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CC/08/8

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD  
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**1,3-BUTADIENE AND NON-HODGKIN'S LYMPHOMA: REVIEW OF THE  
EVIDENCE FOR IARC'S RECLASSIFICATION OF 1,3-BUTADIENE TO  
GROUP 1 CARCINOGEN**

**Introduction**

1. 1,3-Butadiene (BD) is a colourless, flammable and volatile gas with a slightly aromatic odour. BD has been used since 1943 as a monomer to make synthetic rubbers, plastics and other polymers/copolymers and as an intermediate to produce other chemicals (IARC, 1999; Graff et al 2005). Exposure occurs via inhalation in occupational settings i.e. during production of monomeric BD as a raw material or BD-based polymers such as styrene-butadiene rubber (SBR); or in the environment i.e. via emissions from facilities making or using BD, engine exhaust<sup>1</sup> or cigarette smoke (IARC, 1999; EPA, 2002). Mobile sources account for the majority of environmental emissions in the UK<sup>2</sup> (Dollard et al., 2001). However, outdoor levels are substantially lower than those found in occupational settings.

2. During the committee's recent review of the possible chemical aetiology of Non Hodgkin's Lymphoma (NHL), the COC was informed that IARC had reclassified BD from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic in humans) based on evidence in humans of an association with chronic lymphocytic leukaemia (CLL) and NHL. It was suggested that the evidence for the reclassification of BD be considered in more detail before any conclusions regarding BD are incorporated into the statement.

3. This paper provides a review of the epidemiological evidence (and associated studies) used to form the basis of this reclassification. Annex A contains detailed table summaries of these studies. Key papers are attached in Annex B. Annex C contains information on occupational and environmental exposure levels of BD.

**IARC Reclassification**

4. IARC previously considered there was limited evidence in humans but sufficient evidence in animals for the carcinogenicity of BD (IARC 1999). The reclassification of BD followed an IARC meeting to reassess<sup>3</sup> the

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<sup>1</sup> BD is a product of petrol and diesel combustion (Dollard et al., 2001)

<sup>2</sup> Engine exhaust accounted for 82 % of total UK BD emissions in 1996 (Dollard et al., 2001)

<sup>3</sup> The reassessment will be published as Volume 97 of IARC monographs (Grosse et al., 2007)

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carcinogenicity of BD (and other chemicals). Grosse et al (2007) summarised the meeting and reported the findings of the following key studies (Annex 2): Graff et al (2005) observed an increased risk of mortality from CLL and leukaemia in highly exposed workers in the styrene-butadiene rubber (SBR) industry; Ward et al (1995) observed an association between NHL and workers involved in BD monomer production (see below for more details).

5. The Working Group classified BD as “carcinogenic to humans” on the basis of sufficient evidence in humans of an increased risk of leukaemias, sufficient evidence of carcinogenicity in animals and supportive evidence from mechanistic studies (Grosse et al., 2007). Dr Cogliano, head of IARC, has been approached about whether the WG also considered that there was an association with NHL in humans but no response has yet been received.

6. The US Environment Protection Agency (EPA) has also reviewed recently the human carcinogenicity data for BD (EPA, 2002). The EPA considered the findings of several studies and concluded that excess lymphohaematopoietic cancers (a classification which includes NHL) in polymer and monomer production workers are causally associated with exposure to BD.

7. The relevant data are considered in detail below.

### **Epidemiological studies investigating the relationship between BD and NHL.**

8. Few studies have investigated whether exposure to BD could be related to an increased risk of NHL. Most research has focussed primarily on two types of exposure situation: (a) workers in the North American SBR industry; (b) workers in the US BD monomer industry (Acquavella & Leonard., 2001).

9. Tables 1 and 2 provide a detailed summary of studies considered for this review that investigated a possible relationship between NHL and exposure to BD in BD-monomer and SBR (BD-polymer) production industries, respectively. A total of nine cohort mortality studies were considered in detail (BD-monomer [5 studies]; BD-polymer [4]). A BD-monomer production study (Cowles et al 1994) was excluded from further analysis as it provided no specific data on NHL. No case-control studies<sup>4</sup> were identified from a subsidiary literature search of NHL and BD exposure.

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<sup>4</sup> Nested case-control studies are reported to be associated with leukaemia in workers employed in the SBR production industry (Santos Burgoa et al., 1992; IARC, 1993); a population based case-control study of NHL (cited by Sathiakumar et al., 1998) found no association between NHL and work in the SBR industry

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10. Earlier studies measured deaths from lymphosarcoma and reticulosarcoma (reticulum cell sarcoma) which is an old classification term<sup>5</sup> for NHL (Vasef et al., 2000).

### BD monomer cohorts

11. Three separate US cohorts of BD monomer production workers have been investigated: the Port Neches, Texas, plant was studied by Downs et al (1987) and Divine & Hartman et al (1996; 2001); the Union Carbide chemical plants, in Kanawha Valley, West Virginia studied by Ward et al (1995); and the Shell Deer Manufacturing Complex by Cowles et al (1994).

12. All 4 studies provide evidence of significant excess mortality from lymphosarcoma/ reticulosarcoma in BD monomer production workers. Downs et al (1987) observed a significant excess mortality from lymphosarcoma/ reticulosarcoma in a cohort of 2586 workers employed at a facility in Texas for at least 6 months (between 1943-79) (SMR=235 [95% CI:101-463]) when compared to national rates. However, this yielded a non-significant elevation when compared to county (local) rates (SMR=182 [95%CI not provided]). Furthermore, the lack of data on work histories and historical hygiene data suggest caution should be used when interpreting this finding.

13. Ward et al (1995) studied a cohort of 364 male workers employed in BD production at facilities in West Virginia between 1940 and 1979, from a total worker cohort of over 29,000 subjects. The SMR for deaths from all causes was 91 and for deaths from all malignant neoplasms was 105 (95% CI: 78-140). A statistically significant excess for lymphosarcoma and reticulosarcoma was observed in the BD cohort; this was the only significantly elevated SMR from any cause. The excess was apparent for comparisons based on both national and local referent rates (SMR=577 [95%CI: 157-1480] n=4 and 578 [95%CI: 157-1480] respectively). Three of the 4 deaths occurred in workers who worked for more than 2 years with more than 30 years latency (SMR=1980 [95%CI: 408-5780]; n=3; p<0.01). It was noted that 2 of the 4 workers who died from lympho/reticulosarcoma worked in the acetaldehyde unit. This study involved a relatively small number of subjects.

14. Divine & Hartman (1996) observed a statistically significant elevated SMR in an update of the Texas facility cohort only after grouping lymphosarcoma and lymphoma into one category (as NHL) (SMR=176 [95% CI:103-282]; 17/9.7). The SMR for all causes of death was 88 [95% CI:83-93], and for all cancer, was 92 [95% CI:82-104]. Non-significant excess mortality rates were observed for workers employed for less than 10 years, hired during WWII, with varied exposures. The authors claim that high peak exposures during early years may be responsible for the observed excesses. However,

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<sup>5</sup> Lymphosarcoma and reticulosarcoma are now included in NHL as per the new classification system adopted by the Revised European-American Lymphoma (REAL) and Leukaemia Society of America (EPA, 2002) first proposed in 1993. Also, both leukaemia and lymphomas are lymphohaematopoietic cancers and thus the lymphohaematopoietic system is considered to be the target organ for BD.

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this cannot be substantiated due to a lack of quantitative exposure data for these time periods. A further follow-up study by the same authors (adding 5 additional years and providing the longest follow-up period of 57 years) confirmed that these excess rates were restricted to those employed before 1950 with a short length of employment (Divine & Hartman., 2001).

15. The above studies were both limited by lack of control for confounding exposures since workers are exposed to other chemicals<sup>6</sup> some of which are known human carcinogens e.g. benzene, ethylene dioxide, etc. However, Ward et al (1995) attempted to account for potential confounding by selecting *a priori* only those departments where BD was the primary product. These authors also attempted to account for the lack of control for exposure to acetaldehyde (which the authors report was linked to an increased risk of NHL in an earlier study) by conducting a further follow up study (up to 1991) of 233 workers from the same parent cohort of >29,000, who had been assigned to the acetaldehyde unit. The findings for this subcohort revealed that these deaths were unlikely to be related to confounding exposure to acetaldehyde (which is further substantiated by experimental evidence).

### BD polymer (SBR) cohorts

16. Several studies have examined the risk of death from NHL/lymphosarcoma/reticulosarcoma in one cohort of North American SBR industry workers working in 7 plants in the US and 1 in Canada (Matanoski & Schwartz (1987); Delzell et al., 1996; Graff et al., 2005). The findings of Delzell et al (1996) were republished to incorporate further analyses of mortality patterns from 'non-leukaemia' causes (Sathiakumar et al 1998).

17. Only one study observed a significant elevated rate of death from NHL, with most reporting unremarkable or negative associations (albeit strongly positive associations with leukaemia). Graff et al (2005) observed a positive, dose-related association between cumulative exposure to 1,3-butadiene and mortality from all leukaemia in a cohort of 12,814 male workers from 6 synthetic rubber plants who worked for a minimum of one year between 1943 and 1998 (and actively working between 1943-50) (RR at the highest exposure level of  $\geq 425.0$  BD ppm-years = 3.7 [95% CI:1.7-8.0] n=18). For death from CLL, the RR at this level = 3.9 [95% CI:1.3-11.0] n=7). However, the increased incidence was non-significant when a multiple agent model was used for the analysis. NB. The authors classed CLL as a specific form of leukaemia and analysed mortality patterns separately from NHL.

18. NHL was found to be more strongly associated with styrene and dimethyldithiocarbamate<sup>7</sup> (DMDTC) exposure than with BD exposure, although the relative risks were not statistically significant (single agent model: for BD at  $>425.0$  ppm-years: RR=1.4 [95% CI: 0.6-3.4] n=9, 29,987 PY; for

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<sup>6</sup> NB. Ott et al (1989; Am J Ind Med; 16:631-643) suggest that the average worker at these plants is exposed to 58 different chemicals

<sup>7</sup> DMDTC is an immune system depressant and it is plausible that it could increase the risk of NHL (Graff et al., 2005)

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styrene (at the highest exposure level of >61.1ppm-yrs): RR=2.3 [95% CI: 0.9-5.9] n=16, 47,008 person years; for DMDTC (>1610.3 mg-yrs/cm): RR= 1.7 [95% CI:0.9-3.5] n=13, 44,334 PY).

19. A study by Sathiakumar et al (1998) found no association between BD and mortality from NHL among 15,649 men employed for at least one year in any of the 8 SBR plants although there was a non-statistically significant increase in NHL mortality among ever hourly subjects with  $\geq 10$  years worked and  $\geq 20$  years since hire (SMR=137 [77-226]; 15/11). A 7-year follow-up of this failed to find a clear relationship between employment in the industry and NHL among 17,924 men in the cohort (Sathiakumar et al 2005). The findings were republished in a Health Effects Institute research report by Delzell et al (2006) which included analyses of cumulative exposure to specific chemicals including BD. In the latter study, the authors reported that BD was weakly associated with CLL (RR in highest exposed group, using multiple agent model 2.7 [0.6-11.2], n=7) but not NHL (RR <1.0), although styrene and DMDTC were positively, though not statistically significantly, associated with NHL (RR: styrene highest exposure group multiple agent model, 2.3 [95% CI: 0.6-9.2], n=16; DMDTC, 1.5 [95% CI: 0.6-3.8], n= 13). There was no trend in RR with exposure to either styrene or DMTDC.

### NHL vs. leukaemia

20. There is an apparent difference in cancer outcome between the monomer and polymer workers. Excesses of NHL (lymphosarcomas/reticulosarcomas) deaths are observed with BD exposure in BD monomer productions workers while an excess of leukaemias is reported with BD exposure in SBR production workers. The US EPA suggest that this could be due to a number of reasons e.g: monomer workers receiving higher BD exposures during wartime compared to the much lower exposures encountered in recent years or in the SBR polymer industry; monomer studies lacking power to detect leukaemia excesses; differences are an artefact arising from the changes in NHL classification (EPA, 2002).

21. Sathiakumar et al (1998) suggest that since NHL has a high survival rate, later clinical stages may transform into leukaemia and be reported as such on death certificates (rather than NHL). It has also been suggested that a necessary co- or modifying factor may be present/absent in the different industries (EPA, 2002).

### General limitations of studies

22. There are several general limiting factors associated with the above studies. In addition to a lack of account of confounding chemical exposures, none of the studies provided an adequate account of the major NHL confounders e.g. immunodeficiency, chronic infection and immunosuppression.

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23. Most studies also failed to provide quantitative exposure data for BD due to lack of air monitoring information. For example, Ward et al (1995) estimated exposure using assumptions based on department codes. This meant there was no way of determining if the levels of BD were higher in those workers who died compared to other members of the cohort. Job title/employment was often used as a measure of exposure to BD, which may not represent the workers' true exposure.

24. Mortality is considered to be less informative than cancer incidence and thus may not be an optimal end point for investigating NHL. Mortality rates do not necessarily provide a true reflection of the number of people with NHL because survival rates after diagnosis are high (mean 5yr survival is 48% for men diagnosed between 1974-89) (Sathiakumar et al 1998) such that subjects who have the disease but are still alive will be overlooked. Many studies also relied on death certificates which may record a symptom of the disease rather than the disease itself as the cause of death. Ward et al (1995) used mortality as an endpoint due to a lack of population-based cancer registries in the Kanawha Valley area.

25. Several studies also grouped all lymphohaematopoietic cancers together which hampered further interpretation of the findings.

### **Conclusion**

26. Positive associations for NHL were found primarily in cohort mortality studies examining exposures to BD in the BD monomer production industry. However, these studies are limited by several factors predominately associated with the lack of control for possible confounding exposures to other chemicals and a lack of quantitative exposure estimates for BD. The use of mortality as an endpoint, particularly in relation to NHL, suggests that the findings should be interpreted with caution given the high survival rate associated with NHL.

### **Question for the Committee**

27. Members are asked to consider the paper and the tables provided in Annex 1 and 2 respectively.

28. Do members consider that there is sufficient evidence to conclude that butadiene causes NHL in humans?

**Secretariat  
March 2008**

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**Annex A to CC/08/8**

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Tables 1 and 2. Summaries of studies investigating the possible relationship between NHL and exposure to BD in BD-monomer and SBR (BD-polymer) production industries (respectively).

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**Table 1. Studies of exposure to 1,3-butadiene (monomer) in 1,3-butadiene production industry workers and NHL risk**

Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIGNIFICANT DATA SHOWN† (ORs/TRENDS)	Study Conclusions	Comments
Downs et al (1987)/ US  <u>Exposure Scenario</u>  To examine cause-specific mortality in a cohort of workers at a butadiene production plant  [Occupational]	Cohort Mortality Study  <u>Exposed (2586):</u> Male workers employed for min 6 months between 1943-1979 in a butadiene facility (that supplied butadiene to 2 SBR <sup>8</sup> plants)  NB. Excluded women and temporary employees  <u>Referents:</u> 1. National (US white males); 2. Local (white males from local	<u>Exposure(s) of interest:</u> Principally 1,3-butadiene  <u>Population of interest:</u> Butadiene monomer workers  <u>Follow up:</u> Vital status determined via SSA <sup>9</sup> and Texas Dept of Public Safety; death certificates were coded by a nosologist. Mean follow-up time=25.1 years Follow-up rate=97.2%  <u>Exposure data ascertainment:</u> No data on work histories and historical hygiene data were available  <u>Exposure characterisation:</u> Via a qualitative scale of exposure based on department codes which define an employees function Following exposure groups were defined (based on industrial hygienist/investigator judgment): Group 1: low exposure (rare); Group 2: routine exposure (daily); Group 3: non-routine exposure (intermittent); Group 4: unknown exposure (varied)	<u>SMR &amp; 95%CI:</u> calculated using national (NSMR) and local (LSMR) comparison populations  <u>RR &amp; 95% CI:</u> Calculated for additional comparisons between various exposure groups  <u>Adjustments</u> Age, race, sex and calendar year	Total no of deaths = 603  Total no of deaths for lymphosarcoma and reticulum cell sarcoma = 8  <b>NSMR=235[101-463] 8/3.4; p&lt;0.05</b> NB. Only statistically significant increase observed for any cause of death;  LSMR was non significant=182 (no CI provided)  Further analyses for duration of employment/ exposure groups cannot be interpreted as NHL/lymposarcoma was grouped with other lymphohaematopoietic cancers  Latency (0-9 yrs and employed less than 10 yrs) NSMR=1198 (no 95%CIs provided); 4/0.33 NB. The NSMR for lymphosarcoma were inversely related to latency (i.e. negative relationship to latency)	(+)  A significantly increased NSMR for lymphosarcoma and reticulum cell sarcoma on the total cohort. However the corresponding SMRs based on national and local rates were not statistically significant  Role of butadiene is unclear (an agent other than butadiene may be responsible for excess NHL deaths observed)	<u>Strengths</u> High follow-up rate Based on large cohort Uses workers employed throughout plant history  <u>Weaknesses</u> Relatively small cohort Lack of data on work histories or historical hygiene data No objective evaluation of exposure categories therefore potential for misclassification of exposure Potential for confounding by other exposures  <u>Overall:</u> marginally adequate study design Inadequate exposure assessment method Inadequate control of major NHL confounders

<sup>8</sup> SBR=styrene butadiene rubber

<sup>9</sup> SSA=Social Security Administration

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Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIGNIFICANT DATA SHOWN† (ORs/TRENDS)	Study Conclusions	Comments
		Exposure also characterised according to no years worked and latency (time since hire to death)				
<p>Ward et al (1995)/ USA</p> <p>To investigate the carcinogenic effect of 1,3 – butadiene in humans and determine whether exposure was associated with excess mortality from malignant neoplasms of the lymphatic and haematopoietic tissue.</p> <p><u>Exposure Scenario</u></p> <p>[Occupational]</p>	<p>Cohort Mortality Study</p> <p><u>Exposed (364):</u> Identified from records of 29,139 workers assigned to any of three Union Carbide chemical plants (1,3B production* units<sup>#</sup>) operating in Kanawha Valley in West Virginia (US); employed between 1940-1979</p> <p>*NB. Also produced other chemicals # South Charleston since 1941; for 24 yrs) Rubber Reserve Unit (since 1943; 3 yrs) Institute plant (since 1959; 12 yrs)</p>	<p><u>Exposure(s) of interest:</u> 1,3-butadiene</p> <p><u>Population of interest:</u> Male workers employed in the butadiene production industry</p> <p><u>Follow up:</u> From initial exposure to death Vital status: (through to 1978) obtained from earlier study; (from 1979-1990) by matching records of National Death Index (NDI) Only 0.8% had unknown vital status</p> <p><u>Exposure data ascertainment:</u> No exposure data was available. Computer records of work history in 1-3B production facilities were used to ascertain employment status.</p> <p><u>Exposure characterisation:</u> Exposure was defined as having ever worked in departments during years when 1,3B was produced</p> <p>Exposure characterised according to (i) duration of employment (ranged from 9-96 months) (ii) latency (time since first</p>	<p><u>SMR &amp; 95%CI:</u> calculated for specific causes of death</p> <p>Exposure analysed according to (i) duration of employment (ii) latency</p> <p>Mortality rates were compared to referents using a modified life table analysis</p> <p><u>Adjustments</u> None specified</p> <p>NB. Latency and duration analyses performed by dichotomising both so that equal no of expected deaths were below /above the cutpoints</p> <p><u>Further analyses</u></p>	<p>Total no of deaths = 185</p> <p>Total no of deaths for lymphosarcoma/reticulosarcoma = 4</p> <p>NB. Lymphosarcoma and reticulosarcoma were the only specific cause of death (out of 92) to produce a significantly elevated SMR</p> <p><b>SMR=5.77[95%CI: 1.57-14.8]n=4*</b> (based on US referent rates) [NOTE: this is how the way the authors expressed 'SMR's in the paper. The figures have been corrected in the main text of CC/08/8].</p> <p><b>SMR=5.78[95%CI: 1.57-14.8]n=4?</b> (based on County referent rates – only covered time period between 1960-90)</p> <p>*3/4 deaths occurred in &gt;2 years duration and &gt; 30 years latency categories <b>SMR=19.8[95%CI: 4.08-57.8]; n=3; p&lt;0.01</b></p> <p><u>Subanalyses:</u> Since 2 of the 4 workers who died from lymphosarcoma/reticulosarcoma also worked in the acetaldehyde unit a further analyse was conducted to account for lack of control for acetaldehyde exposure. 233 workers assigned to the acetaldehyde unit were followed up to 1991. Findings</p>	<p>(+)</p> <p>Findings add to the weight of evidence suggesting that butadiene is carcinogenic in humans</p>	<p><u>Strengths</u> Attempted to account for several limitations</p> <p>Long follow up period (ranged from 25-36 yrs) High follow-up rate (99.2%)</p> <p><u>Weaknesses</u> Small sample size (although authors attempted to account for this in the analysis) No quantitative exposure information available Lack of control for other possible confounders although authors attempted to account for this</p> <p><u>Overall:</u> Small sample size; limited exposure assessment; inadequate control of major NHL confounders; however attempted to control for some of these limitations</p>

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Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIFIGNIFICANT DATA SHOWN <sup>†</sup> (ORs/TRENDS)	Study Conclusions	Comments
	<u>Referents:</u> US and/or Kanawha County	employment in 1,3B production processes)		revealed that the deaths were unlikely to be related to acetaldehyde.		
Divine & Hartman (1996)/ US  An update of a study examining cause-specific mortality in a cohort of workers at a butadiene production plant providing four additional years of follow-up  NB. Is an update of Downs et al 1987 (There have been subsequent updates since then)  <u>Exposure Scenario</u>  [Occupational]	Cohort Mortality Study  <u>Exposed (2795):</u> Male workers employed at least 6 months between 1942-1994 at a 1,3-butadiene monomer production facility in Port Neches, Texas; all assumed to be white due to low no of non-whites/those unknown; females/ temp workers excluded; includes persons first employed after the eligibility period for earlier updates;  <u>Referents:</u> US white male population	<u>Exposure(s) of interest:</u> 1,3-butadiene  <u>Population of interest:</u> Butadiene monomer workers  <u>Follow up:</u> Covered the period from 1943 to 1994; 89581 person yrs mean follow up duration=32.1 yrs Vital status info obtained via SSA and Health Care Financing Administration (HCFA); death certificates coded by a trained nosologist Follow-up rate (79.5%) although most of those lost were known to be alive up to end 1993  <u>Exposure data ascertainment:</u> Work history records/use of industrial hygiene records since 1980  <u>Exposure characterisation:</u> Job/unit exposure classification scheme developed by scoring jobs wrt potential for BD exposure (frequency and intensity); used to categorise following groups: Background, low and varied exposure  Exposure analysed by length of	<u>SMR &amp; 95%CI:</u> Calculated as a measure of association  <u>RR &amp; 95% CI:</u> Calculated for ??  <u>Adjustments</u> ?? RR: exposure and hire age	Total No of deaths= 1222  No of decedents with lymphosarcoma = 9  <u>SMR (lymphosarcoma)</u> Total cohort SMR =191[87-364]9/4.7 (non significant)  Length of employment: <5 yrs: SMR=261[95-568]; 6/2.3 (n.s) 5-19 yrs: SMR=182[20-656]; 2/1.1(n.s) >20yrs: SMR was lowered  Time first employed: <1946: SMR=241[97-497]; 7/2.9 1946-9: SMR was lowered >1950: 185[2-1027]; 1/0.5  Length of employment (for varied exposure group): marginally sig elevation SMR=249[100-513]; 7/2.8  <u>RR:</u> Hire age: NHL = 1.09[1.04-1.14]; n=17 Lymphosarcoma = 1.07[1.00-1.14]; n=9 (no sig associations between BD cumulative exposure and NHL)  NB. Lymphosarcoma and NHL analysed separately  <u>Grouping lymphosarcoma and lymphoma into one category (NHL) then:</u>	(+)  Statistically significant elevated SMR for LHC Authors ascribe this to non sig excesses in lymphosarcoma apparent in those employed for > 10 yrs, hired during WWII with varied exposure.  Authors suggest that high exposures to BD in early years of plants operation may be a factor for increased NHL risk	<u>Strengths</u> Complete work histories Long follow-up period (52 years) Largest group of individuals studied involved solely in the manufacture of BD Incorporated quantitative data into exposure estimate  <u>Weaknesses</u> Relatively small cohort Industrial sampling hygiene data available for only last 14 years of study  No info on other confounding factors (potential for confounding exposures)  <u>Overall:</u> Marginally adequate study design Acceptable exposure assessment method (with limitations) Inadequate control of major NHL confounders

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Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIFIGNIFICANT DATA SHOWN† (ORs/TRENDS)	Study Conclusions	Comments
		<p>employment; time of first employment and by exposure group</p> <p>Cumulative exposure also estimated to provide a qualitative measure of BD exposure; each exposure estimate weighted by exposure class and calendar time</p>		<p>Total No deaths (NHL) = 17 <b>SMR=176[103-282]; 17/9.7</b></p>		
<p>Divine &amp; Hartman (2001)/US</p> <p>An update to examine the patterns of mortality (for five years follow-up) of butadiene production workers</p> <p>NB. Is an update of Divine &amp; Hartman (adds 5 yrs)</p> <p><u>Exposure Scenario</u></p> <p>[Occupational]</p>	<p>Cohort Mortality Study</p> <p><u>Exposed (2800):</u> Male workers employed at least 6 months between 1942-1999 at a 1,3-butadiene monomer production facility in Port Neches, Texas; all assumed to be white due to low no of non-whites/those unknown; females/temp workers excluded; includes persons first employed after the eligibility period for earlier updates; includes persons</p>	<p><u>Exposure(s) of interest:</u> 1,3-butadiene</p> <p><u>Population of interest:</u> Butadiene monomer workers</p> <p><u>Follow up:</u> Covered the period from 1943 to 1999; 99447 person yrs mean follow up duration=35.4 yrs Vital status info obtained via SSA, pension records and National Death Index (NDI); death certificates coded by a trained nosologist Follow-up rate (93.3%)</p> <p><u>Exposure data ascertainment:</u> Work history records/use of industrial hygiene records since 1980</p> <p><u>Exposure characterisation:</u> Job/unit exposure classification scheme developed by scoring jobs wrt potential for BD exposure (frequency and intensity); used to categorise following groups:</p>	<p><u>SMR &amp; 95%CI:</u> Calculated as a measure of association</p> <p><u>RR &amp; 95% CI:</u></p> <p><u>Adjustments</u> SMR: Age, race and calendar time</p>	<p>Total no of deaths=1422 NHL deaths = 19 Lymphosarcoma deaths = 9</p> <p><u>SMR</u> <b>SMR (NHL) =148[89-231]; 19/12.9</b> SMR (lymphosarcoma)=203[93-386];9/4.4</p> <p>Length of employment: {&lt;5 yrs):- <b>:SMR (NHL)=197[101-344]; 12/6.1</b> <b>:SMR (lymphosarcoma)=280[102-610];6/2.1</b> {5-19 yrs): :SMR (NHL)=175[19-633]; 2/1.1 :SMR (lymphosarcoma)=127[25-372-610];3/2.4</p> <p>Time first employed: {Before 1950): SMR (NHL)=160[93-257]; 17/10.6 SMR (lymphosarcoma)=203[88-400];8/3.9 {After 1950): : Non sig elevations with wide CI or SMR decreased</p> <p>Length of employment (for varied exposure group) {&lt;5 yrs):-</p>	<p>(+)</p> <p>Excess NHL in workers employed &lt; 5yrs and before 1950; excess continues to be restricted to those first employed before 1950 and those with short length of employment</p> <p>However, no additional deaths from lymphosarcoma since 1981 (suggests NHL grouping is a more appropriate category)</p> <p>SMRs higher in varied exposure group (potential for routine exposure to butadiene)</p>	<p><u>Strengths</u> Combined SMR rates for lymphosarcoma and lymphoma to generate rates for NHL Complete work histories/qualitative measures of exposure available Long follow-up period (57 years) Largest group of individuals studied involved solely in the manufacture of BD Incorporated quantitative data into exposure estimate</p> <p><u>Weaknesses</u> Relatively small cohort Industrial sampling hygiene data not available for years prior to 1981 No info on other confounding factors (potential for confounding exposures)</p> <p><u>Overall:</u> Marginally adequate study design Acceptable exposure assessment method (with limitations) Inadequate control of major NHL confounders</p>

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Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIGNIFICANT DATA SHOWN† (ORs/TRENDS)	Study Conclusions	Comments
	first employed between 1994-1996  <u>Referents:</u> US population	Background, low and varied exposure  Exposure analysed by length of employment; time of first employment and by exposure group  Cumulative exposure also estimated to provide a qualitative measure of BD exposure; each exposure estimate weighted by exposure class and calendar time		: <b>SMR (lymphosarcoma)=373[120-870]5/1.3</b> : SMR (NHL)=199[85-393]; 8/4 {>5yrs} : Non sig elevations with wide CI  Further analysis of workers employed (1942-9) Highest (non-sig) elevations n those employed > 5 yrs : SMR 183[67-400]; 6/3.3  <u>Cumulative exposure</u> Estimates were neutral (indicates lack of dose response effect)	SMRs decreased with increasing length of employment	

†Non-significant data is included if relevant to author's conclusions

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**Table 2. Studies of exposure to 1,3-butadiene (polymer) in styrene-butadiene rubber industry workers and NHL risk**

Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIGNIFICANT DATA SHOWN <sup>†</sup> (ORs/TRENDS)	Study Conclusions	Comments
<p>Matanoski &amp; Schwartz 1987/US &amp; Canada</p> <p>To report on the mortality of workers employed in the production of synthetic rubber</p> <p><u>Exposure Scenario</u> [Occupational]</p>	<p>Cohort Mortality Study</p> <p><u>Exposed</u> (13920): males who worked in 8 SBR polymer manufacturing plants in US &amp; Canada for min 1yr</p> <p><u>Referents:</u> US male pop</p>	<p><u>Exposure(s) of interest:</u> Chemicals used/produced in SBR industry</p> <p><u>Population of interest:</u> Male workers in SBR manufacturing industry (North American)</p> <p><u>Follow up:</u> From 1943-1979 Vital status determined via SSA and Motor Vehicle Administration records (US), and company sponsored insurance records (Canada) Follow-up rate= 93.7%</p> <p><u>Exposure data ascertainment:</u> Via employee records to construct a job dictionary</p> <p><u>Exposure characterisation:</u> Jobs combined into four general work activities Dates of first and last employment used as a measure of total duration of employment</p>	<p><u>SMR &amp; 95%CI:</u> Calculated as a measure of association</p> <p><u>Adjustments</u> SMR standardised for age, race and calendar time</p>	<p>Total No of deaths = 1995 No of lymphosarcoma/reticulum cell sarcoma deaths = 5</p> <p>SMR= 0.49[<u>further details not provided</u>]</p> <p>All lymphopietic cancers were grouped together in further analyses</p>	<p>(-)</p> <p>No excess mortality for any cause of death</p>	<p><u>Strengths</u> Large cohort Long follow-up period (36 yrs)</p> <p><u>Weaknesses</u> No quantitative 1,3 butadiene exposure data</p> <p><u>Overall:</u> Acceptable study design Limited exposure assessment method Inadequate control of major NHL confounders</p>
<p>Dellzell et al (1996)/US &amp; Canada</p> <p>To evaluate the possible carcinogenic effects of</p>	<p>Retrospective Cohort Mortality Study</p> <p><u>Exposed</u> (15649): men employed for at least 1 yr at any</p>	<p><u>Exposure(s) of interest:</u> 1,3-butadiene and styrene</p> <p><u>Population of interest:</u> Male workers in SBR manufacturing industry (North American)</p>	<p><u>SMR &amp; 95%CI:</u> Calculated as a measure of association for overall and cause-specific mortality</p> <p><u>Adjustments</u></p>	<p>Total no of deaths = 3976 No of lymphosarcoma deaths = 11</p> <p>SMR=80[40-144]11/14</p> <p>Ever hourly white males employed after 1985 : SMR=284[77-726]; 4/1.4</p>	<p>(-)</p> <p>Overall mortality rate was lower than that for general pop</p> <p>Suggest exposure to chemicals in the</p>	<p><u>Strengths</u> Large cohort Long follow up period Exposure assessment based on detailed account of job history</p> <p><u>Weaknesses</u></p>

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Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIGNIFICANT DATA SHOWN <sup>†</sup> (ORs/TRENDS)	Study Conclusions	Comments
<p>exposure to the monomers used to make SBR</p> <p><u>Exposure Scenario</u></p> <p>[Occupational]</p>	<p>of 8 North American styrene-butadiene plants; 12605 (US) and 5359 (Canada)</p> <p>75% of cohort exposed to BD</p> <p><u>Referents:</u> general pop of US and Ontario</p>	<p><u>Follow up:</u> (1943-1991) Total 386172 person years; av 25 person-yrs (max follow up being 49 yrs) Vital status determined from NDI (US) and plant personnel/benefit records linked with the Canadian Mortality Database; death certificates reviewed by trained nosologist Follow-up rate=95%</p> <p><u>Exposure data ascertainment:</u> Detailed work history records</p> <p><u>Exposure characterisation:</u> Work area groups developed</p> <p>Cumulative exposure estimated (by linking work history with job exposure matrices specific for work group area or calendar time)</p>	<p>Age, race and calendar time</p>	<p>Other analyses according to work area groups yielded elevated SMRs with wide CIs.</p> <p>NB. Study also analysed other lymphopietic cancers as a separate category that included NHL</p>	<p>SBR industry have had little impact on disease.</p> <p>No persuasive evidence of an association between SBR work and forms of lymphopietic cancer other than leukaemia</p>	<p>Unable to identify individual subjects or determine subjects included in earlier investigations (may be huge overlap) who terminated employment before 1950 Work histories were non-specific or incomplete for 12% of subjects No quantitative 1,3 butadiene exposure data Confirmation of death by "other lymphopietic cancers (incl's NHL) limited</p> <p><u>Overall:</u> Acceptable study design (with limitations) Adequate exposure assessment method (with limitations) Inadequate control of major NHL confounders</p>
<p>Sathiakumar et al 1998/US &amp; Canada</p> <p>Third in a series of reports describing a study of workers in the synthetic rubber industry in US and Canada, providing further data on mortality patterns</p>	<p>Retrospective Cohort Follow-Up Mortality Study</p> <p><u>Exposed (15649):</u> males employed for at least 1 yr at any of 8 North American styrene-butadiene plants; 7 US (Texas, Louisiana &amp; Kentucky); 1</p>	<p><u>Exposure(s) of interest:</u> Chemicals within SBR industry (notably butadiene and styrene)</p> <p><u>Population of interest:</u> Male workers in SBR manufacturing industry (North American)</p> <p><u>Follow up:</u> Av 25 yrs per subjects; max (1943-1991) Total 386172 person years; av 25 person-yrs (max follow up being 49 yrs)</p>	<p><u>SMR &amp; 95%CI:</u> Calculated as a measure of association for overall and specific mortality and never/ever hourly and years since hire</p> <p><u>Adjustments</u> Age, race and calendar time</p>	<p>Total No of deaths = 3976</p> <p>No of NHL deaths = 28</p> <p>SMR for non-leukaemia deaths (e.g. NHL) close or below null value</p> <p>SMR=137[77-226]; 15/11</p> <p>Analysis by work area/duration of employment/years since hire produced unremarkable results for NHL</p>	<p>(-)</p> <p>Deaths from NHL did not seem to be related to occupational exposure</p>	<p><u>Strengths</u> Large cohort Long follow-up period Exposure assessment based on detailed account of job history</p> <p><u>Weaknesses</u> Relied on death certificates to identify cases No quantitative exposure information available</p> <p><u>Overall:</u> Acceptable study design (with limitations) Adequate exposure assessment method</p>

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Ref/Country Aim/	Study design	Exposure Assessment	Analysis of Data/Confounding	Findings NB. ONLY SIGNIFICANT DATA SHOWN <sup>†</sup> (ORs/TRENDS)	Study Conclusions	Comments
<p><u>Exposure Scenario</u></p> <p>[Occupational]</p> <p>NOTE: This is a republication of Delzell et al 1996</p>	<p>Canada (Ontaria)</p> <p><u>Referents:</u> US and Ontario male general pop</p>	<p>Vital status determined from NDI (US) and plant personnel/benefit records linked with the Canadian Mortality Database; death certificates reviewed by trained nosologist Follow-up rate=95%</p> <p><u>Exposure data ascertainment:</u> Detailed work history records</p> <p><u>Exposure characterisation:</u> Work area groups developed</p> <p>Cumulative exposure estimated (by linking work history with job exposure matrices specific for work group area or calendar time)</p>				<p>(with limitations) Inadequate control of major NHL confounders</p> <p>NB. A 7-yr follow-up study by the same author also failed to find a clear relationship with NHL and exposure to BD from employment in SBR industry (Sathiakumar et al 2005). These findings were republished in a research report by Delzell et al 2006 with additional information on cumulative BD exposures. Non-significant elevated RR were observed for CLL (RR=2.7[0.6-11.2] n=7 (multiple agent model); while NHL was positively (yet non-significantly) associated with exposure to styrene and DMDTC</p>
<p>Graff et al (2005)/ US &amp; Canada</p> <p>A follow-up to a previous cohort study to specifically examine the relationship between mortality from lymphohaemato poietic cancers and exposure to several chemicals (incl butadiene).</p> <p><u>Exposure</u></p>	<p>Cohort Mortality Study</p> <p><u>Exposed (12814):</u> Identified from 16579 male workers from 6 synthetic rubber plants (US/Canada); all had worked for min 1 yr at any plant by end 1991 (and actively working from 1943 to 1950)</p> <p><u>Referents:</u></p>	<p><u>Exposure(s) of interest:</u> 1,3-B among other chemicals (styrene and dimethyldithiocarbamate - DMDTC)</p> <p><u>Population of interest:</u> Synthetic rubber industry workers</p> <p><u>Follow up:</u> 1943 – 1998; 500, 174 person years; vital status info obtained via social security administration and internal revenue records, pension benefits information and national death index/Canadian mortality database. Cause of death info obtained from death certificates</p>	<p><u>SMR &amp; 95%CI:</u> Calculated as a measure of association; used state specific rates and population rates from occupational mortality analysis programs.</p> <p><u>RR &amp; 95% CI:</u> Poisson regression analysis used to calculate the RR (relative rates) for death for leukaemia and NHL for cumulative exposure to</p>	<p>Total No of deaths = 5703</p> <p>No of NHL deaths = 58 (NB. NHL recorded as underlying cause of death in only 43 subjects – in remaining 15 decedents NHL either contributed to death or was detailed in medical history)</p> <p>NOTE: Authors class CLL as a specific form of leukaemia</p> <p><u>RR:</u> &gt;&gt;&gt;For &gt;425 BD ppm-years (highest butadiene exposure category): <b>RR (CLL)=3.9[1.3-11.0]n=7</b> (19146 person years (single agent model); although there was a non significant elevation when using the multiple agent model RR=2.7[0.6-11.2])</p>	<p>(+)</p> <p>CLL was positively associated most consistently (but weakly) with butadiene</p> <p>NHL was associated with styrene and DMDTC (although neither RRs displayed consistent exposure response patterns)</p> <p>NB. DMDTC is an immune system</p>	<p><u>Strengths</u> Large sample size Long follow up period High follow-up rate (US: 93%; Can: 97%) Exposure assessment based on detailed account of job history</p> <p><u>Weaknesses</u> Lack of complete work history data Models used to estimate exposures based on many assumptions Exposure estimates lacked comprehensive validation No quantitative exposure information available Limited account of major NHL confounders</p>

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Scenario [Occupational]	national/state male population	<p>with the help of a nosologist Follow-up rate=??</p> <p><u>Exposure data ascertainment:</u> Employment records providing info on dates, work area, job titles</p> <p><u>Exposure characterisation:</u> Exposure estimated by calculating exposure indices and compiling job-exposure matrices. These were used to obtain the following cumulative exposure estimates/indices:</p> <ul style="list-style-type: none"> <li>▪ Butadiene total ppm-years</li> <li>▪ Butadiene ppm-years due to exposures to intensities ≤ 100ppm or &gt; 100 ppm</li> <li>▪ Total no of butadiene peaks (&gt; 100ppm)</li> </ul>	<p>butadiene ppm-years (both single and multiple agents models used)</p> <p><u>Adjustments</u> SMR: Age, race, country, gender calendar period RR: adjusted for age and years since hire (single models – multiple models included adjustments for exposure to 2 other agents)</p>	<p>RR (NHL*)=Marginally elevated non-significant (1.4[0.6-3.4]n=9; 29987 PY; single agent model</p> <p>*NB. Authors report that NHL was most strongly associated with styrene ppm-years although data was not statistically significant</p> <p><u>SMR:</u> &gt;&gt;&gt; For &gt;184.7 BD ppm-years (medium and highest butadiene exposure categories):</p> <p>SMR were elevated but non-significant For medium category: 184.7- &lt;425 ppm- yrs</p> <p>SMR(CLL)=162[65-334]n=7</p> <p>SMR (NHL) =177[89-317]n=11</p> <p>Highest cat: &gt;425 ppm-years</p> <p>SMR(CLL)=355[97-908]n=4</p> <p>SMR (NHL) = =185[85-352]n=9</p>	depressant and it is plausible that it could increase the risk of NHL	<p><u>Overall:</u></p> <p>Good study design; adequate exposure assessment (with limitations); inadequate control of major NHL confounders</p>

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**Annex B to CC/08/8**

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD  
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**1,3-BUTADIENE AND NON-HODGKIN'S LYMPHOMA: REVIEW OF THE  
EVIDENCE FOR IARC'S RECLASSIFICATION OF 1,3-BUTADIENE TO  
GROUP 1 CARCINOGEN**

The following key papers are attached for members' reference:

1. Downs et al (1987). Mortality Among Workers at a Butadiene Facility. Am J Ind Med; (12):311-29
2. Ward et al (1995). Mortality Study of Workers in 1,3-Butadiene Production Unit Identified from a Chemical Workers Cohort. Environ Health Perspect 103:598-603
3. Divine & Hartman (1996). Mortality update of butadiene production workers. Tox; 113:169-81
4. Graff et al (2005). Chemical Exposures in the Synthetic Rubber Industry and Lymphohematopoietic Cancer Mortality. J Occup Environ Med; 47:916-932

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Annex C to CC/08/8

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD  
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**1,3-BUTADIENE AND NON-HODGKIN'S LYMPHOMA: REVIEW OF THE  
EVIDENCE FOR IARC'S RECLASSIFICATION OF 1,3-BUTADIENE TO  
GROUP 1 CARCINOGEN**

Ambient UK Levels of BD

Low level environmental exposure is reported to range from <1 to 10 ppb (<2.21 to 22.1 ug/m<sup>3</sup>) which is orders of magnitude less than experimental or occupational settings (Graff et al 2005; Hurst, 2007). The UK Hydrocarbon Monitoring Network characterised the current ambient levels of BD in 13 sites across the UK and noted hourly maximum BD concentrations of up to 10 ppb (22.1 ug/m<sup>3</sup>)<sup>10</sup> and monthly mean concentrations ranging from 0.1 to 0.4 ppb (0.22 to 0.88 ug/m<sup>3</sup>) (Dollard et al 2001). These levels are declining at a rate of 10% per year.

NB. Assessing the significance of environmental human exposures to BD remains a major challenge as exposures may persist for long periods or involve unknown but potentially significant sensitivities in the general population (Hurst, 2007).

Occupational Levels of BD

Workplace concentrations in Canada, the USA and Western Europe are generally below 2 mg/m<sup>3</sup> but can be higher in countries that use older technologies (Grosse et al 2007). BD levels for a full shift are generally below 22 mg/m<sup>3</sup> (IARC, 1999). However these levels can be exceeded during short term activities e.g. to approximately 200 mg/m<sup>3</sup> (Grosse et al 2007). Before mid-80s some jobs in the synthetic rubber industry entailed butadiene exposures > 25 ppm (55.3 mg/m<sup>3</sup>) (8-hour TWA) with peak exposures of several hundred ppm (Graff et al., 2005).

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<sup>10</sup> Conversion factors (only for the gaseous form): To convert concentrations in air (at 25°C) from ppm to mg/m<sup>3</sup>: mg/m<sup>3</sup> = (ppm) × (molecular weight of the compound)/(24.45). For 1,3-butadiene: 1 ppm = 2.21 mg/m<sup>3</sup>. <http://www.epa.gov/ttn/atw/hlthef/butadien.html>