

Table 2. 1 Epidemiological studies of exposure to 1,3-butadiene and the risk for lympho-haematopoietic neoplasms

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
<i>Butadiene monomer production</i>								
Ward, E.H. et al. (1995, 1996), USA	364 male workers in three units	Employment in butadiene departments; no benzene or ethylene oxide present	Lymphatic and haematopoietic	Lymphosarcoma and reticulosarcoma (200)	7	SMR 1.8 (0.7–3.6)	Age, time period; county reference rates	All 4 cases of lympho/reticul osarcomas had been employed > 2 years ,3 worked in the rubber reserve plant.
				Leukaemia (204–208)	4	5.8 (1.6–14.8)		
					2	1.2 (0.2–4.4)		
Divine & Hartman (2001), USA	2 800 male workers employed > 6 months in 1943–96	Industrial hygiene sampling data	Lymphohaematopoietic (200–209)	Total cohort	50	SMR 1.4 (1.0–1.9)	Age, time period, age at hire	Update of Downs et al. (1987).
				Employed < 5 years	26	1.6 (1.0–2.3)		
				5–19 years	8	1.2 (0.5–2.4)		
				> 20 years	16	1.3 (0.8–2.2)		
				High exposure < 5 years	20	1.8 (1.1–2.8)		
				> 5 years	14	1.5 (0.8–2.5)		
				First employed 1942–49	46	1.5 (1.1–2.1)		
> 1950	4	0.7 (0.2–1.8)						

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Divine & Hartman (2001) (contd)			Non-Hodgkin lymphoma (200, 202)	Total cohort	19	1.5 (0.9–2.3)			
				Employed					
				< 5 years	12	2.0 (1.0–3.4)			
				5–19 years	3	1.3 (0.2–3.7)			
				> 20 years	4	0.9 (0.2–2.3)			
				High exposure					
				< 5 years	8	1.1 (0.3–2.9)			
			> 5 years	4	1.6 (0.9–2.6)				
			First employed						
			1942–49	17	1.6 (0.9–2.6)				
			> 1950	2	0.9 (0.1–3.2)				
			Leukaemia (204–207)	Total cohort	18	1.3 (0.8–2.0)			
				Employed					
				< 5 years	9	1.4 (0.6–2.6)			
5–19 years	2	0.7 (0.1–2.6)							
> 20 years	7	1.5 (0.6–3.1)							
High exposure									
< 5 years	8	1.9 (0.8–3.7)							
> 5 years	5	1.4 (0.4–3.2)							
First employed									
1942–49	18	1.5 (0.9–2.4)							
> 1950	0	0 (0–178)							

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Tsai et al. (2001), USA	614 male workers	Employed \geq 5 years in butadiene production.	Lymphatic and haematopoietic (200–209)		3	SMR 1.1 (0.3–1.5)	Age, race, calendar year; reference county-specific rates	A concurrent morbidity study failed to show differences in haematological values between butadiene-exposed and unexposed workers within the complex.
<i>Styrene–butadiene rubber (SBR) production</i>								
McMichael et al. (1976), USA	Cohort of 678 male rubber workers	Employment for > 2 years in SBR production based on work histories	All lymphatic and haematopoietic (200–9) Lymphatic leukaemia (204)	All work areas > 5 years in synthetic plant All work areas > 5 years in synthetic plant	51 14	N.A. 6.2 (4.1–12.5) ^a N.A. 3.9 (2.6–8.0) ^a	Age	Update of McMichael et al. (1974).

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Meinhardt et al. (1982), USA	2 756 white men employed for at least 6 months (Plant A, 1 662 men; Plant B, 1 094 men) followed retrospectively 1943-1976	Duration and time of employment	Lymphatic and haematopoietic (200-5)	Plant A, total	9	SMR 1.6	Age, time period, race	
				Plant A, working 1943-45	9	2.1		
			Lymphosarcoma and reticulosarcoma (200)	Plant B, total	2	0.8		
				Plant A, total	3	1.8		
			Leukaemia (204)	Plant A, working 1943-45	3	2.2		
				Plant B, total	1	1.3		
				Plant A, total	5	2.0		
				Plant A, working 1943-45	5	2.8		
				Plant B, total	1	1.0		
			Matanoski et al., 1990 USA and Canada	12110 males who had worked in eight styrene-butadiene manufacturing plants for at least a year, followed from 1943 to 1982	Employment for at least a year	All lymphopoietic (200-208)		
Leukemia (204-208)	Total	22				1.0 (0.6-1.5)		
All lymphopoietic Leukemia	White: (2753 workers)	13				1.1 (0.6-1.9)		
	Black: (371 workers)	6				0.8 (0.2-2.2)		
All lymphopoietic Leukemia		3				5.1 (1.9-11.1)		
						6.6 (1.4-19.1)		

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Delzell et al. (1996), USA and Canada	15649 workers employed for at least 1 year in eight production plants in 1943–91	8 281 unique combinations of work area/job title, grouped in 308 work areas with similar exposure	Lymphosarcoma (200) Other lymphopoietic (202) Leukaemia (204–208)	Five main process groups and seven sub-groups	11	0.8 (0.4–1.4)	Age, race, calendar time	Includes data from cohorts studied by Meinhardt et al. (1982), Matanoski & Schwartz, (1987), Lemen et al. (1990), Matanoski et al. (1990, 1993), and Santos-Burgoa et al. (1992).
				Maintenance	42	1.0 (0.7–1.3)		
				Polymerization	48	1.3 (1.0–1.7)		
				Labour	15	2.5 (1.4–4.1)		
				Laboratories	12	1.1 (0.6–1.9)		
				Ever hourly workers	16	2.2 (1.3–3.6)		
				Worked for > 10 years and hired > 20 years ago	10	4.3 (2.1–7.9)		
					45	1.4 (1.0–1.9)		
	28	2.2 (1.5–3.2)						
Macaluso et al. (1996), USA and Canada	12 412 subjects with exposure to butadiene of 16610 in combined cohorts	Retrospective quantitative estimates of exposure to butadiene, styrene and benzene by work area	Leukaemia (204–208)	<i>Butadiene (ppm-years)</i>		SMR	Age, race, co-exposure to styrene and benzene; Mantel-Haenszel rate ratios adjusted by race, cumulative exposure to styrene	6 of the 8 plant cohorts studied by Delzell et al (1996), Including 7 decedents for whom leukaemia was listed as contributory cause of death
				0	8	0.8		
				< 1	4	0.4		
				1–19	12	1.3		
				20–79	16	1.7		
				> 80	18	2.6		
						Mantel-Haenszel		
				0		1.0		
				< 1		2.0		
				1–19		2.1		
				20–79		2.4		
				> 80		4.5		
<i>p</i> -trend		0.01						

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Matanoski et al. (1997), USA and Canada	Nested case-control study of 58 lymphopoietic cancers and 1242 controls of similar age distribution	Estimated cumulative exposure and average intensity of exposure to butadiene	Hodgkin lymphoma (201) Leukaemia (204-207)	Average intensity of exposure to butadiene, 1 ppm compared with 0 ppm	8 26	1.7 (0.99–3.0) 1.5 (1.1–2.1)	Birth year, age at hire before 1950, race, length of employment	Cases and controls derived from cohort of Matanoski et al., (1990). Update of Santos-Burgoa et al., (1992). Non-Hodgkin lymphoma and multiple myeloma were not associated with exposure to butadiene.
Sathiakumar et al. (1998), USA and Canada	15649 subjects, 11,460 in an hourly job	As Macaluso et al. (1996)	Lymphopoietic system (200-208) Leukemia (204-208) Non-Hodgkin lymphoma (202)	Hourly workers > 10 years worked > 20 years since hire	49 28 15	SMR 1.5 (1.1-2.0) 2.2 (1.5-3.2) 1.4 (0.8–2.3)	Age, race, calendar time	Same cohorts as Delzell et al., (1996) No pattern for non-Hodgkin lymphoma by duration of employment, time since hire, period of hire or process group

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Delzell et al. (2001), USA and Canada	13130 men employed for at least 1 year during 1943–91 at 6 SBR plants	Quantitative estimates based on 8281 unique job title work area combinations. Cumulative exposure estimates for butadiene, styrene and dimethyldithiocarbamate (DMDTC)	Leukaemia (204–208)	<i>Butadiene ppm–years</i>		Poisson regression		Revision of exposure estimates for cohorts studied by Delzell et al (1996)			
				0	7	1.0	Age, years since hire, co-exposure to other agents				
				> 0– < 86.3	17	1.3 (0.4–4.3)					
				86.3– < 362.2	18	1.3 (0.4–4.6)					
				> 362.2	17	2.3 (0.6–8.3)					
				<i>Butadiene ppm–years exposure intensity < 100 ppm</i>							
				0	7	1.0	Age, years since hire				
				> 0– < 37.8	17	1.1 (0.5–2.7)					
				37.8– < 96.3	17	2.8 (1.2–6.8)					
				>96.3	18	3.0 (1.2–7.1)					
				<i>p-trend</i>		0.25					
				<i>Butadiene ppm–years exposure intensity > 100 ppm</i>							
0	7	1.0	Age, years since hire								
> 0– < 46.5	17	2.1 (0.9–5.1)									
46.5– < 234.3	17	2.8 (1.2–6.7)									
> 234.3	18	5.8 (2.4–13.8)									
<i>p-trend</i>		0.01									

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Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments	
Graff et al. (2005), USA and Canada	16579 men working at 6 plants > 1 year by 1991 and followed through 1998	Historical estimation methods by Macaluso et al (2004) with development of cumulative exposure estimates for butadiene, styrene and DMDTC	Leukaemia (204–208)	<i>Butadiene ppm–years</i>		Poisson regression		Age, years since hire, other agents	Update of Delzell et al (2001). SMR analyses with external reference rates (national and state-specific) also conducted and results for leukaemia consistent with those of internal analysis using Poisson regression models.
				0	10	1.0			
				> 0– < 33.7	17	1.4 (0.5–3.9)			
				33.7– < 184.7	18	0.9 (0.3–2.6)			
				184.7– < 425.0	18	2.1 (0.7–6.2)			
				> 425.0	18	3.0 (1.0–9.2)			
				<i>Butadiene ppm–years due to exposure intensities >100ppm</i>					
				0	10	1.0	Age, years since hire, other agents		
				> 0– < 33.7	17	2.8 (1.0-7.7)			
				33.7– < 184.7	18	1.7 (0.6-4.7)			
				184.7– < 425.0	18	3.0 (1.0-8.5)			
				> 425.0	18	3.7 (1.3-11.1)			
		<i>Butadiene ppm–years</i>							
		Chronic lymphocytic leukaemia (204.1)	< 33.7	7	1.0	Age, years since hire, other agents			
			33.7– < 425.0	11	0.9 (0.3–3.0)				
			> 425.0	7	2.7 (0.6–11.2)				
		Chronic myelogenous leukaemia (205.1)	< 33.7	3	1.0	Age, years since hire, other agents			
			33.7– < 425.0	8	2.0 (0.4–11.0)				
			> 425.0	5	7.2 (1.1–47.6)				

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Sathiakumar et al. (2005), USA and Canada	17924 male workers employed >1 year before 1992 followed through 1998	Same as Delzell et al. (1996)	Hodgkin lymphoma (201)	All workers	12	SMR 1.1 (0.6–2.0)	Age, race, calendar period	Companion paper to Graff et al. (2005), based on same cohort	
				Hourly workers	26	1.0 (0.6–1.4)			
				Multiple myeloma (203)	All workers	53			1.0 (0.8–1.3)
				Hourly workers	49	1.1 (0.8–1.5)			
				Non-Hodgkin lymphoma (200, 202)	Hourly workers	71			1.2 (0.9–1.5)
				> 20 years since hire	63	1.2 (0.9–1.6)			
				Leukaemia (204–208)	–10 years worked in:				
				Production	19	2.6 (1.6–4.0)			
				Polymerization	18	2.0 (1.2–3.2)			
				Coagulation	10	2.3 (1.1–4.2)			
				Finishing	19	1.6 (0.9–2.4)			
				Labour maintenance	15	2.0 (1.1–3.4)			
				Laboratories	14	3.3 (1.8–5.5)			
				Chronic lymphocytic leukaemia (204.1)	All workers	16			1.5 (0.9–2.5)
				Hourly workers:					
				Production	15	1.7 (1.0–2.8)			
				Polymerization	8	5.0 (2.1–9.8)			
Coagulation	5	6.1 (2.0–14.2)							
Finishing	7	3.4 (1.4–7.1)							
Labour maintenance	4	3.1 (0.8–7.9)							
Laboratories	4	5.6 (1.5–14.3)							
Chronic myelogenous leukaemia (205.1)	All workers	11	1.7 (0.8–3.0)						
Hourly workers:									
Production	11	2.0 (1.0–3.6)							
Polymerization	2	2.0 (0.2–7.3)							

Elevated SMR also for acute myelogenous leukaemia in Labour maintenance lwork group (5 cases; SMR, 3.0; 95% CI:

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Sathiakumar et al. (2005) Contd.				Coagulation	1	1.9 (0.0-10.5)		1.0–6.9)
				Finishing	2	1.3 (0.1-4.6)		
				Labour	1	1.0 (0.0-5.6)		
				maintenance				
				Laboratories	3	5.2 (1.1-15.3)		
Delzell et al. (2006), USA and Canada	Same as Sathiakumar et al. (2005)	Same as Graff et al. (2005)	Leukaemia	<i>Butadiene ppm–years</i>			Age, years since hire, other agents	A more detailed report of the Graff et al. (2005) and Sathiakumar et al. (2005) studies incorporating a reassessment of records of lymphohematopoietic cancers.
				0	10	1.0		
				> 0– < 33.7	17	1.4 (0.5-3.9)		
				33.7– < 184.7	18	0.9 (0.3-2.6)		
				184.7– < 425.0 □	18	2.1 (0.7-6.2)		
				425.0	18	3.0 (1.0-9.2)		
				<i>Butadiene ppm–years due to concentrations > 100ppm</i>				
				0	10	1.0		
				0–<16.3	17	2.8 (1.0-7.7)		
				16.3–<96.5	18	1.7 (0.6-4.7)		
				96.5–<247.6	18	3.0 (1.0-8.5)		
≥ 247.6	18	3.7 (1.3-11.1)						
							Uncertainty analyses of 1000 alternative data sets of exposure estimates indicated a minimum RR for the highest	

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Delzell et al. (2006) Contd.				<i>Butadiene ppm-years</i>					butadiene exposure quartile of 2.3, a maximum of 4.3, and a mean and medium of 3.3.
				Chronic myelogenous leukaemia (205.1)	<33.7	3	1.0		
					33.7-<425.0	8	2.0 (0.4-10.0)		
					≥ 425.0	5	7.2 (1.1-47.6)		
				Non-Hodgkin lymphoma (200, 202)	0	11	1.0		
					> 0- < 33.7	16	1.0 (0.4-2.6)		
					33.7- < 184.7	10	0.4 (0.1-1.2)		
					184.7- < 425.0	12	0.9 (0.3-2.7)		
					> 425.0	9	0.7 (0.2-2.3)		
				Non-Hodgkin lymphoma and chronic lymphocytic leukaemia (200, 202, 204.1)	0	12	1.0		
					> 0- < 33.7	18	0.9 (0.4-2.1)		
					33.7- < 184.7	14	0.4 (0.2-1.1)		
					184.7- < 425.0	17	1.0 (0.4-2.7)		
> 425.0	14	0.9 (0.3-2.7)							
Multiple myeloma (203)	0	4	1.0						
	> 0- < 33.7	6	1.8 (0.3-10.9)						
	33.7- < 184.7	8	3.7 (0.6-21.6)						
	184.7- < 425.0	2	2.0 (0.2-17.8)						
	> 425.0	7	6.2 (0.9-43.2)						

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Delzell et al. (2006) Contd.			Lymphoid neoplasms (200–204)	0	24	1.0			
				> 0–< 33.7	28	0.9 (0.5–2.0)			
				33.7–< 184.7	25	0.7 (0.3–1.6)			
				184.7–< 425.0	21	1.3 (0.6–3.1)			
				> 425.0	22	1.5 (0.6–3.8)			
				Myeloid neoplasms (205, 206 together)	< 33.7	19	1.0		
					33.7–< 184.7	15	0.8 (0.3–1.7)		
				with erythroleukaemia, myelofibrosis, myelodysplasia, polycythemia vera, myeloproliferative disease)	184.7–< 425.0	11	1.6 (0.6–4.1)		
					> 425.0	11	2.4 (0.9–6.8)		

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Cheng et al. (2007), USA and Canada	Same as Sathiakumar et al. (2005) Analyses based upon 16091 subjects	Same as Graff et al. (2005)	Leukaemia (204–208)	<i>Butadiene ppm-years</i>			Age, year of birth, race, plant, years since hire, DMDTC exposure	Cox regression coefficient (β) 3.0×10^4 for exposure-response SE, 1.4×10^4 , $P = 0.04$	
				0	10	1.0			
				>0-<12.1	7	1.0 (0.4-2.6)			
				12.1-<22.9	7	1.7 (0.6-4.5)			
				22.9-<38.8	7	1.4 (0.5-4.0)			
				38.8-<78.1	7	0.8 (0.3-2.3)			
				78.1-<184.6	7	0.6 (0.2-1.7)			
				184.6-<251.1	7	1.8 (0.6-5.2)			
				251.1-<318.5	7	2.5 (0.8-7.4)			
				318.5-<450.9	7	2.0 (0.6-5.9)			
				450.9-<829.6	7	1.9 (0.6-5.6)			
				≥ 829.6	8	2.6 (0.8-7.7)			
				<i>Butadiene number of peaks</i>					$\beta = 5.6 \times 10^5$ SE 2.4×10^5 , $P = 0.02$
				0	10	1.0			
				>0-<22.8	8	3.6 (1.4-9.2)			
				22.8->241.9	7	1.2 (0.5-3.3)			
				241.9-<295.1	7	8.9 (3.4-23.4)			
				295.1-<434.9	7	4.0 (1.5-10.5)			
				434.9-<985.4	7	1.6 (0.6-4.2)			
				985.4-<1878.9	7	2.3 (0.9-6.1)			
1878.9-<2901.2	7	3.7 (1.4-9.8)							
2901.2-<3837.8	7	6.9 (2.6-18.2)							
3837.8-<5715.5	7	5.8 (2.2-15.2)							
≥ 5715.5	7	4.3 (1.6-11.2)	Lymphoid neoplasms associated with butadiene ppm-years and myeloid neoplasms with butadiene peaks; neither trend significant after adjusting for covariates.						

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Sathiakumar & Delzell (2009), USA and Canada	4863 women working in the same plants as Sathiakumar et al. (2005), followed 1943-2002.	Same as Graff et al. (2005)	All lymphopoietic (200-208)	Total	34	1.0 (0.7-1.3)		Increased risk of lung and bladder cancer also found in ever hourly workers
				Ever hourly	12	1.0 (0.5-1.7)		
			Non-Hodgkin lymphoma (200, 202)	Total	15	1.0 (0.6-1.7)		
				Ever hourly	7	1.5 (0.6-3.2)		
Leukaemia (204-208)	Total	10	0.8 (0.4-1.4)					
	Ever hourly	2	0.5 (0.1-1.6)					
Sathiakumar et al. (2009), USA and Canada	Men and women from Sathiakumar et al. (2005) and Sathiakumar & Delzell (2009),	Same as Graff et al. (2005)	Lung cancer	Women ever exposed to Butadiene	43	2.0 (1.3-3.1)	Age, year of birth, race, years since hire, plant and pay status	After adjustment for exposure to styrene, the RR for women ever having been exposed to butadiene was 4.1 (95%CI 1.3- 12.8). There was a lack of any consistent or monotonically increasing exposure-response trend.
Men ever exposed to Butadiene	434	0.9 (0.7-1.1)						

CI, confidence interval; DMDTC, dimethyldithiocarbamate; ICD, International Classification of Diseases; NR, not reported; SE, standard error; SMR, standardized mortality ratio; TWA, time-weighted average

^a 99.9% confidence interval