Recommendation from the Scientific Committee on Occupational Exposure Limits: Risk assessment for 1,3-butadiene

MAC/3981
61-27

Substance

1,3-butadiene $CH_2 = CH–CH = CH_2$
Synonyms: buta-1,3-diene; diethylene; divinyl; vinylethylene
Einecs No: 203-450-8
EEC No: 601-013-00-X Classification: R 13 Carc Cat. 2: R45
CAS No: 106-99-0
MWt: 54.09
Conversion factor (20 °C, 101 kPa): 2.25 mg/m³ = 1 ppm

Occurrence/use

1,3-butadiene is a colourless gas with a mild aromatic or gasoline-like odour. It has an MPt of – 109 °C, a BPt of – 4.4 °C and a vapour pressure of 248 kPa at 20 °C. The vapour density is 1.9 times that of air, and it is explosive in the range 2.0–11.5 % in air. The odour threshold is about 2 ppm (approx. 4 mg/m³).

Butadiene is a highly reactive material which can polymerise readily, particularly in the presence of oxygen. The principal uses of 1,3-butadiene (BD) are in the manufacture of synthetic rubber such as styrene-butadiene rubber (SBR) or polybutadiene rubber used in tyres and tyre products, thermoplastic resins used in automotive parts and business machines, and styrene-butadiene latex suspensions used in paints and carpet backings. It is also used as a chemical intermediate in the production of neoprene and adiponitrile. Butadiene is a major commodity chemical of the petrochemical industry with a production level within the EU in excess of 1 million tonnes per annum.

Health significance

The main documentation used by the SCOEL in the evaluation of butadiene was a criteria document prepared by Ecetoc (1997).

Butadiene is well-absorbed through the lungs and distributed widely in the body. Metabolic elimination of butadiene is linearly related to ambient exposure concentration up to about 1 000 ppm (2 250 mg/m³) in rats and mice, with mice showing higher elimination rates. The metabolic pathways appear to be saturated above 1 000 ppm (2 250 mg/m³) in rats and mice and above 300 ppm (675 mg/m³) in monkeys (Kreiling et al., 1986, 1987; Sabourin et al., 1992). Butadiene is rapidly metabolised by cytochrome P450-dependent mono-oxygenases to 1,2-epoxy-3-butene, which is further metabolised by three pathways: (i) hydrolysis by epoxide hydrolases to 3-butene-1,2-diol; (ii) further epoxidation to 1,2,3,4-diepoxybutane; (iii) conjugation with glutathione (Malvoisin et al., 1979; Malvoisin and Roberfroid, 1982). According to both *in vitro* and *in vivo* data, the biotransformation appears to be qualitatively similar across species, including humans (Kreuzer et al., 1991; Csanády et al., 1992; Sabourin et al., 1992). However, because of differences in uptake and kinetics, the steady-state blood and tissues levels are quantitatively different. The body burden for 1,2-epoxy-3-butene appears to be up to three times higher for mice than for rats (Kreiling et al., 1986, 1987; Bond et al., 1986; Dahl et al., 1991). *In vivo* data on primates and *in vitro* data on human tissues suggest that humans and other primates are closer to rats than mice with regard to the metabolism of butadiene and resultant body burden of 1,2-epoxy-3-butene (Sabourin et al., 1992).

There have been no reports of skin or eye irritation for butadiene, and it has a low acute and subchronic toxicity. The target organs in mice are the central nervous system and bone marrow. A NOAEL of 625 ppm (1 406 mg/m³) was established following exposure for 6 hrs/day, 5 days/week for 14 weeks (NTP, 1984). Exposure of rats and guinea pigs to butadiene at 0, 600, 2 300 or 6 700 ppm (0, 1 350, 5 175, 15 075 mg/m³), 7.5 hrs/day, 6 days/week for 8 months, resulted in reduced body-weight gain at the top concentration (Carpenter et al., 1944). No effects were reported in animals exposed to 600 or 2 300 ppm (1 350 or 5 175 mg/m³) butadiene.

Fertility studies revealed no adverse effects in guinea pigs, rabbits and rats at exposure concentrations up to 6 700 ppm (15 075 mg/m³) for 8 months (Carpenter et al., 1944). Developmental toxicity studies have shown no effects at exposures below those causing maternal toxicity (Hackett et al., 1987a, b; Irvine, 1981, 1982).

Butadiene has been tested in a wide variety of *in vitro* and *in vivo* genotoxicity assays. It is not genotoxic in the absence of metabolic activation but its epoxide metabolites react with DNA to form alkylation products and inter-strand cross-links (Arce et al., 1990). *In vivo* assays have generally produced positive results in mice and negative results in rats (Cunningham et al., 1986; Jelitto et al., 1989; Tice et al., 1987).

The carcinogenicity of butadiene has been studied in Sprague-Dawley rats (Owen, 1981a, b; Owen, 1987) and in B6C3F1 mice (NTP, 1984; Melnick and Huff, 1992). Butadiene is a potent carcinogen in mice, with tumours found in lungs of females exposed at 6.25 ppm (14.1 mg/m³), 6 hrs/day, 5 days/week for up to 2 years (Melnick and Huff, 1992). This was the lowest concentration tested. At higher concentrations, butadiene produced a dose-related incidence of multiple types of tumours in both sexes, including T-cell lymphoma, haemangiosarcoma, alveolar bronchiolar neoplasms, squamous cell neoplasm, hepatocellular neoplasm and Harderian gland neoplasm. In contrast, in rats exposed to butadiene at 1 000 ppm (2 250 mg/m³) for up to 2 years, a statistically significant increase in tumour incidence was only seen in the mammary gland, the majority of the tumours being benign (Owen and Glaister, 1990). At 8 000 ppm (18 000 mg/m³), tumours were also seen in the pancreas, thyroid and Leydig cells of the testes.

In several studies in mice and rats, reviewed by Himmelstein et al. (1997) and Pacchierotti et al. (1998), a correlation between the levels of the butadiene monoepoxide adduct N-(2-hydroxy-3-butenyl)valine in haemoglobin and the butadiene concentration has been observed (e.g. Osterman-Golkar et al., 1993). The dose–response curve for rats became flatter above 500 ppm (1 125 mg/m³).

This haemoglobin adduct has also been detected in workers (Osterman-Golkar et al., 1993, 1996, Sorsa et al., 1996). Levels were 0.05, 0.16, 0.5 and = 2.6 pmol/g for butadiene exposures of less than 0.5, 5, = 3 and = 3.5 ppm (1.125, 11.25, = 6.75 and = 7.875 mg/m³) respectively. The levels for control persons were below the detection limit of 0.5 pmol/g haemoglobin.

In two workers exposed to butadiene below 3 ppm (6.75 mg/m³), the adduct level of the diepoxide was five times that of the control value and about 70 times that of the monoepoxide adduct (Perez et al., 1997). In rats, the ratio of the diepoxide and monoepoxide adducts ranged from 4 to 26, and the level of the diepoxide adducts was the same after 50 ppm and 500 ppm (112.5 and 1 125 mg/m³) exposure (Perez et al., 1997), which indicates saturation of metabolic formation of the reactant.

Studies of HPRT mutations and chromosomal aberrations in the lymphocytes of persons exposed to butadiene were reviewed by Himmelstein et al. (1997) and Pacchierotti et al. (1998). These yielded contradictory results which may be explained by differences in exposure levels and detection methods.

A number of cancer epidemiology studies on occupational cohorts with exposure to 1,3-butadiene have been conducted. A mortality study of almost 3 000 US workers employed for at least six months, between 1942 and 1994, in the manufacture of 1,3-butadiene was recently updated. All-cancer mortality was not increased (282 deaths, SMR = 0.92, 95 % CI = 0.82–1.04). Lymphohaematopoietic cancers were more prevalent (42 deaths, SMR = 1.47, 95 % CI = 1.06–1.98); 31 of these deaths were in workers employed in operating units, laboratories and maintenance with a potential for highest exposure (SMR = 1.72, 95 % CI = 1.17–2.44). The SMRs for the lymphohaematopoietic cancers had an inverse relation (decreased) with length of employment and duration of employment. No significant increases at any other cancer site were seen (Divine and Hartman, 1996). A smaller cohort of 364 men assigned to 1,3-butadiene production was also studied in the United States. All-cancer mortality was not increased (48 deaths, SMR = 1.05, 95 % CI = 0.78–1.40); lymphatic and haematopoietic cancers showed a non-significant increase (seven deaths, SMR = 1.75, 95 % CI = 0.70–3.61), whereas lymphosarcoma and reticulosarcoma were excessively prevalent among workers with duration of employment > 2 years, even in comparison with local rates (four deaths, SMR = 5.77, 95 % CI = 1.57–14.8). The largest occupational cohort study, recently updated, included some 16 000 men employed for at least one year in eight styrene-butadiene rubber plants in the United States and Canada (Delzell et al., 1996; Sathiakumor et al., 1998). Cancer mortality was lower than expected (950 deaths, SMR = 0.93, 95 % CI = 0.87–0.99). There were 11 lymphosarcoma (SMR = 0.80, 95 % CI = 0.40–1.44) and 42 other lymphatic cancers (SMR = 0.97,

95 % CI = 0.70–1.52). Leukaemia deaths were in excess among 'ever hourly subjects' (45 deaths, SMR = 1.43, 95 % CI = 1.04–1.91), and most clearly after 10 years worked and 20 years since hire (28 deaths, SMR = 2.24, 95 % CI = 1.49–3.23). An analysis of leukaemia mortality by cumulative exposure estimates to styrene (STY), butadiene and benzene was performed in a largely overlapping cohort of workers (Macaluso et al., 1996). A statistically significant trend for leukaemia deaths by cumulative exposure to butadiene, adjusted by age, gender, styrene exposure and race was found (RRs of 1.0, 2.0, 2.1, 2.4, 4.5 for exposure to 0, 0–1, 1–19, 20–80, 80 + ppm-years). No dose-related increases were seen for styrene and benzene cumulative exposure.

Subsequently, the procedures for exposure estimation to 1,3-butadiene and styrene in this cohort were revised, and exposure estimates for sodium dimethylithiocarbamate (DMDTC), used as a shortstop in synthetic rubber polymerisation, and considered by some a possibly relevant confounding factor, were also developed (Delzell et al., 2001). Leukaemia mortality was positively associated with BD ppm-years (RRs of 1.0, 1.2, 2.0 and 3.8 for exposure to 0, 0–86.3, 86.3–362.2, and 362.2 + ppm). A positive association was also seen for STY, but the relation disappeared after controlling for the other two agents. DMDTC was positively associated with leukaemia, even after adjusting for BD and STY. However, no monotonic D-R relation was found (RRs of 1.0, 2.3, 4.9, and 2.9 for 0, 0–566.6, 566.6–1 395.1 and 1 395.1 + mg/m^3).

In 1998, a working group convened by the International Agency for Research on Cancer reviewed and evaluated all the available scientific information and concluded that the evidence regarding carcinogenicity of 1,3-butadiene was sufficient in animal experiments and limited in human epidemiological studies (IARC, 1998). Other data suggested that the metabolism was qualitatively similar in human beings and experimental animals; in mammals, epoxy metabolites of 1,3-butadiene interact with DNA. The overall evaluation was that 1,3-butadiene is probably carcinogenic to humans (category 2A).

The SCOEL agreed that 1,3-butadiene should be considered probably carcinogenic to humans and thus adopted the established approach for carcinogenic substances (see SCOEL key documents). In line with this approach, the risk entailed in working for a lifetime at various average airborne concentrations of 1,3-butadiene was estimated (Zocchetti, 2002) based on data from the recent epidemiological studies in styrene-butadiene rubber industry workers, which included quantitative estimates of exposure to 1,3-butadiene (Delzell et al., 1996 and 2001; Macaluso et al., 1996; Ecetoc, 1997).

Two different methods were used to estimate a risk coefficient (β) per unit of exposure. One was based on an excess relative risk 'linear model' without a threshold. To obtain the risk coefficient per unit of exposure, each observed excess risk (RR or SMR-1) was divided by the associated cumulative exposure. When a set of median cumulative exposures and associated relative risks were available, the risk coefficient per unit exposure was obtained by applying a linear interpolation to the data via Poisson regression techniques. The second method was a 'step model' in which the risk coefficient per exposure unit remains constant in a certain range of exposure and then changes abruptly (step) moving to the next range. Here, ranges of cumulative exposure above 0.0 ppm and associated relative risk estimates were combined with a dummy variable indicating a specific range.

The number of expected deaths from leukaemia in the absence of relevant exposure was estimated in a reference population (England and Wales) with a life-table approach, taking into account the mortality decline that naturally occurs in an ageing population. Assuming that exposure lasts for a working life (40 years, between the ages of 20 and 65), the number of predicted leukaemia deaths associated with different cumulative exposure to 1,3-butadiene were calculated, using the estimated coefficients indicating the excess relative risk for each ppm of cumulative exposure, for a population of 1 000 exposed male workers between the ages of 20 and 85. Predicted and expected deaths were compared, and results expressed as either additional deaths (predicted deaths – expected deaths) or excess SMR (predicted deaths/expected deaths).

The annexed table summarises the results. In the first column, the basic epidemiological data adopted are referenced. In the second column, the RR or SMR and the excess (RR or SMR-1) risk taken from the literature are indicated. In the third column, the cumulative exposure associated in the literature with the reported risk is shown. Then comes the assessment of the number of excess deaths or excess SMR obtained by using different data and methods (single combination of relative risk and cumulative exposure, Poisson model, step model). The 'step model' was considered the most appropriate (Zocchetti, 2002).

Recommendation

1,3-butadiene was tested adequately for carcinogenicity in mice and rats by inhalation. In independent experiments in mice, tumours were induced in both sexes, at multiple sites, at concentrations ranging from 6.25 to 1 250 ppm. Exposure-related increases were observed for numerous cancer types, including heart angiosarcoma, malignant lymphomas, lung alveolar/bronchiolar adenomas and carcinomas, and forestomach papillomas and carcinomas. In one experiment in rats, multiple-site increased tumour incidence was only seen at 8 000 ppm.

The recent updating of the follow-up on a large North American cohort of styrene-butadiene rubber workers revealed a greater than twofold increase in leukaemia mortality among long-term workers, with a significant dose–response relationship to cumulative exposure to butadiene after adjusting for styrene exposure (but not vice-versa). Two smaller cohort studies of butadiene production workers showed slight excesses of lymphohaemopoietic cancers, but these were not considered to be associated with butadiene exposure.

On the basis of the available evidence, the SCOEL agreed that 1,3-butadiene should be treated as a human carcinogen, operating via a genotoxic mechanism. Hence, according to the established approach for such carcinogenic substances, the excess risk entailed in exposure during a working life to various concentrations of butadiene has been calculated using various models; the results produced are illustrated in the annexed table.

As an example of how to read the annexed table, the table below summarises the 'step model' estimates for exposure to 1ppm in the various referenced exposure scenarios.

Exposure estimate	Excess leukaemia deaths for 1 ppm each year of exposure
Table XXIX[b] (Ecetoc, 1997)	4.76
Table XXX[c] (Ecetoc, 1997)	4.76
Table XXX[d] (Ecetoc, 1997)	0.00
Table XXX[e] (Ecetoc, 1997)	2.36
Table XXX[f] (Ecetoc, 1997)	0.95
Table 4 (Macaluso, 1996)	7.01
Table 2, single agent (Delzell et al., 2001)	1.02
Table 2, multiple agents (Delzell et al., 2001)	1.53
Table 2, single agent, BD total peaks > 100 ppm (Delzell et al., 2001)	7.13
Table 2, multiple agents, BD total peaks > 100 ppm (Delzell et al., 2001)	4.59
Table 6, single agent (Delzell et al., 2001)	0.77
Table 6, multiple agents (Delzell et al. 2001)	1.19

From this example, the calculated additional leukaemia risk associated with exposure to 1 ppm 1,3-butadiene over 40 years, according to the 'step model', and using the exposure estimates and their associated RRs reported in the most recent epidemiological study (Delzell et al., 2001), may be illustrated as follows: 'In a population of 1 000 adult males experiencing a mortality rate similar to that of the male population of England and Wales, occupational exposure to 1 ppm of 1,3-butadiene for a working life (40 years between the ages of 25 and 65), will cause from 0.77 to 7.13 extra leukaemia deaths between the ages 20–85 years, in addition to the five leukemia deaths expected to occur in the absence of exposure to 1,3-butadiene.'

No STEL or 'skin' notation was considered necessary.

At the levels discussed, no measurement difficulties are anticipated.

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Summary table

		Data from published literature				NUMBER OF EXCESS LEUKAEMIA DEATHS AND SMR BASED ON RISK ASSESSMENT													
						Exposure (ppm, each year)													
		EXCESS		CUM. EXP.		0.1		0.2		0.5		1		2		5		10	
STUDY	MODEL	RR/SMR	RR/SMR	Median	Range	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR	EXCESS DEATHS	SMR
Table XXIX[b]		1.1	0.1	5.4	0.1–19	0.29	1.06	0.57	1.11	1.42	1.28	2.85	1.56	5.68	2.11	14.12	3.79	27.96	6.58
Ecetoc, 1997		2	1	42.7	20–99	0.36	1.07	0.72	1.14	1.80	1.35	3.60	1.70	7.18	2.41	17.81	4.53	35.18	8.05
		2.1	1.1	134.1	100–199	0.13	1.02	0.25	1.05	0.63	1.12	1.26	1.25	2.52	1.49	6.29	2.23	12.52	3.47
		3.6	2.6	311.9	200+	0.13	1.03	0.26	1.05	0.64	1.13	1.28	1.25	2.56	1.50	6.39	2.25	12.72	3.51
	Poisson [a]					0.06	1.01	0.12	1.02	0.30	1.06	0.60	1.12	1.20	1.23	3.00	1.59	5.98	2.17
	Step					0.51	1.10	0.51	1.10	1.07	1.21	4.76	1.93	4.93	1.97	6.44	2.26	12.57	3.48
Table XXX[c]		1.1	0.1	5.4	0.1–19	0.29	1.06	0.57	1.11	1.42	1.28	2.85	1.56	5.68	2.11	14.12	3.79	27.96	6.58
Ecetoc, 1997		2	1	42.7	20–99	0.36	1.07	0.72	1.14	1.80	1.35	3.60	1.70	7.18	2.41	17.81	4.53	35.18	8.05
		2.4	1.4	134.1	100–199	0.16	1.03	0.32	1.06	0.80	1.16	1.61	1.31	3.21	1.63	7.99	2.57	15.90	4.14
		4.6	3.6	311.9	200+	0.18	1.03	0.36	1.07	0.89	1.17	1.78	1.35	3.55	1.69	8.83	2.74	17.56	4.47
	Poisson [a]					0.07	1.01	0.14	1.03	0.35	1.07	0.71	1.14	1.42	1.28	3.53	1.69	7.05	2.38
	Step					0.51	1.10	0.51	1.10	1.07	1.21	4.76	1.93	4.93	1.97	8.27	2.63	17.26	4.41
Table XXX[d]		1.3	0.3	134.1	100–199	0.03	1.01	0.07	1.01	0.17	1.03	0.34	1.07	0.69	1.13	1.72	1.34	3.44	1.67
Ecetoc 1997		2.5	1.5	311.9	200+	0.07	1.01	0.15	1.03	0.37	1.07	0.74	1.14	1.48	1.29	3.69	1.72	7.37	2.45
	Poisson [a]					0.06	1.01	0.12	1.02	0.29	1.06	0.58	1.11	1.17	1.23	2.92	1.57	5.83	2.14
	Step					0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	2.16	1.42	7.12	2.40
Table XXX[e]		1.5	0.5	42.7	20–99	0.18	1.04	0.36	1.07	0.90	1.18	1.80	1.35	3.60	1.70	8.96	2.76	17.81	4.53
Ecetoc 1997		1.9	0.9	134.1	100–199	0.10	1.02	0.21	1.04	0.52	1.10	1.03	1.20	2.06	1.40	5.15	2.01	10.26	3.02
		3.7	2.7	311.9	200+	0.13	1.03	0.27	1.05	0.67	1.13	1.33	1.26	2.66	1.52	6.63	2.30	13.21	3.61
	Poisson [a]					0.07	1.01	0.14	1.03	0.35	1.07	0.71	1.14	1.42	1.28	3.53	1.69	7.05	2.38
	Step					0.00	1.00	0.00	1.00	0.31	1.06	2.36	1.46	2.46	1.48	5.52	2.08	12.91	3.55
Table XXX[f]		1.2	0.2	42.7	20–99	0.07	1.01	0.14	1.03	0.36	1.07	0.72	1.14	1.44	1.28	3.60	1.70	7.18	2.41
Ecetoc 19971.4		0.4	134.1	100–199	0.05	1.01	0.09	1.02	0.23	1.04	0.46	1.09	0.92	1.18	2.29	1.45	4.58	1.90	
		2.6	1.6	311.9	200+	0.08	1.02	0.16	1.03	0.39	1.08	0.79	1.15	1.58	1.31	3.94	1.77	7.86	2.54
	Poisson [a]					0.06	1.01	0.12	1.02	0.29	1.06	0.58	1.11	1.17	1.23	2.92	1.57	5.83	2.14
	Step					0.00	1.00	0.00	1.00	0.12	1.02	0.95	1.19	0.98	1.19	2.70	1.53	7.64	2.50
Macaluso, 1996		2	1		0–1														
Table 4		2.1	1.1		1–19														
		2.4	1.4		20–79														
		4.5	3.5		80+														
	Step					5.59	2.10	5.60	2.10	5.79	2.14	7.01	2.38	8.37	2.64	17.01	4.36	17.37	4.44

Summary table — continued

Data from published literature

STUDY	MODEL	EXCESS RR/SMR	EXCESS RR/SMR	CUM. EXP. Median	CUM. EXP. Range	NUMBER OF EXCESS LEUKAEMIA DEATHS AND SMR BASED ON RISK ASSESSMENT — Exposure (ppm, each year)											
						0.1 EXCESS DEATHS	0.1 SMR	0.2 EXCESS DEATHS	0.2 SMR	0.5 EXCESS DEATHS	0.5 SMR	1 EXCESS DEATHS	1 SMR	2 EXCESS DEATHS	2 SMR	5 EXCESS DEATHS	5 SMR	10 EXCESS DEATHS	10 SMR
Delzell, 2001		1		0													
Table 2 [g]		1.2	0.2	0	0–86												
BD ppm-Years		2.0	1.0	86	86–362												
Single agent		3.8	2.8		> 362												
	Step					1.02	1.20	1.02	1.20	1.02	1.20	1.02	1.20	1.02	1.20	4.82	1.95	7.38	2.45
Delzell, 2001		1		0													
Table 2 [h]		1.3	0.3	0	0–86												
BD ppm-Years		1.3	0.3	86	86–362												
Multiple agent		2.3	1.3		> 362												
	Step					1.53	1.30	1.53	1.30	1.53	1.30	1.53	1.30	1.53	1.30	1.53	1.30	2.88	1.56
Delzell, 2001		1		0													
Table 2 [g]		2.4	1.4	0	0–426												
BD total peaks > 100 ppm		2.5	1.5	426	426–2 893												
Single agent		5.8	4.8		> 2 893												
	Step					7.13	2.40	7.13	2.40	7.13	2.40	7.13	2.40	7.13	2.40	7.13	2.40	7.13	2.40
Delzell, 2001		1		0													
Table 2 [h]		1.9	0.9	0	0–426												
BD total peaks > 100 ppm		1.4	0.4	426	426–2 893												
Multiple agent		2.7	1.7		>2 893												
	Step					4.59	1.90	4.59	1.90	4.59	1.90	4.59	1.90	4.59	1.90	4.59	1.90	4.59	1.90
Delzell et al.,2001		1		0													
Table 6 [g]		1.1	0.1	0	0–39												
BD ppm-years		1.4	0.4	39	39–124												
Single agent		2.0	1.0	124	124–287												
		2.9	1.9	287	287–642												
		4.7	3.7		> 642												
	Step					0.51	1.10	0.51	1.10	0.51	1.10	0.77	1.15	1.93	1.38	4.40	1.86	7.75	2.52
Delzell et al., 2001		1		0													
Table 6 [h]		1.3	0.3	0	0–39												
BD ppm-years		0.9	-0.1	39	39–124												
Multiple agent		1.0	0.0	124	124–287												
		1.70.7		0287	0287–642												
		3.4	2.4		> 642												
	Step					1.53	1.30	1.53	1.30	1.53	1.30	1.19	1.23	0.00	1.00	0.00	1.00	2.21	1.43

[a] For this model, the reported excess RR/SMR is not taken from the literature but is estimated using Poisson regression analysis, and represents a 1 ppm/year increase in excess RR/SMR.
[b] Adjusted for age, years since hire, calendar year and race, and styrene exposure.
[c] Adjusted for age, years since hire, calendar year and race, not for styrene exposure.
[d] Adjusted for age, years since hire, calendar year and race, and for the cumulative average annual frequency of peak exposure to 100 + ppm 1,3-BD for any period during the performance of a task.
[e] Adjusted for age, years since hire, calendar year and race, and for the cumulative average annual frequency of peak exposure to 500 + ppm 1,3-BD for any period during the performance of a task.
[f] Adjusted for age, years since hire, calendar year and race, and years of definite exposure to 1,3-BD peaks.
[g] Adjusted for age, years since hire.
[h] Adjusted for age, years since hire, styrene and DMDTC (dimethyldithiocarbamate) exposure.