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CC/07/15

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

**DRAFT WORKING PAPER ON: NON-HODGKIN'S LYMPHOMA**

**Introduction**

1. Non-Hodgkin's lymphoma (NHL) is one of two main types of tumours of the lymphatic system. Hodgkin's lymphoma (HL) accounts for 10% of all malignant lymphomas worldwide and is distinguished by the presence of an abnormal lymphocyte termed the Reed-Stenberg cell. Lymphomas lacking the Reed-Stenberg cell are classified as NHL. NHL is not considered to be a single disorder but a mixture of different disease entities. According to the most widely used classification, the Revised European American Lymphoma (REAL)/WHO classification, there are 36 subtypes of NHL. The majority of NHL malignancies are B-cell in origin and arise in the lymph nodes.

2. NHL is the seventh most common cancer in men and the sixth most common cancer in women in the UK (CRUK, 2007). NHL is also the third most common cancer of childhood (Shukla & Trippett, 2006). Around 8,450 new cases of NHL are diagnosed each year in the UK (LRF, 2005). In 2005, NHL was reported to be the ninth largest cause of death from cancer in the UK (2005 data), with 4,451 deaths, accounting for around 3% of cancer deaths in males and females. Around 74% of these deaths are in people aged over 65 years (CRUK, 2007).

3. Cancer statistics indicate that the incidence of NHL is increasing. The Committee was asked to advise on whether there were any chemical exposures which might account for the increase in incidence. It considered a discussion paper (<http://www.advisorybodies.doh.gov.uk/pdfs/cc0707.pdf>) prepared by the DH Toxicology Unit (Imperial College London) at its July 2007 meeting, which reviewed the scientific literature since 1 January 1997 on NHL and certain occupations and chemical risk factors.

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#### **Temporal Trends in Incidence of NHL in the UK**

4. Incidence rates for NHL have increased in all age groups in Great Britain in recent years, particularly during the early 1980s and 1990s (CRUK, 2007). Cancer Research UK reported a 10.3% increase in NHL incidence in Great Britain between 1993 and 2002, with an annual average increase of 1.2% (CRUK, 2007). Part of this increase is thought to be accounted for by the HIV/AIDS epidemic (which is a significant risk factor for NHL). However, an increased NHL incidence is reported to have existed prior to the epidemic (Ekstrom-Smedby 2006). Rates continued to increase after the mid-1990s in those aged 45 years and over, particularly in the over-65s.

5. According to the literature, trends in NHL incidence should be interpreted with caution because some of the increase is thought to be due to changes in the diagnosis and classification. We agree that recent changes in the diagnosis and classification of NHL, and the categorisation of lymphomas and leukaemias, are likely to have affected recorded incidence rates. Nevertheless, there has probably also been real increase in incidence of NHL (Barnes et al, 1986).

6. We note that there is a decreasing trend in mortality from NHL in recent years (CRUK, 2007). Cause of death is more frequently being given as malignancy rather than infection and, therefore, the decreasing trend in mortality rates cannot be attributed to changes in diagnostic practice.

#### **Risk factors for NHL**

7. There are a number of suspected risk factors for NHL. The proposed non-chemical causes have been listed in Table 1, categorised according to the strength of available evidence (Grulich & Vadjich., 2005; Ekstrom-Smedby, 2006). The strongest and most well-established factors are characterised by dysregulation or suppression of T-cell function (i.e. factors/conditions that

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precipitate chronic antigenic stimulation or immunosuppression) (Ekstrom-Smedby, 2006). These include specific infections such as HIV/AIDS, immune deficiency and organ transplantation. However, the known risk factors are considered to account for only a small percentage of NHL cases.

Table 1. List of non-chemical risk factors of NHL categorised according to strength of available evidence (Grulich & Vadjich., 2005; Ekstrom-Smedby., 2006).

Evidence for an association	Proposed risk factor
Good	<ul style="list-style-type: none"> <li>- Hereditary disorders of immune dysfunction e.g. ataxia-telangiectasia, severe combined immunodeficiency</li> <li>- HIV/AIDS</li> <li>- Immunosuppressive therapy following organ transplantation.</li> <li>- Positive family history of haematolymphoproliferative malignancies: risk of NHL is increased about 2-3-fold in first-degree relatives of patients with lymphoma or haematopoietic cancer.</li> <li>- Infectious agents including Epstein-Barr virus, HHV-8 (Kaposi sarcoma herpes virus), HTLV-1 and Helicobacter pylori. Infections tend to be associated with specific NHL subtypes.</li> <li>- Autoimmune disorders e.g. Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus</li> </ul>
Weak or conflicting	<ul style="list-style-type: none"> <li>- Other infectious agents e.g. hepatitis C infection, SV40 (monkey polyoma virus), several pathogens.</li> <li>- Ultraviolet radiation.</li> <li>- Increased consumption of red meat and dairy products.</li> <li>- Blood transfusion.</li> <li>- Various pharmaceuticals: results may be confounded by an association between NHL and the underlying disease</li> <li>- Obesity.</li> <li>- HRT (evidence conflicting, also data in support of protective effect)</li> <li>- Electromagnetic fields</li> <li>- Smoking</li> </ul>
Inverse	<ul style="list-style-type: none"> <li>- Allergic and atopic conditions and their correlates, such as early birth order.</li> <li>- Breast feeding – protective effect for mother (one study)</li> <li>- Consumption of fruit and vegetables</li> <li>- Alcohol consumption</li> </ul>

**Chemical exposures associated with NHL**

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8. The Department of Health Toxicology Unit reviewed 57 studies obtained from the scientific literature by a systematic search (<http://www.advisorybodies.doh.gov.uk/pdfs/cc0707.pdf>). We note that none of the studies were from the UK and that only those considered to be of adequate quality formed the basis of the evaluation in the discussion paper.

### Pesticides

9. A number of studies report an increased risk of NHL associated with occupational exposure to pesticides (Baris et al., 1998; Lee et al 2004; Fritschi et al 2005a; Mills et al 2005; Purdue et al 2006). Lower risks were reported in studies examining non-occupational exposure to pesticides (Buckley et al., 2000; Hartge et al., 2005; Colt et al., 2006). However, on balance, we consider that no specific pesticide or group of pesticides among those studied yielded consistent positive results of an association with NHL. Differences in the exposure classification of individual studies may partly explain these inconsistent findings.

### Organic solvents

10. Studies investigating the possible association between occupational exposure to organic solvents and NHL are conflicting (Boice et al ., 1999; Wong & Raabe, 2000; Fabbro-Perray et al., 2001; McDuffie et al., 2002; Raaschou Nielsen et al., 2003; Dryver et al., 2004; Miligi et al., 2006). We note that the available reviews on organic solvents have also reached contradictory conclusions.

11. The Committee reviewed the association between NHL and occupational exposure to the organic solvents tetrachloroethylene (TTCE) and trichloroethylene (TCE) in 1996 (COC, 1996). This followed the reclassification by the International Agency for Research on Cancer (IARC) of both TTCE and TCE from Group 2B (possibly carcinogenic to humans) to Group 2A (probably carcinogenic to humans). At that time the committee

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concluded that, overall, there was inadequate evidence to draw any conclusions for TTCE and it had considerable difficulties deriving an overall conclusion for TCE. No further conclusion can be reached following review of the more recent literature.

12. The limitations and inconsistencies of the studies on organic solvents as a whole do not appear to provide any additional significant support for any association.

#### Industrial chemicals

13. The Committee considered the carcinogenicity of tetrachlorodibenzo-p-dioxin (TCDD) in 2001 (COC, 2001). A 20-year mortality study by Bertazzi et al (2001) had reported that the risk of NHL was increased after 15 years in a cohort of residents exposed to dioxin following the Seveso accident in 1976, although an increased risk of lymphohaematopoeitic cancers had not been identified in the industrial cohorts exposed to TCDD. On the basis of all the data on the carcinogenicity of TCDD, it was concluded that TCDD should be regarded as a probable human carcinogen. However, any increased risk of cancer at background levels of exposure was considered likely to be extremely small and not detectable by current epidemiological methods. We note that a recent, non-occupational study by de Roos et al (2005) reported a 4-fold increase in NHL with increasing blood concentrations of a 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin.

14. Two recent studies have examined non-occupational exposure to non dioxin-like PCBs and the risk of NHL (Rothman et al., 1997; Colt et al., 2005). A positive association with PCBs was reported by Colt et al. (2005) who observed a 1.7-fold increased risk of NHL in US residents with increasing carpet dust levels of PCB 180. However, the study failed to provide any indication of the levels of PCB 180 inhaled and, since inhalation of PCBs is not considered to contribute significantly to the body burden in the general population (EFSA, 2005), these findings should be interpreted with caution.

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15. There is a good dose-response relationship between occupational exposure to PCBs and NHL and reasonably strong evidence for an association. A recent, nested case control study by Engel et al (2007) reported positive associations between blood concentrations of non dioxin-like PCB congeners 118, 138 and 153 and an increased risk of NHL. There is a plausible mechanism of action for PCBs in NHL development. PCBs can act as tumour promoters by means of their induction of xenobiotic metabolizing enzymes (EFSA, 2005). They have been shown to alter immune function in animals and may cause subtle immunological changes in exposed humans. However, an association with PCBs does not explain the trends in incidence of NHL, because levels of PCB in the environment have fallen since the 1970s. We consider that it would be valuable for the data on PCBs to be considered in more detail, preferably in the form of a meta-analysis or pooled analysis.

16. We are aware that IARC has recently reclassified the industrial monomer 1,3-butadiene<sup>1</sup> from Group 2A to a Group 1 (carcinogenic to humans), based on evidence in humans of an association with chronic lymphocytic leukaemias<sup>2</sup> (CLL) and NHL. We recommended that the data on 1,3-butadiene is considered in more detail.

### Chemicals associated with lifestyle

17. The previous evidence on the relationship between NHL risk and tobacco smoking and/or alcohol consumption, and previous reviews by the Committee indicated that there was no association with these exposures. However, we note that there are some studies which report increased risks of NHL associated with exposure to tobacco smoke. Morton et al (2005)

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<sup>1</sup> 1,3-butadiene is used as a monomer in the manufacture of rubber and other polymers, and is also produced as an intermediate during the manufacture of various other chemicals (IARC, 1999). Most evidence of its carcinogenicity in humans arises from studies reporting increased leukaemia risks in occupational cohorts (IARC, 1999); non-occupational exposure is thought to occur from engine exhaust and cigarette smoke.

<sup>2</sup> CLL is a newly recognised NHL subtype (Erkstrom Smedby, 2006)

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reported a 1.3-fold increased risk of follicular lymphoma in current smokers and observed differential susceptibility to NHL associated with different genetic polymorphisms in the *N*-acetyltransferase enzymes NAT1/NAT2 (Morton et al, 2006). In view of these studies, we have included smoking in the 'weak or conflicting evidence of an association' category.

18. Findings of studies examining the putative link between personal use of hair dyes and NHL are largely conflicting and further limited by the fact that the authors examined hair dyes as a group rather than on the basis of individual constituents (since most hair dyes differ in composition) (Holly et al., 1998; Alterkruse et al 1999; Zhang et al., 2004; Miligi et al., 2005; Takkouche et al., 2005). However, we are informed that the EU Scientific Committee on Consumer Products (SCCP) is currently reviewing<sup>3</sup> ingredients of hair dyes and that this is likely to result in a change in the composition of these products in future. Therefore, historical studies will be of little relevance in assessing current risk. We are also informed that, in 2008, a Working Group for IARC Monograph Volume 99 will reevaluate the current Group 2A classification for occupation as a hairdresser and Group 3 classification for personal use of hair colourants (IARC, 2007). We wish to see the result of this reevaluation in due course.

### **Conclusions**

- 19.
- i. There is limited evidence of an increased risk of NHL following occupational exposure to PCBs. It would be valuable for the data on PCBs to be considered in more detail, preferably in the form of a meta-analysis or pooled analysis. However, any association with PCBs would not explain the trends in incidence of this cancer.

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<sup>3</sup> The deadline for Industry to submit safety files for hair dyes which use a combination of substances in permanent formulations is December 2007 (EUROPA, 2007). Any permanent or non-permanent hair dyes receiving a negative SCCP opinion or for which no safety files have been submitted will be banned.

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- ii. (Conclusion on 1,3-butadiene to be added after a further review, in view of IARC's reclassification of 1,3-butadiene as a Group 1 carcinogen on the basis of CLL/NHL in humans).
- iii. (Conclusion on benzene and NHL to be added following review of paper by Vineis et al (2007)) .
- iv. After reviewing the available data, we conclude that, with the exception of PCBs, (1,3-butadiene and benzene), there is no convincing evidence from epidemiological studies that that environmental chemicals are responsible for the reported increased trend in NHL incidence which has occurred over the past 3 to 4 decades.

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