

STATEMENT ON NON-HODGKIN'S LYMPHOMA

COC/09/S1 – January 2009

Introduction

1. Malignant tumours of the lymphoid system, lymphoma, are divided into two major groups: Hodgkin's disease and non-Hodgkin's lymphoma (NHL). NHL is not a single disease but a mixture of disease entities. There are several schemes that have been used to characterise the disease. The majority of NHLs are of B lymphocyte origin, arising in lymph nodes. Treatment and prognosis depend on subtype.

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 has increased since the 1970s. 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.

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). The age-standardised incidence rate for NHL increased by over 50% in the twenty-year period between 1986-2005 (CRUK, 2007). Part of this increase is thought to be accounted for by an increased prevalence of HIV/AIDS (which is a significant risk factor for NHL). However, an increased NHL incidence is reported to have existed before the rise in HIV/AIDS (Ekstrom-Smedby 2006). Rates continued to increase after the mid-1990s in those aged 45 years and over, particularly in the over-65s. 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 a real increase in incidence of NHL (Barnes et al, 1986).

5. We note that there is a decreasing trend in mortality from NHL in recent years (CRUK, 2007), which cannot be attributed to changes in practice in recording cause of death.

Risk factors for NHL

6. 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 & Vajdic., 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 precipitate chronic antigenic stimulation or immunosuppression) (Ekstrom-Smedby, 2006). These include specific infections such as HIV/AIDS, immune deficiency and organ transplantation. Risk factors for which there is strong evidence of an association are considered to account for only a small percentage of total NHL cases.

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

Evidence for an association	Proposed risk factor
Strong	<ul style="list-style-type: none"> - Hereditary disorders of immune dysfunction e.g. ataxia-telangiectasia, severe combined immunodeficiency. - HIV/AIDS. - Immunosuppressive therapy following organ transplantation. - 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. - 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. - Autoimmune disorders e.g. Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus.
Weak or conflicting	<ul style="list-style-type: none"> - Other infectious agents e.g. hepatitis C infection, SV40 (monkey polyoma virus), several pathogens. - Ultraviolet radiation. - Increased consumption of red meat and dairy products. - Blood transfusion. - Various pharmaceuticals: results may be confounded by an association between NHL and the underlying disease. - Obesity. - HRT (evidence conflicting, also data in support of protective effect). - Electromagnetic fields. - Smoking.
Inverse	<ul style="list-style-type: none"> - Allergic and atopic conditions and their correlates, such as early birth order.

	<ul style="list-style-type: none"> - Breast feeding – protective effect for mother (one study). - Consumption of fruit and vegetables. - Alcohol consumption.
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Chemical exposures associated with NHL

7. The Department of Health Toxicology Unit reviewed 57 studies which were obtained from the scientific literature by a systematic search and which met the inclusion criteria (see <http://www.advisorybodies.doh.gov.uk/pdfs/cc0707.pdf>). None of the studies were from the UK.

Pesticides

8. A number of studies report an increased risk of NHL associated with both occupational and non-occupational exposure to pesticides (Buckley et al., 2000; Baris et al., 1998; Lee et al 2004; Fritschi et al 2005; Hartge et al., 2005; Mills et al 2005; Colt et al., 2006; Purdue et al 2007). The increases tended to be higher in the occupational than in the non-occupational studies. 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

9. Studies investigating the possible association between occupational exposure to organic solvents and NHL have produced conflicting results (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 a number of good reviews have been published on organic solvents (e.g. Smith et al., 2007), and that these have also reached contradictory conclusions.

10. During our meeting in July 2007, we were notified of a large population-based case-control study in Italy which investigated the relationship between NHL and exposure to a range of chemicals in residents living in eight areas with manufacturing industries where solvents had been largely used (Vineis et al., 2007). The study reported a non-statistically significant increased risk of NHL in those with both exposure to benzene and a history of autoimmune disease (OR = 16.3 [95% CI: 0.8-321]), and a strongly significant association between exposure to benzene and NHL in the presence of a family history of haematolymphopoietic malignancies (OR=29.8 [95% CI:1.4-650.2]). These findings were discussed further at the November 2007 COC meeting. Unfortunately, this study does not assist with assessing whether there is an association between exposure to benzene and NHL in the general population, although it identifies a subset of individuals who may be at risk.

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 COC 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 provide support for an association with NHL in the general population.

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 lymphohaematopoietic cancers had not been identified in industrial cohorts exposed to TCDD. On the basis of the data on the carcinogenicity of TCDD at multiple sites, it was concluded that TCDD should be regarded as a probable human carcinogen, but that “any increased risk of cancer at background levels of exposure was considered likely to be extremely small and not detectable by current epidemiological methods” (COC, 2001). We note that a recent non-occupational study by de Roos et al (2005) reported statistically significant increasing trends ($p < 0.05$) with increasing blood lipid concentrations of each of the 4 polychlorinated dibenzofuran (PCDF) congeners studied, including a 4-fold increase in NHL at > 13.3 pg 1,2,3,4,6,7,8-heptachlorodibenzofuran/g lipid. No association was found with increasing blood lipid concentrations of each of the 3 polychlorinated dibenzodioxin congeners or the 2 coplanar PCBs studied.

14. Two recent studies have examined non-occupational exposure to non dioxin-like PCBs¹ 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.

15. A recent, nested case-control study by Engel et al (2007) reported positive associations between blood concentrations of non dioxin-like PCB

¹ 209 PCB congeners are theoretically possible. Of these, 12 non-*ortho* or mono-*ortho* compounds exhibit similar biological activity to PCDDs and PCDFs, and are therefore referred to as “dioxin-like PCBs”. The other PCBs are referred to as “non dioxin-like PCBs”.

congeners 118², 138 and 153 and risk of NHL. There is a possible mechanism of action for PCBs in NHL development. PCBs can act as tumour promoters like several other inducers of drug metabolizing enzymes (EFSA, 2005). They have been shown to alter immune function in animals and may cause subtle immunological changes in exposed humans (ATDSR, 2000). However, a causal association with PCBs does not explain the trends in incidence of NHL, because levels of PCB in the environment have fallen since the 1970s. 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 from Group 2A to a Group 1 (carcinogenic to humans), based on evidence in humans of an association with chronic lymphocytic leukaemia (CLL)³ and NHL. 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; non-occupational exposure is thought to occur from engine exhaust and cigarette smoke (IARC, 1999). Most human data reviewed by IARC derived from studies which reported an increased risk of leukaemia risks in occupational cohorts (IARC, 1999). We have reviewed the epidemiology of human exposure to 1,3-butadiene and consider that the available evidence does not provide a convincing case for an association between 1,3-butadiene and NHL in humans. However, we will examine the IARC conclusion in detail when the relevant monograph is published.

Chemicals associated with lifestyle

17. The previous literature on the relationship between NHL risk and tobacco smoking and/or alcohol consumption, and previous reviews by the Committee indicated that there was little evidence of an 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) reported an increased risk of follicular lymphoma in current smokers (OR=1.3 [1.1-1.5]) 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

² PCB congener 118 is known to exhibit both dioxin-like and non-dioxin-like properties (EFSA, 2005).

³ CLL is newly recognised as an NHL subtype.

Consumer Products (SCCP) is currently reviewing⁴ ingredients of hair dyes and that this is likely to result in a change in the composition of these products in future (EUROPA, 2007). In February 2008, a Working Group for IARC Monograph Volume 99 re-evaluated the then Group 2A classification for occupation as a hairdresser and Group 3 classification for personal use of hair colorants (Baan et al., 2008; IARC, 2007) and reaffirmed these classifications. We will ascertain whether IARC considered data on NHL when the relevant monograph is published.

Conclusions

19.
 - i. There is limited evidence of an increased risk of NHL following non-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 positive association with PCBs would not explain the trends in incidence of this cancer, given that PCB levels in the environment have decreased over the last few decades.
 - ii. The available evidence on exposure to 1,3-butadiene and NHL do not provide convincing evidence of an association.
 - iii. There is no clear evidence of an association between benzene exposure and NHL in the general population. One study has shown an increased risk of NHL from benzene in those with a family history of malignant haematologic neoplasms (Vineis et al (2007)).
 - iv. After reviewing the available data, we conclude that there is no convincing evidence from epidemiological studies that environmental chemicals are responsible for the reported increase in NHL incidence which has occurred over the past 3 to 4 decades. As noted above, there is limited evidence of an association between NHL and non-occupational exposure to PCBs.

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⁴ 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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