 agents in each job held. The proportion of ever-exposed controls was 1.5%. The odds ratio for the association between ever exposure to styrene and risk of cancer of the lung was 0.70 (95% CI, 0.42–1.18). For tertiles of cumulative exposure to styrene (0.01–2.75 ppm-years, 2.76–12.50 ppm-years, and > 12.50 ppm-years), odds ratios were 1.15 (95% CI, 0.55–2.41), 0.37 (95% CI, 0.13–1.08), and 0.53 (95% CI, 0.20–1.43), respectively. After excluding exposures of low confidence, no associations were observed using lifetime duration and frequency-weighted duration of exposure across several sensitivity analyses. [Although this study benefited from the detailed exposure assessment and the ability to adjust for smoking and other occupational exposures, the Working Group noted that risk estimates were imprecise because of the limited number of exposed cases.]

A case–control study of mortality from cancer of the breast was conducted by Cantor et al. (1995) based on information from a database of death certificates covering 24 states across the USA for the period 1984–1989, and for which occupation and industry codes were assigned to the usual occupation. Cases (n = 33 509) were women with cancer of the breast as the underlying cause of death, and 4 controls per case (n = 117 794) were randomly selected from all non-cancer deaths, frequency matched to cases by age and race. Subjects with a usual occupation

of homemaker (i.e. not in paid employment) were excluded. Semiquantitative indices for the probability and level of exposure to 31 agents were assigned using a JEM based on occupation and industry. Among controls, 4.9% of White women and 2.6% of Black women were assigned an exposure to styrene. Odds ratios for the risk of mortality from cancer of the breast by probability and level of exposure were computed separately by race. Increases in mortality from cancer of the breast were observed for all probability categories and all levels of exposure to styrene for both racial groups. For instance, odds ratios for increasing levels of exposure to styrene were 1.16 (95% CI, 1.10–1.30), 1.13 (95% CI, 1.00–1.30), and 1.19 (95% CI, 0.90–1.60) among White women, and 1.59 (95% CI, 1.20–2.10) and 1.41 (95% CI, 1.00–1.90) among Black women. Risk estimates were higher when women with a low probability of exposure were excluded. [A strength of this study was that it was based on a large sample. However, the use of a population-based JEM likely resulted in substantial misclassification of exposure. Further, the limited information available from death certificates did not allow for other known risk factors for cancer of the breast, the duration of employment, or other jobs held during the lifetime to be taken into account. The Working Group could not exclude potential confounding from well-identified risk factors for cancer of the breast.]

Four case–control studies have also been conducted among children from the general population using the same database, focusing on prenatal and infant exposure to styrene in ambient air. Potential associations between prenatal or early exposure to ambient levels of environmental contaminants and the incidence of several types of cancer among children younger than 6 years were investigated in a registry-based study in California (Heck et al., 2013, 2014, 2015; von Ehrenstein et al., 2016). The types of cancer evaluated included neuroblastoma (n = 75) (Heck et al., 2013), ALL (n = 69) and AML (n = 46) (Heck et al., 2014), retinoblastoma (n = 103) (Heck et al., 2015), and medulloblastoma (n = 34), primitive neuroectodermal tumour (n = 43), and astrocytoma (n = 106) (von Ehrenstein et al., 2016). Cases were identified through the California Cancer Registry for the period 1990–2007 and linked to birth certificate records; population controls (between 2994 and 30 569 depending on the cancer site) were selected from birth certificates and frequency matched to cases by year of birth. Exposure to concentrations of styrene from ambient air recorded by California's network of air monitoring stations were assigned to subjects based on the nearest station and averaged by trimester of pregnancy, total pregnancy period, and first year of life. The average styrene concentration measured by the stations over the period 1990–2007 was 0.159 ppb (Heck et al., 2013). Analyses were restricted to subjects living (at birth) within a set radius from a monitoring station, with a distance varying between 2 km for ALL (Heck et al., 2014) and 5 miles for retinoblastoma (Heck et al., 2015). Exposure to styrene (expressed per increase of one interquartile range of 0.137 ppb) during pregnancy was positively associated with risk of AML (OR, 1.38; 95% CI, 0.94–2.03), as was exposure in the first year of life (OR, 1.63; 95% CI, 0.93–2.83). Corresponding figures for retinoblastoma were 1.28 (95% CI, 0.96–1.69) and 1.64 (95% CI, 1.12–2.39), respectively. For primitive neuroectodermal tumour, elevated risks were observed for an exposure during the first (OR, 1.31; 95% CI, 0.99–1.73) and second (OR, 1.24; 95% CI, 0.94–1.64) trimesters (von Ehrenstein et al., 2016). [The Working Group noted that the strengths of the study included the use of registry information and of measurements made at several time-points, although exposures were not measured at the individual level. However, the study was weakened by the small number of subjects, and assessment of the cancer hazard posed by a single agent was limited by the relatively high correlations of exposure between the

agents. There was no available information on other sources of exposure or on indoor exposure (see Section 1.4.1); indoor exposure could have been higher than outdoor exposure, especially in households with smokers (Adgate et al., 2004). No information was available on maternal smoking. Finally, the use of home addresses only did not consider other locations and moves were not taken into account. Zip code centroids, rather than exact addresses, were used for some subjects.]

2.4 Human cancer evidence synthesis

Several epidemiological studies have reported on styrene exposure and cancer outcomes. Cohort studies have been conducted in three main industries: reinforced plastics, synthetic rubber, and styrene monomer and polymers. Most of the industry studies have studied cancer mortality rather than incidence of cancer; this has implications for the strength of the studies as well as a potential bias towards more aggressive tumours or factors related to access to health care. Several population-based case–control studies are also available; most of these assessed occupational styrene exposure for adult cancers, and a small number assessed the association between styrene in ambient air and childhood cancers.

In assessing the human carcinogenicity of styrene, cohort studies in the reinforced plastics industry were considered to be the most informative. There were indications of a higher prevalence of smoking among short-term workers compared with the general population (Wong, 1990; Boffetta et al., 1998; Christensen et al., 2017; Bertke et al., 2018); for that reason, most emphasis was placed on internal analyses. Workers were exposed to the highest concentrations of styrene in this industry compared with the other industries studied. Other suspected workplace carcinogens, if present, were usually measured at low concentrations. Cancer risk was assessed in five cohorts of workers exposed to styrene in the reinforced plastics industry, including industry-wide studies in Europe (Kogevinas et al., 1994; Loomis et al., 2019), Denmark (Christensen et al., 2017), the United Kingdom (Coggon et al., 2015), and the USA (Collins et al., 2013; Wong, 1990), and a small study of two boatbuilding facilities in Washington State, USA (Ruder et al., 2016; Bertke et al., 2018). There were large partial overlaps with respect to study participants and follow-up periods between the European (Kogevinas et al., 1994; Loomis et al., 2019), Danish (Christensen et al., 2017), and United Kingdom cohorts (Coggon et al., 2015). In contrast to most other studies that only included mortality data, the Danish study (Christensen et al., 2017) (the largest of the industry-wide cohort studies) provided data on the incidence of cancer.

Workers in the synthetic rubber industry were exposed to styrene at average concentrations of about 10–50 times lower than those in the reinforced plastics industry; however, because employment duration was longer in the synthetic rubber industry than in the reinforced plastics industry, cumulative exposure was similar. All of the relevant findings from the synthetic rubber industry come from a large and long-running study of the mortality experience of workers at eight North American factories producing styrene–butadiene rubber (Macaluso et al., 1996; Graff et al., 2005; Sathiakumar et al., 2015). Exposure to styrene was observed to be highly correlated with exposure to butadiene, a known human carcinogen, in the styrene–butadiene rubber cohort.

Exposure to styrene in the styrene monomer and polymer industry was found to be comparable to that in the synthetic rubber industry, but there was also potential for the co-exposure of workers to benzene and butadiene, known human carcinogens. Four mortality cohort studies of workers have been published from this

industry (Frentzel-Beyme et al., 1978; Nicholson et al., 1978; Hodgson & Jones, 1985; Bond et al., 1992), but only the United States mortality study (Bond et al., 1992) of workers in four plants developing and producing styrene-based products was considered to be informative, as the other studies had very few cancer deaths.

General-population studies included seven case–control studies of occupational exposure to styrene and four case–control studies of prenatal and infant exposure to styrene in ambient air. All but one of these studies evaluated the incidence of cancer as opposed to mortality from cancer. Based on their exposure assessment methods, overall quality, and size, the more informative of these studies assessing occupational exposure to styrene were the Epilymph study of lymphoma (Cocco et al., 2010), a study of cancer of the lung (Scélo et al., 2004), a study of renal cell carcinoma (Karami et al., 2011), and a study of 15 different cancer types in Canada (Gérin et al., 1998).

2.4.1 *All lymphohaematopoietic malignancies*

The classification of lymphohaematopoietic malignancies has changed over time, which makes the comparison of results for subtypes at different time periods difficult to interpret. The overall category of non-Hodgkin lymphoma (NHL) used in older studies corresponds mostly to the category B-cell lymphoma in more recent publications; in addition, chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM) are currently classified as lymphomas. Wherever feasible, the findings discussed in the following sections are based on the current classification.

(a) Non-Hodgkin lymphoma (all types combined)

In the reinforced plastics industry, the risk of mortality from NHL was observed to increase with average concentration of exposure, but not cumulative exposure, to styrene in the large European industry-wide cohort (Loomis et al., 2019). The four other cohort studies within this industry showed no association between exposure to styrene and NHL (Collins et al., 2013; Coggon et al., 2015; Bertke et al., 2018; Christensen et al., 2018).

For workers in the synthetic rubber industry, a positive association between cumulative exposure to styrene and NHL was observed (Graff et al., 2005), with the risk estimated to be 2.3 times higher in the groups exposed to the highest concentrations compared with the groups exposed to the lowest concentrations. The only informative styrene monomer and polymers production industry study from the USA (Bond et al., 1992) showed some evidence of excess mortality from NHL, but this was based on only 7 deaths.

Two population-based studies considered the risk of NHL. An Italian case–control study observed a marginal increase in risk of NHL with exposure to medium and/or high concentrations of styrene (Miligi et al., 2006). In the Canadian case–control study, ever exposure compared with no exposure was associated with a 2-fold increase in risk of NHL, but there was poor precision in this estimate (Gérin et al., 1998).

(b) T-cell lymphoma

In the Danish reinforced plastics industry-wide cohort study, the incidence of T-cell lymphoma was strongly associated with cumulative exposure to styrene; the risk of incidence was more than 3 times higher for workers with a high cumulative exposure compared with those with a low cumulative exposure to styrene, but there was low precision in the risk estimate (Christensen et al., 2018). The Epilymph case–control study reported no association between exposure to styrene and T-cell lymphoma, based on only 2 exposed cases (Cocco et al., 2010).

(c) B-cell lymphoma

In the Danish reinforced plastics industry-wide cohort study, there was no evidence of any association between exposure to styrene and incidence of B-cell, follicular B-cell, or diffuse B-cell lymphoma (Christensen et al., 2018). A decreased incidence of chronic B-cell leukaemia was observed with increasing cumulative exposure to styrene. In the synthetic rubber industry, mortality from CLL increased with increasing cumulative exposure to styrene; the risk was 2.6 times higher for workers with the highest cumulative exposure compared with those with the lowest cumulative exposure.

The Epilymph case–control study reported a strong association between B-cell lymphoma in 66 cases ever exposed to styrene compared with unexposed controls, with additional evidence of a positive exposure–response relationship (Cocco et al., 2010). A positive relationship with cumulative exposure was also suggested for diffuse B-cell and follicular B-cell lymphomas, and for CLL. Compared with unexposed subjects, a marginal increase in small lymphocytic NHL with exposure to styrene at medium and/or high concentrations was observed in an Italian case–control study (Miligi et al., 2006).

The United Kingdom reinforced plastics industry-wide cohort study reported a doubled risk of MM for the group exposed to the highest concentration of styrene versus the lowest, but this was based on only 5 exposed cases (Coggon et al., 2015). A reanalysis of the European cohort suggested an association between mean exposure lagged for 5 years and MM (Loomis et al., 2019). The other cohort studies in this industry showed little evidence of an association between exposure to styrene and MM (Collins et al., 2013; Bertke et al., 2018; Christensen et al., 2018). In the synthetic rubber industry cohort study, no positive association between exposure to styrene and risk of mortality from MM was found (Sathiakumar et al., 2015). The most informative study in the styrene monomer and polymers production industry reported an excess of MM mortality, based on 7 deaths (Bond et al., 1992). The Epilymph study reported no association between exposure to exposure and MM, based on 6 exposed cases (Cocco et al., 2010).

(d) Hodgkin lymphoma

The Danish reinforced plastics industry-wide cohort study showed an elevated incidence of Hodgkin lymphoma (HL) with cumulative exposure to styrene, with an increased risk by a factor of 1.6 for high versus low concentration of exposure (Christensen et al., 2018). The four other cohort studies in this industry showed little or no evidence of an association between exposure to styrene and HL (Kogevinas et al., 1994; Collins et al., 2013; Coggon et al., 2015; Bertke et al., 2018). In the synthetic rubber industry cohort study there were 12 deaths from HL, but no risk estimates were reported (Graff et al., 2005). The only informative cohort study in the styrene monomer and polymers production industry reported some evidence of excess deaths from HL, based on only 5 deaths (Bond et al., 1992). The risk of HL was not elevated with ever exposure to styrene compared with no exposure in the Epilymph study (Cocco et al., 2010).

(e) All leukaemias

The European reinforced plastics industry-wide cohort study found increasing risk of mortality from all leukaemias with time since first exposure, largely based on the Danish data (Kogevinas et al., 1994). The Danish cohort study found an increased incidence during the early years of first exposure, which was considered to be indicative of a high concentration of exposure, but not with duration of employment (Kolstad et al., 1994). The United States boatbuilding cohort study showed a strong association between increasing mortality from all leukaemias and duration of employment in jobs involving exposure to styrene at high concentrations (Bertke et

al., 2018). The remaining two cohort studies in this industry (one based in the United Kingdom, the other in the USA) showed no increasing mortality from all leukaemias with higher cumulative exposure or a longer duration of exposure to styrene, but the findings in the United Kingdom study were based on small numbers and there were limitations in the exposure assessment in the United States industry-wide study (Collins et al., 2013; Coggon et al., 2015).

In the synthetic rubber industry, mortality from all leukaemias was strongly elevated among male workers exposed to styrene at high concentrations compared with the general population and compared with increasing cumulative exposure to styrene within the industry (Graff et al., 2005; Sathiakumar et al., 2005, 2015). The only informative study in the styrene monomer and polymers production industry showed a slightly increased mortality from all leukaemias, but this was based on only 9 deaths (Bond et al., 1992). It should be noted that these analyses of all leukaemias included both lymphoid and myeloid leukaemias. There were no informative findings from the case–control studies for all leukaemias or their subtypes.

(f) Myeloid leukaemias

In the reinforced plastics industry, the most informative study (Danish) showed that the incidence of acute myeloid leukaemia (AML) increased strongly with increasing cumulative exposure to styrene when accounting for a latency period of 15 years (Christensen et al., 2018). This study also found that the incidence of AML for high cumulative exposure to styrene was twice that for low cumulative exposure in the previous 15–29 years. Increased mortality from myeloid (not specifying whether acute or chronic) leukaemia was reported for the highest cumulative exposure to styrene category in the United States industry-wide cohort study when compared with the general population (Collins et al., 2013). There was no overall increased mortality from AML and chronic myeloid leukaemia (CML) combined observed in the reanalysis of the European reinforced plastics industry cohort study, but an increase was observed with mean intensity of exposure in a 10-year lag analysis (Loomis et al., 2019). In the Danish study, no increased incidence of CML was found after exposure to styrene (Christensen et al., 2018). The remaining reinforced plastics industry cohort studies and the only informative study of the styrene monomer and polymers production industry did not report on myeloid leukaemia subtypes (Bond et al., 1992; Kolstad et al., 1994; Coggon et al., 2015; Bertke et al., 2018). There was no clear association between mortality from AML and cumulative exposure to styrene observed in the synthetic rubber industry study (Graff et al., 2005).

Because of some commonalities in cell lineages of origin and in risk factors, the Working Group assessed the pattern of the findings for lymphohaematopoietic malignancies as a whole; it was considered that there was not enough information on specific lymphohaematopoietic malignancies to permit separate conclusions. While noting inconsistent findings across the lymphohaematopoietic malignancies as a whole, the Working Group considered that there was more consistency within specific subtypes, especially for leukaemias and in particular myeloid leukaemia. The Working Group also placed greater weight on the findings of the Danish reinforced plastics industry-wide cohort study because of its large size, the fact that it reported incidence rather than mortality, and the lack of confounding by other occupational carcinogens. However, effect estimates were often small with low precision and many different analyses were undertaken using several different exposure metrics, so chance findings could not be discounted.

2.4.2 Lung

In external analyses of mortality from or incidence of cancer of the lung in the reinforced plastics industry, modest increases were observed in four of the five cohort studies (Collins et al., 2013; Coggon et al., 2015; Christensen et al., 2017; Bertke et al., 2018) (not in the European cohort study) (Kogevinas et al., 1994; Loomis et al., 2019). In internal analyses, mortality from cancer of the lung showed a decreasing trend in two United States studies of boat builders (Collins et al., 2013; Bertke et al., 2018), and a lower incidence in long-term workers than in short-term workers or in the general population in the Danish study (Christensen et al., 2017). No positive trend was reported in the reanalysis of the European study with higher cumulative exposure to styrene or longer duration of employment (Loomis et al., 2019). In the synthetic rubber industry cohort study, results for cancer of the lung were not consistent between workers of different sex in a single study. Confounding by cigarette smoking could not be ruled out. In the styrene monomer and polymers production industry, the only informative cohort study found fewer than expected deaths from cancer of the lung (Bond et al., 1992).

Two case–control studies of cancer of the lung reported no association with exposure to styrene according to various exposure metrics (Scélo et al., 2004; Gérin et al., 1998). Smoking and exposure to many known workplace carcinogens were adjusted for in both studies.

In conclusion, the Working Group attributed more weight to the null findings from the internal analyses that were less likely to be influenced by confounding and lack of direct adjustment for cigarette smoking. The panel also attributed weight to the null findings from the case–control studies in which adjustment for smoking and work co-exposures was performed. The Working Group concluded that these findings do not support an association between incidence of or mortality from cancer of the lung and exposure to styrene.

2.4.3 Sinonasal cavity

The Danish reinforced plastics cohort study, which was the only informative study on cancer of the sinonasal cavity, found an elevated incidence of unspecified cancer of the sinonasal cavity compared with the general population (Christensen et al., 2017). In a follow-up study of the same cohort, a 5-fold increased incidence of adenocarcinoma, adjusted for age, sex, and whether employed in the wood industry, was observed for high versus low cumulative styrene exposure (Nissen et al., 2018); however, this result was based on only 9 cases with resulting low precision. The Working Group noted the high concentration of exposure to styrene in this single study for a very rare cancer, as well as adjustment for other potential confounding factors, and considered this to be a noteworthy result that requires further investigation; however, the possible explanations of chance or confounding by wood dust could not be confidently ruled out.

2.4.4 Kidney

There was a modest increase in mortality from or incidence of cancer of the kidney reported from three (Danish, United Kingdom, and USA) of the five reinforced plastics industry cohort studies (Collins et al., 2013; Coggon et al., 2015; Christensen et al., 2017). One of the cohort studies reported a positive exposure–response relationship (Collins et al., 2013). The initial analyses of the European cohort study showed a positive exposure–response relationship (Kogevinas et al., 1994), but a recent reanalysis using different exposure metrics found no exposure–response relationship (Loomis et al., 2019). The cohort study of United States boat builders (Bertke et al., 2018), the single informative study in the styrene monomer and polymers

production industry (Bond et al., 1992), and the synthetic rubber industry cohort study found no association between exposure to styrene and the incidence of cancer of the kidney (Sathiakumar et al., 2005; Sathiakumar & Delzell, 2009). Based on 17 exposed cases, a European case–control study of renal cell carcinoma found an elevated risk for higher cumulative exposure to styrene, but not with increased duration or average exposure.

The Working Group noted some isolated modest associations and some exposure–response relationships for some exposure metrics for cancer of the kidney; however, considering the lack of consistency in the findings and lack of adjustment in the cohort studies for lifestyle factors (e.g. cigarette smoking) or possible work co-exposures, the Working Group concluded that there was no convincing evidence for an association between exposure to styrene and cancer of the kidney.

2.4.5 Bladder

The United Kingdom reinforced plastics industry-wide cohort study (Coggon et al., 2015) and the study of the two United States boatbuilding facilities reported modest excesses of deaths from cancer of the bladder (Bertke et al., 2018). The other three reinforced plastics industry-wide cohort studies showed no consistent associations (Kogevinas et al., 1994; Collins et al., 2013; Christensen et al., 2017). A synthetic rubber industry study reported a higher than expected number of deaths from cancer of the bladder in women exposed to styrene but not in men (Sathiakumar et al., 2005; Sathiakumar & Delzell, 2009). There was no association between exposure to styrene and cancer of the bladder in the Canadian case–control study, in which risk estimates were adjusted for smoking, and exposure to several non-occupational factors and aromatic amines (Gérin et al., 1998). The Working Group concluded that there was no convincing evidence of an association from these studies; confounding by cigarette smoking in the cohort studies could not be ruled out.

2.4.6 Breast

None of the five reinforced plastics industry cohort studies or the synthetic rubber industry cohort study found an association between exposure to styrene and cancer of the breast (Kogevinas et al., 1994; Sathiakumar & Delzell, 2009; Collins et al., 2013; Coggon et al., 2015; Christensen et al., 2017; Ruder & Bertke, 2017; Bertke et al., 2018). A case–control study of cancer of the breast using death certificates reported elevated risks of cancer of the breast with exposure to styrene among White and Black women (Cantor et al., 1995). However, the study only considered usual job and did not consider duration of exposure or any known risk factors for cancer of the breast. The Working Group therefore concluded that there was no convincing evidence of an association from these studies.

2.4.7 Oesophagus

A reanalysis of the European reinforced plastics industry cohort study found an association between mean styrene exposure, as well as cumulative exposure lagged by 20 years, and cancer of the oesophagus (Loomis et al., 2019). Further, the United States boatbuilding facility study found an excess risk of cancer of the oesophagus with increasing duration of high concentrations of styrene exposure (Bertke et al., 2018). The United Kingdom study also found an excess of cancer of the oesophagus with exposure to styrene (Coggon et al., 2015) but the larger Danish study, based on incidence and not mortality, did not find an excess in the incidence of cancer of the oesophagus (Christensen et al., 2017). In the synthetic rubber industry cohort study there were fewer than expected deaths compared with the reference population (Sathiakumar et al.,

2005). The Working Group concluded that there was no convincing evidence of an association.

2.4.8 Prostate

Two of the smaller studies – the case–control study reporting incidence of cancer of the prostate (Gérin et al., 1998) and the United States boatbuilding facility study assessing mortality from cancer of the prostate (Bertke et al., 2018) – showed positive associations, but the larger Danish and European studies of reinforced plastics workers found no positive association with incidence or mortality (Kogevinas et al., 1994; Christensen et al., 2017; Loomis et al., 2019).

2.4.9 Other cancers

Several other cancers were investigated in relation to styrene exposure, including cancers of the colon, rectum, stomach, pancreas, larynx, pharynx, brain, and central nervous system (including childhood cancers), and melanoma. However, the Working Group concluded that no reliable conclusions could be made either because of the small number of studies reporting results, inconsistencies in the findings, or the use of weak method(s) for assessing exposure to styrene.

3. Cancer in Experimental Animals

3.1 Styrene

3.1.1 Mouse

See Table 3.1.

(a) Transplacental exposure and oral administration (by gavage)

Female O20 or C57BL mice were exposed by gavage to a single dose of styrene (purity, 99%) at 0 (vehicle), 300 (C57BL), or 1350 (O20) mg/kg body weight (bw) in olive oil on gestational day 17 (Ponomarkov & Tomatis, 1978). Male and female progeny were then similarly exposed once per week from weaning for 16 weeks for O20 mice (dosing was stopped at 16 weeks due to toxicity, instead of occurring over the lifespan of the progeny as originally intended) or 120 weeks for C57BL mice. All surviving mice were killed at experimental week 120, although very few O20 mice survived to the end of study. For O20 mice, 6/47 female untreated controls, 0/9 female dams treated with olive oil only, 0/22 female progeny treated with olive oil only, 0/29 female dams exposed to styrene, 0/39 female progeny exposed to styrene, 7/54 male untreated controls, 0/20 male progeny treated with olive oil only, and 0/45 male progeny exposed to styrene survived until week 120. The effective number of animals used for tumour evaluation was the number of survivors in all groups at the time of the first tumour. In male O20 mice progeny, there was a significantly increased incidence of adenoma or adenocarcinoma (combined) of the lung after exposure to styrene compared with male mice progeny given olive oil only ($P < 0.01$). In female O20 mice progeny, there was a significantly increased incidence of adenoma or adenocarcinoma (combined) of the lung after exposure to styrene compared with female mice progeny given olive oil only ($P < 0.01$) and compared with untreated female controls ($P < 0.001$). There was also a significantly increased incidence of adenocarcinoma of the lung in female mice progeny after exposure to styrene compared with female mice progeny given olive oil only [$P < 0.01$]. Tumours appeared at or before week 57 in male O20 mice or week 65 in female O20 mice. For C57BL mice, 19/49 female untreated controls, 3/5 female dams given olive oil only, 4/13 female progeny given olive oil only, 4/15 female dams exposed to styrene, 12/27 female progeny exposed to styrene, 33/51 male untreated controls, 7/12 male progeny given olive oil alone, and 15/27 male progeny exposed to styrene survived until week 120. There were no significant differences in the incidence of tumours of the lung in