Chemical exposures and risk of chronic lymphocytic leukaemia

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Summary

Literature on the role of chemicals in the development of chronic lymphocytic leukaemia (CLL) and monoclonal B-cell lymphocytosis in humans is sparse. This research is complicated by the rarity of these outcomes and the different disease classifications used over time. Several studies have noted excesses of CLL among farmers and a few have pointed to specific chemicals. Reports suggesting elevated CLL rates in the rubber and petroleum industries point to a possible role for solvents and other chemicals. The few studies that focus on specific chemicals suggest that CLL should be more carefully evaluated in relation to possible exposure to chemicals and solvents, particularly for benzene and butadiene. Pooled analyses of CLL studies within consortia offer an opportunity to investigate the possible aetiological role of chemical exposures with improved statistical power.

Keywords: chronic lymphocytic leukaemia, lymphoid malignancy, monoclonal B-cell lymphocytosis, occupation, chemicals.

Background

Chronic lymphocytic leukaemia (CLL) represents approximately one-third of all leukaemias diagnosed in the United States and is the most common type in adults (Jemal *et al*, 2007). Whereas several environmental risk factors for acute myeloid leukaemia have been established (e.g. exposure to benzene, smoking, ionizing radiation and treatment with alkylating agents used in chemotherapy), the aetiology of CLL and its suspected precursor condition, monoclonal B-cell lymphocytosis (MBL), remains poorly understood.

The most suggestive evidence regarding a possible role for chemicals in the development of CLL has come from studies of occupational exposures. The establishment of benzene as a myeloid leukemogen (Linet *et al*, 2006) spurred many toxicological and epidemiological studies to evaluate the potential hazard of solvents and other chemicals in the development of leukaemias and other haematopoetic cancers. Several chemicals and other environmental factors have been associated with cancer of the lymphatic and haematopoietic system in laboratory animals (Gold *et al*, 2001) and humans (Siemiatycki *et al*, 2006), although usually for histological types other than CLL. Most of these studies have been limited in their ability to study CLL because of the rarity of this disease and the general tendency to group CLL with other haematopoietic malignancies rather than treating it as a separate outcome. Nonetheless, evidence of excess risk for certain industries, occupations and workplace exposures has been reported.

Herein, we review the epidemiological and experimental literature regarding the role of chemicals in the development of CLL. We also briefly review the literature on non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) because information on these lymphoid malignancies, which are also mainly of B-cell origin, may provide additional insight into the possible role of chemicals in the aetiology of CLL and related disorders.

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Animal bioassays

There are about 100 chemicals that have caused haematopoietic cancer in at least one sex of one species in animal bioassays (Gold *et al*, 2001) (Table I). Some of these chemicals have widespread use. Although there is no specific haematopoietic cancer in rodents that exactly corresponds to CLL in humans, transgenic mouse models of B-cell CLL have been developed (Pekarsky *et al*, 2007). Chemicals that have widespread use and the ability to cause various haematopoietic cancers in rodents raise concerns about human exposure. The chemicals positive in animal bioassays do not fall into any particular chemical grouping and include drugs, flavours and fragrances, food dyes, pesticides, solvents and other industrial chemicals. Several chemicals are positive in both mice and rats; these include allyl isovalerate, chlorambucil, dacarbazine, cyclophosphamide, procarbazine, ethylene oxide, formic acid, tetrafluoroethylene and thio-tepa. Allyl isovalerate is a fragrance used in soaps, creams and perfumes since the 1950s. Chlorambucil, cyclophosphamide, dicarbazine and procarbazine are alkylat-

First published online 24 October 2007
doi:10.1111/j.1365-2141.2007.06874.x

Table I. Chemicals that induce tumours of the haematopoietic system in laboratory animals (Modified from Gold *et al*, 2001).

Species	Chemicals
Mouse	Acetamide, Aflatoxin, Illyl isovalerate, Thiazole, 2-Aminoanthraquinone, 5-Azacytidine, Azathioprine, Benzene, 1,4-Benzoquinone, Benzotrichloride, Benzoyl hydrazine, 1,3-Butadiene, 1,2-di-n-Nutylhydrazine.2HCl, Captafol, Chlorambucil, Chlorinated paraffins, Cyclophosphamide, Dacarbazine, DDT, Dibromodulcitol, Dibromomannitol, Dioxins, Estradiol mustard, Ethylene oxide, 5-Flourouracil, Formamide, Formic acid, Genitian violet, Hexanamide, 2-Hydrazino-4-(p-aminphenyl)thiazole, 2-Hydrazino-4-(p-nitrophenyl)thiazole), 1-(2-Hydroxyethyl)-1-nitrosourea, ICRF-159, Isophosphamide, Isoprene, MeIQx, Melphalan, Methyl methanesulfonate, 4,4′-Methylenedianiline.2HCl, Metronidazole, Phenesterin, Phenolphthalein, PhIP.HCL, Phorbol, Procarbazine.HCL, Strobane, Tetrafluoroethylene, Thio-tepa, Tolylurea, Tris(2-chloroethyl)phosphate, Urethane, C.I. vat yellow no. 4
Rat	Allyl isovalerate, Atrazine, Benzidine, 2,2-Bis(bromomethyl)-1,3-propanediol, Direct blue 15, Cadmium chloride, Chlorambucil, 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, Cyclophosphamide, Dacarbazine, Dichloroacetylene, 3,3′Dichlorobenzidine, Dichlorvos, Dimethoxane, 3,3;Dichlorobenzidine-4,4″diisocyanate, Dimethyl morpholinophosphoramidate, Ethylene oxide, Formaldehyde, Formic acid, Furan, Glycidol, FD and C green number 1 and 2, Haematoxylin, Hydroquinone, Iodinated glycerol, Lasiocarpine, 2-Mercaptobenzothiazole, Metepa, Methyl *tert*-butyl ether, Mirex, Nitrosourea, Nitroanisole, Nitropyrene, Nitroso-ethylamine, N-Nitroso diethanolamine, PhIP.HCl, Procarbazine.HCl, Propane sultone, FD and C Red number 4, Tetrachloroethylene, Tetrafluoroethylene, Thio-tepa, Trichlorophenol, Trp-P-2 acetate
Monkey	Procarbazine. HCL

ing agents used in chemotherapy to treat a variety of cancers. Thio-tepa was also used as an antineoplastic drug to treat lymphoma until the 1970s and is still used for other cancers. Ethylene oxide is an industrial intermediate and a sterilant for foodstuffs and medical supplies. Tetrafluoroethylene is used to produce polymers such as Teflon. Formic acid, the simplest carboxylic acid, is used as a chemical intermediate and is the venom in bee and ant stings.

Industries

Both case-control and cohort studies have reported links between occupations and/or occupational exposures and CLL, but none are conclusive. Excesses have been reported in some studies among workers in the petroleum, rubber, mining, wood and agricultural industries, and workers exposed to solvents, styrene, butadiene and ethylene oxide, but there are also studies that show no excesses (Linet *et al*, 2006). Table II describes studies that link CLL with specific occupations, industries or chemical exposures.

Agriculture

CLL. Several studies of farmers suggest an association with leukaemia (Blair *et al*, 1992). However, the results from the few studies that have specifically evaluated CLL are inconsistent, reporting both positive (Blair & White, 1985; Brown *et al*, 1990; Nanni *et al*, 1996; Zheng *et al*, 2002; Miligi *et al*, 2003) and negative findings (Blair & Watts, 1981; Brownson & Reif, 1988). Although exposure to pesticides is a concern for any cancer excess observed among farmers (Malone *et al*, 1989), few studies have evaluated risks from specific chemicals or chemical groups. Excesses of CLL have been linked to use of certain classes of pesticides (Brown *et al*, 1990; Nanni *et al*, 1996; Miligi *et al*, 2003) and contact with animals (Svec *et al*, 2005). The Agricultural Health Study, a large prospective study of farmers in the United States, has found some evidence for associations between leukaemia and alachlor (Lee *et al*, 2004), diazinon (Freeman *et al*, 2005) and fonofos (Mahajan *et al*, 2006), but the numbers of cases were too small to evaluate specific histological types. Waterhouse *et al* (1996) found an elevated standardized incidence rate of 1·75 for CLL among residents of a county with intensive use of agricultural pesticides.

NHL and MM. These malignancies have been consistently associated with employment in agriculture (Khuder & Mutgi, 1997; Fabbro-Peray *et al*, 2001; De Roos *et al*, 2006; Hartge *et al*, 2006; Boffetta & de Vocht, 2007). NHL has been linked to exposure to phenoxyacetic acid herbicides and organochlorine and organophosphate insecticides (Zahm *et al*, 1997). Hardell *et al* (1994) reported phenoxyacetic acids were associated with several NHL subtypes, including well-differentiated lymphocytic, which is mainly composed of small cell lymphocytic lymphoma and chronic lymphocytic leukaemia. The phenoxyacetic acid herbicides are of special concern because of their widespread use and because they are contaminated with dioxins and dibenzofurans (International Agency for Research on Cancer; IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 1997).

Petroleum

CLL. In a meta-analysis of CLL among petroleum workers, four of 17 studies had standardized mortality ratios (SMRs) >1·0, but only one was statistically significant and the meta-SMR was 0·84 (Raabe & Wong, 1996). A study of active and terminated refinery and petrochemical workers found a significant excess of leukaemia mortality among workers in Louisiana, which was largely because of CLL (SMR = 351)

Table II. Studies that provide relative risks for chronic lymphocytic leukaemia (CLL) or monoclonal B-cell lymphocytosis (MBL) by occupation and by chemical exposure.

Citation	Geographical location	Study design	Cancer type	Findings
Burmeister *et al*, 1982	Iowa, USA	Case-control	CLL mortality	Farmers (OR = 1·70*)
Wolf *et al*, 1981	USA	Case-control	Lymphatic leukaemia mortality	Work locations in the rubber industry – compounding and mixing (OR = 2·5), general service (OR = 2·2)
Giles *et al*, 1984	Tasmania, Australia	Case-control	CLL incidence	Mining (RR men = 3·67*; women = 8 cases/0 controls*; farmers and laborers (RR men = 2·00; women = 3·67*), production trades (RR men = 3·50), service industries (RR women = 2·00)
Blair & White, 1985	Nebraska, USA	Case-control	CLL mortality	Farmers (OR = 1·67*)
Alavanja *et al*, 1988	USA	Proportionate mortality	CLL mortality	Agricultural extension agents (PMR = 206, (PMR = 5·40* for those working >14 years)
Flodin *et al*, 1988	Sweden	Case-control	CLL incidence	DDT (OR = 6·1*), fresh wood (OR = 3·2*), engine exhausts (OR = 2·5*)
Malone *et al*, 1989	Washington, Utah, Michigan, USA	Case-control	CLL incidence	Aliphatic hydrocarbons (RR = 1·6*), chlorinated hydrocarbons (RR = 1·5*), pesticides (RR = 1·5), acids (RR = 1·7*), other caustics (RR = 2·1*), petroleum industry (RR = 1·9*)
Pearce *et al*, 1989	New Zealand	Case-control	CLL incidence	Electrical workers (OR = 3·36* aged 20–64 and 1·67 aged 65 years or older)
Brown *et al*, 1990	Iowa and Minnesota, USA	Case-control	CLL incidence	Men only. Farmers (RR = 1·4*), used fungicides (RR = 1·4*), used herbicides (RR = 1·4*), used insecticides (RR = 1·3*)
Pasqualetti *et al*, 1991	Italy	Case-control incidence	CLL and MG	CLL and asbestos (OR = 4·71*) and pesticides (OR = 4·00*); MG and asbestos (OR = 4·61*), fertilizers (OR = 3·13*), mineral oils (OR = 3·00*) and pesticides (OR = 3·55*)
Floderus *et al*, 1994	Sweden	Cohort	CLL mortality	Cohort of railway workers (engine drivers RR = 2·7*, engine drivers and conductors RR = 1·9)
Amadori *et al*, 1995	Italy	Case-control	CLL and NHL incidence	Animal farmers (OR = 1·79*)
Nanni *et al*, 1996	Italy	Case-control incidence	CLL and low grade NHLs	Insecticides in general (OR = 2·46*), carbamates (OR = 3·08*) and organophosphates (OR = 2·97*)
Raabe & Wong, 1996	USA, United Kingdom	Cohort mortality	CLL	Petroleum workers meta SMR = 0·84
Waterhouse *et al*, 1996	Michigan, USA	Cohort incidence	CLL	Residing in heavy pesticide use area (SIR = 1·75)
Blair *et al*, 2000	Iowa and Minnesota, USA	Case-control	CLL incidence	Manufacturing managers (OR = 2·9*), lodging and related jobs (OR = 5·0*), janitors (OR = 2·1*), medicine and health (OR = 1·6), truck drivers (OR = 3·0)

Table II. (*Continued*).

Citation	Geographical location	Study design	Cancer type	Findings
Lewis *et al*, 2000	USA	Cohort	CLL mortality	Refinery/petrochemical workers (SMR = 351*)
Costantini *et al*, 2001	Italy	Case-control	CLL and NHL incidence	Managers and clerks (OR = 1·8*), cooks, waiters, bartenders (OR = 1·5), and cleaners, charworkers and related workers (OR = 1·9)
Bouchardy *et al*, 2002	Switzerland	Case-control incidence	CLL	Butchers (OR = 2·0*), leather industries (OR = 2·5*)
Zheng *et al*, 2002	Nebraska, USA	Case-control	CLL and small lymphocytic lymphoma incidence	Farmers (RR men = 11·6*; women = 2·3*)
Glass *et al*, 2003	Australia	Nested case-control	CLL incidence	Benzene ppm-years (OR = 2·76 for 4–8; OR = 4·52 for >8)
Miligi *et al*, 2003	Italy	Case-control	CLL and NHL incidence	No significant excesses with crops grown, excesses among women (but not men) exposed to dinocap (RR = 5·9*), ziram (RR = 1·9), cyclohexames (RR = 2·5), amides (RR = 3·2), triazines (RR = 2·0)
Beard *et al*, 2003	New South Wales, Australia	Cohort	Lymphocytic leukaemia mortality	No significant excesses associated with possible exposure to pesticides to control ticks on livestock
Hauptmann *et al*, 2003	USA	Cohort	Lymphatic leukaemia mortality	Formaldehyde – no clear trend
Mills *et al*, 2005	California, USA	Case-control	Lymphocytic leukaemia incidence	Non-significant RRs of about 2·0 were observed among farm workers with possible exposure to several pesticides
Graff *et al*, 2005	USA and Canada	Cohort	CLL mortality	Excess from butadiene in highest exposure category (RR = 2·7), but not for styrene or dimethyldithiocarbamate
Svec *et al*, 2005	USA	Case-control	CLL mortality	Exposure to animals (CLL = 1·24*)
Ji & Hemminki, 2006	Sweden	Cohort	CLL incidence	Sales agents (SIR = 1·22* men) launders and drycleaners (SIR = 1·54* women) and mechanics (SIR = 2·71* women), non-significant excesses among physicians (SIR = 1·34 men), miners (SIR = 1·25 men), printers (SIR = 1·20 men)
Seidler *et al*, 2007	Germany	Case-control	Lymphomas (but CLL listed separately)	Carbon tetrachloride (OR = 2·7*), chlorinated hydrocarbons (OR = 1·8)

NHL, non-Hodgkin lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia; SIR, standardized incidence rate; SMR, standardized mortality ratio; OR, odds ratio; RR, relative risk; MG, monoclonal gammopathies.
*$P < 0{\cdot}05$.

(Lewis *et al*, 2000). However, a follow-up investigation of haematopoietic cancer in this cohort did not observe an association with incident CLL. No excess risk for work in the petroleum industry was found in a case-control study in the Midwest (Blair *et al*, 1993), but risk was increased in another study (OR = 1·9 among self-respondents)(Malone *et al*, 1989).

NHL and MM. These tumours have not generally been found in excess among persons employed in the petroleum industry (De Roos *et al*, 2006; Hartge *et al*, 2006). However, a slight excess was observed in a case-control study of NHL in the Midwest (Blair *et al*, 1993).

Rubber

CLL. Leukaemia tends to be elevated among workers in the rubber industry (Kogevinas *et al*, 1998). Most studies do not present specific information for CLL, but excesses of lymphocytic leukaemia have been reported in a few studies (Wolf *et al*, 1981; Linet *et al*, 2006). Specific agents have not been identified, although it has been speculated that solvents (including benzene) used as glues, binders, and release agents in the industry may play a role (Kogevinas *et al*, 1998).

NHL and MM. Studies of these tumours among workers in the rubber industry have mixed results (Kogevinas *et al*, 1998; De Roos *et al*, 2006; Hartge *et al*, 2006; Linet *et al*, 2006).

Chemicals

Benzene

CLL. Benzene, an established cause of acute myeloid leukaemia, traditionally has not been associated with CLL (Linet *et al*, 2006). A non-significant excess was recently reported among Australian petroleum industry workers exposed to benzene (Glass *et al*, 2003).

NHL and MM. Although NHL has not traditionally been considered a benzene-related disease, a recent review of the epidemiological literature concluded that the evidence supports an association (Smith *et al*, 2007). NHL has been associated with solvents other than benzene, including xylene and toluene (Vineis *et al*, 2007). MM was not associated with benzene in a study from Australia (Glass *et al*, 2003), but it has been linked to this exposure in a few studies (De Roos *et al*, 2006). The issue of benzene and MM is far from settled (Bergsagel *et al*, 1999; Goldstein & Shalat, 2002). Small lymphocytic lymphoma was associated with benzene, styrene, xylene, toluene and dichloromethane in a case-control study in Italy (Miligi *et al*, 2006); diffuse small cell lymphoma was linked with solvents in a case-control study in the United States (Tatham *et al*, 1997), and several different subtypes of lymphoma were associated with benzene and other solvents in a case-control study from Sweden (Hardell *et al*, 1994).

Dioxins

CLL. Chronic lymphocytic leukaemia has not been evaluated in cohorts of dioxin workers; however, leukaemia overall does not appear to be elevated with this exposure (Kogevinas *et al*, 1997; Steenland *et al*, 1999).

NHL and MM. Both NHL and MM have been non-significantly associated with exposure to dioxins and dioxin-containing compounds (Kogevinas *et al*, 1997; Steenland *et al*, 1999).

Formaldehyde

CLL. Leukaemia has been associated with formaldehyde in two industrial cohorts (Hauptmann *et al*, 2003; Pinkerton *et al*, 2004), but not in another (Coggon *et al*, 2003). This association was considerably stronger for myeloid than for lymphocytic leukaemia.

NHL and MM. Small and non-significant excesses associated with formaldehyde exposure were observed for NHL and MM in one cohort (Hauptmann *et al*, 2003).

Ethylene oxide

CLL. Concern about ethylene oxide was raised by large excesses of haematopoietic cancer reported in three small cohort studies in Sweden (Hogstedt *et al*, 1986). However, larger studies in Germany, the United Kingdom, Italy, and the United States did not confirm these large excesses, although slight elevations were observed in some subgroups (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 1994). Although the IARC classified ethylene oxide as a human carcinogen, it found that the epidemiologic data were limited. No specific associations with CLL have been reported, but lymphoid leukaemia and lymphoma excesses have been observed.

NHL and MM. A recent follow-up of a large cohort in the United States did not report on CLL separately, but did find an increased risk for lymphoid tumours (NHL, MM and lymphocytic leukaemia) among men (Steenland *et al*, 2004).

Other occupations and chemicals

Other interesting associations with specific chemicals noted in individual studies include a link between monoclonal gammopathies and exposure to asbestos, fertilizers and mineral oils (Pasqualetti *et al*, 1991). CLL has also been linked to butadiene (Graff *et al*, 2005), carbon tetrachloride and chlorinated hydrocarbons (Seidler *et al*, 2007), launderers and drycleaners (Ji & Hemminki, 2006), cleaners or janitors (Blair *et al*, 2000; Costantini *et al*, 2001), and individuals working with fresh wood (Flodin *et al*, 1988). NHL has also been associated with most of these exposures (Divine & Hartman, 2001; Hartge *et al*, 2006).

Conclusions

Information on the role of chemical exposures in the development of CLL is quite limited. Several factors contribute to this paucity of data. First, leukaemia is not a common disease and it would take large studies to be able to evaluate risks specifically for CLL. This is especially difficult for cohort studies of occupational or industrial groups, which have provided much of the information on chemical exposures and human cancer. Second, the lack of consistency in the classification of leukaemia in epidemiological studies complicates interpretation. In earlier studies, CLL was typically included in studies of leukaemia while, more recently, it is often grouped with other B-cell lymphoid malignancies as in the current World Health Organization classification system (Turner *et al*, 2004). For example, the studies listed in Table II, have cancer classifications for CLL, CLL and NHL, CLL and low-grade NHL, and lymphatic leukaemia. Third, although bioassays have identified a number of chemicals that cause cancer of the haematopoietic system in laboratory animals, there is no leukaemia in animals strictly analogous to CLL. We have included some information on the role of chemicals in the development of NHL and MM, two other closely related malignancies that consist mainly of neoplastic B cells, to assist in evaluation of chemical exposures and CLL.

There are a few reported associations that deserve attention. Links with farmers, agricultural occupations, or agricultural chemicals provide the strongest leads. These associations have been observed in several studies of different designs and in different geographical locations. Several pesticides (atrazine, dichlorvos and dichloro-diphenyl-trichloroethane) cause haematopoietic cancers in rodents (Gold *et al*, 2001). Associations between agricultural exposures and NHL and MM provide additional support that CLL might result from agricultural exposures. Few studies, however, have evaluated specific agricultural agents that might be involved. These have tended to focus on pesticides, but other possible exposures (e.g. fertilizers, solvents, engine exhausts and microbes) deserve attention.

Excesses of CLL in the few studies of the rubber and petroleum industries suggest that links with benzene and other solvents should be further evaluated. Benzene causes haematopoietic cancer in rodents and acute myeloid leukaemia in humans, and has been associated with NHL (Smith *et al*, 2007); however, findings for CLL have been generally null. The animal and human data suggest that the CLL – benzene relationship should be further evaluated. Few other solvents have been evaluated with regard to CLL.

Other chemicals that deserve some attention regarding CLL include dioxins, formaldehyde, butadiene and ethylene oxide. Dioxins are classified as human carcinogens by IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (1997) and B cells are particularly sensitive to their immunotoxic effects (Schwartz, 1997). There is no evidence that they cause CLL in humans, but haematopoietic cancer has occurred in animals and NHL and MM in humans. Butadiene causes haematopoietic cancer in rodents and has been linked to CLL, acute myeloid leukaemia and NHL in human studies (Divine & Hartman, 2001; Graff *et al*, 2005; Cheng *et al*, 2007). Formaldehyde has been associated with leukaemia in humans (Hauptmann *et al*, 2003), but the relationship is stronger for myeloid leukaemia. Formaldehyde has caused lymphomas in rodents, but there is no evidence that it is linked to NHL or MM in humans. Ethylene oxide causes haematopoietic cancer in rodents and has been associated with NHL, but not CLL, in humans (Steenland *et al*, 2004). Table III summarizes the evidence for the role for specific chemicals in the development of CLL. Pesticides, solvents and butadiene seem the most likely candidates.

Table III. Summary of evidence regarding chemicals and CLL.

Chemical	Evidence in humans		Haematoxicity in animals
	CLL	NHL/MM	
Pesticides	Yes	Yes	Yes
Solvents	Yes	Yes	Yes
Benzene	One study	Yes	Yes
Butadiene	Yes	Yes	Yes
Formaldehyde	No	No	Yes
Dioxins	No	Yes	Yes
Ethylene oxide	No	Yes	Yes

NHL, non-Hodgkin lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia.

It is unclear how chemical exposures might increase the risk of CLL. Immune system dysregulation is suspected to be a central factor underlying the development of CLL and other lymphoid neoplasms. There are several reports linking exposure to solvents and pesticides with impaired immune function (Bergamaschi *et al*, 1995; Colosio *et al*, 1998; Blakley *et al*, 1999; Palermo-Neto *et al*, 2001; Lan *et al*, 2004) and it is possible that chemicals may influence the development of CLL on this basis. Some of the chemicals discussed have also been demonstrated to induce chromosomal rearrangements (Garry *et al*, 1992; Khalil, 1995; Biro *et al*, 2002; Lander *et al*, 2000; Bolognesi, 2003; Lebailly *et al*, 2003; Holeckova *et al*, 2004; Kim *et al*, 2004), a common feature of CLL (Stilgenbauer *et al*, 2002). Such clastogenic effects may be an important mechanism through which some chemicals contribute to the pathogenesis of this malignancy.

In summary, a variety of chemical exposures provide suggestive evidence of an association with CLL. However, the evidence to date is inconclusive. Future investigations of chemicals and CLL are warranted, although it is important that such work overcome past study limitations (small sample size, insufficient detail of disease classification) to be truly informative. Pooled analyses of CLL within consortia offer an opportunity to investigate the aetiological relevance of occupational exposures with high statistical power. Another potentially fruitful area of research is the development of cross-sectional studies among industrial workers with specific chemical exposures, where practical, to investigate associations with MBL, the suspected precursor condition for CLL.

Acknowledgements

This research was supported, in part, by the NIH Intramural Research Program (Division of Cancer Epidemiology and Genetics, National Cancer Institute).

References

Alavanja, M.C.R., Blair, A., Merkle, S., Teske, J. & Eaton, B. (1988) Mortality among agricultural extension agents. *American Journal of Industrial Medicine*, **14,** 167–176.

Amadori, D., Nanni, O., Falcini, F., Saragoni, A., Tison, V., Callea, A., Scarpi, E., Ricci, M., Riva, N. & Buiatti, E. (1995) Chronic lymphocytic leukemias and non-Hodgkin's lymphoma by histological type in farming – animal breeding workers – a population case-control study based on job titles. *Occupational and Environmental Medicine*, **52,** 374–379.

Beard, J., Sladden, T., Morgan, G., Berry, G., Brooks, L. & McMichael, A. (2003) Health impacts of pesticide exposure in a cohort of outdoor workers. *Environmental Health Perspectives*, **111,** 724–730.

Bergamaschi, E., Smargiassi, A., Mutti, A., Franchini, I. & Lucchini, R. (1995) Immunological changes among workers occupationally exposed to styrene. *International Archives of Occupational and Environmental Health*, **67,** 165–171.

Bergsagel, D.E., Wong, O., Bergsagel, P.L., Alexanian, R., Anderson, K., Kyle, R.A. & Raabe, G.K. (1999) Benzene and multiple myeloma: appraisal of the scientific evidence. *Blood*, **94,** 1174–1182.

Biro, A., Pallinger, E., Major, J., Jakab, M.G., Klupp, T., Falus, A. & Tompa, A. (2002) Lymphocyte phenotype analysis and chromosome aberration frequency of workers occupationally exposed to styrene, benzene, polycyclic aromatic hydrocarbons or mixed solvents. *Immunology Letters*, **81,** 133–140.

Blair, A. & Watts, D.W. (1981) Death certificate study of leukemia among farmers from Wisconsin. *Journal of National Cancer Institute*, **66,** 1027–1030.

Blair, A. & White, D.W. (1985) Leukemia cell types and agricultural practices in Nebraska. *Archives of Environmental Health*, **40,** 211–214.

Blair, A., Zahm, S.H., Pearce, N.E., Heineman, E.F. & Fraumeni, Jr, J.F. (1992) Clues to cancer etiology from studies of farmers. *Scandinavian Journal of Work, Environment and Health*, **8,** 209–215.

Blair, A., Linos, A., Stewart, P.A., Burmeister, L.F., Gibson, R., Everett, G., Schuman, L. & Cantor, K.P. (1993) Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case-control study. *American Journal of Industrial Medicine*, **23,** 301–312.

Blair, A., Zheng, T., Linos, A., Stewart, P.A., Zhang, Y.W. & Cantor, K.P. (2000) Occupation and leukemia: a population-based case-control study in Iowa and Minnesota. *American Journal of Industrial Medicine*, **40,** 3–14.

Blakley, B., Brousseau, P., Fournier, M. & Voccia, I. (1999) Immunotoxicity of pesticides : a review. *Toxicology and Industrial Health*, **15,** 119–132.

Boffetta, P. & de Vocht, F. (2007) Occupation and the risk of non-Hodgkin lymphoma. *Cancer Epidemiology, Biomarkers and Prevention*, **16,** 369–372.

Bolognesi, C. (2003) Genotoxicity of pesticides: a review of human biomonitoring studies. *Mutation Research*, **543,** 251–272.

Bouchardy, C., Schuler, G., Minder, C., Hotz, P., Bousquet, A., Levi, F., Fisch, T., Torhorst, J. & Raymond, L. (2002) Cancer risk by occupation and socioeconomic group among men – a Study by the Association of Swiss Cancer Registries. *Scandinavian Journal of Work, Environment and Health*, **28**(Suppl. 1)**,** 1–88.

Brown, L.M., Blair, A., Gibson, R., Everett, G.D., Cantor, K.P., Schuman, L.M., Burmeister, L.F., Van Lier, S.F. & Dick, F. (1990) Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Research*, **50,** 6585–6591.

Brownson, R.C. & Reif, J.S. (1988) A cancer registry-based study of occupational risk for lymphoma, multiple myeloma, and leukemia. *International Journal of Epidemiology*, **17,** 27–32.

Burmeister, L.F., Van Lier, S.F. & Isacson, P. (1982) Leukemia and farm practices in Iowa. *American Journal of Epidemiology*, **115,** 720–728.

Cheng, H., Sathiakumar, N., Graff, J., Mathews, R. & Delzell, E. (2007) 1,3-Butadiene and leukemia among synthetic rubber industry workers: exposure-response relationships. *Chemico-Biological Interactions*, **166,** 15–24.

Coggon, D., Harris, E.C., Poole, J. & Palmer, K. (2003) Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *Journal of National Cancer Institute*, **95,** 1608–1615.

Colosio, C., Corsini, E., Barcellini, W. & Maroni, M. (1998) Immune parameters in biological monitoring of pesticide exposure: current knowledge and perspectives. *Toxicology Letters*, **108,** 285–295.

Costantini, A.S., Miligi, L., Kriebel, D., Ramazzotti, V., Rodella, S., Scarpi, E., Stagnaro, E., Tumino, R., Fontana, A., Masala, G., Vigano, C., Vindigni, C., Crosignani, P., Benvenuti, A. & Vineis, P. (2001) A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. *Epidemiology*, **12,** 78–87.

De Roos, A.J., Baris, D., Weiss, N.S. & Herrington, L.J. (2006) Multiple myeloma. In: *Cancer Epidemiology and Prevention* (ed. by D. Schottenfeld & J.F. Fraumeni Jr), pp. 919–945. Oxford University Press, New York, NY.

Divine, B.J. & Hartman, C.M. (2001) A cohort mortality study among workers at a 1,3 butadiene facility. *Chemico-Biological Interactions*, **135,** 535–553.

Fabbro-Peray, P., Daures, J.P. & Rossi, J.F. (2001) Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes and Control*, **12,** 2001–2212.

Floderus, B., Tornqvist, S. & Stenlund, C. (1994) Incidence of selected cancers in Swedish railway workers, 1961–79. *Cancer Causes and Control*, **3,** 189–194.

Flodin, U., Fredriksson, M., Persson, B. & Axelson, O. (1988) Chronic lymphatic leukaemia and engine exhausts, fresh wood, and DDT: a case-referent study. *British Journal of Industrial Medicine*, **45,** 33–38.

Freeman, L.E.B., Bonner, M.R., Blair, A., Hoppin, J.A., Sandler, D.P., Lubin, J.H., Dosemeci, M., Lynch, C.F., Knott, C. & Alavanja, M.C.R. (2005) Cancer incidence among pesticide applicators in the agricultural health study cohort exposed to diazinon. *American Journal of Epidemiology*, **162,** 1070–1079.

Garry, V.F., Danzl, T.J., Tarone, R., Griffith, J., Cervenka, J., Krueger, L., Whorton, E.B. & Nelson, R.L. (1992) Chromosome rearrangements in fumigant appliers: possible relationship to non-Hodgkin's lymphoma risk. *Cancer Epidemiology, Biomarkers and Prevention*, **1,** 287–291.

Giles, G.G., Lickiss, J.N., Baikle, M., Lowenthal, R.M. & Panton, J. (1984) Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972–80, occupational and familial aspects. *Journal of National Cancer Institute*, **72,** 1233–1240.

Glass, K.C., Gray, C.N., Jolley, D.J., Gibbons, C., Sim, M.R., Fritschi, L., Adams, G.G., Bisby, J.A. & Manuell, R. (2003) Leukemia risk associated with low-level benzene exposure. *Epidemiology*, **14,** 569–577.

Gold, L.S., Manley, N.B., Slone, T.H. & Ward, J.M. (2001) Compendium of chemical carcinogens by target organ: results of chronic bioassays in rats, mice, hamsters, dogs, and monkeys. *Toxicologic Pathology*, **29,** 639–652.

Goldstein, B.D. & Shalat, S.L. (2002) The causal relation between benzene exposure and multiple myeolma. *Blood*, **95,** 1512–1513.

Graff, J.J., Sathiakumar, N., Macaluso, M., Moldonado, G., Mathews, R. & Delzell, E. (2005) Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *Journal of Occupational and Environmental Medicine*, **47,** 916–932.

Hardell, L., Eriksson, M. & Degerman, A. (1994) Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical locatization of non-Hodgkin's lymphoma. *Cancer Research*, **54,** 2386–2389.

Hartge, P., Wang, S.S., Bracci, P.M., Devesa, S.S. & Holly, E.A. (2006) Non-Hodgkin lymphoma. In: *Cancer Epidemiology and Prevention* (ed. by D. Schottenfeld & J.F. Fraumeni Jr), pp. 898–918. Oxford University Press, New York, NY.

Hauptmann, M., Lubin, J.H., Stewart, P.A., Hayes, R.B. & Blair, A. (2003) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *Journal of National Cancer Institute*, **95,** 1615–1623.

Hogstedt, C., Aringer, L. & Gustavsson, A. (1986) Epidemiologic support for ethylene-oxide as a cancer-causing agent. *Journal of the American Medical Association*, **255,** 1575–1578.

Holeckova, B., Piesova, E., Sivikova, K. & Dianovsky, J. (2004) Chromosomal aberrations in humans induced by benzene. *Annals of Agricultural and Environmental Medicine*, **11,** 175–179.

IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (1994) IARC Working Group on the evaluation of carcinogenic risk to humans: some industrial chemicals. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, **60,** 89–97.

IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (1997) IARC Working Group on the evaluation of carcinogenic risk to humans: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, **69,** 1–666.

Jemal, A., Siegel, R., Ward, E., Murray, T., Xu, J. & Thun, M.J. (2007) Cancer statistics, 2007. *CA: A Cancer Journal for Clinicians*, **57,** 43–66.

Ji, J. & Hemminki, K. (2006) Socioeconomic/occupational risk factors for lymphoproliferative diseases in Sweden. *Annals of Epidemiology*, **16,** 370–376.

Khalil , A.M. (1995) Chromosome aberrations in blood lymphocytes from petroleum refinery workers. *Archives of Environmental Contamination and Toxicology*, **28,** 236–239.

Khuder, S.A. & Mutgi, A.B. (1997) Meta-analyses of multiple myeloma and farming. *American Journal of Industrial Medicine*, **32,** 510–516.

Kim, Y.J., Cho, Y.H., Paek, D. & Chung, H.W. (2004) Determination of chromosome aberrations in workers in a petroleum refining factory. *Journal of Toxicology and Environmental Health. Part A*, **67,** 1915–1922.

Kogevinas, M., Becher, H., Been, T., Bertazzi, P.A., Boffetta, P., Dueno-de-Mesquite, H.B., Coggon, D., Colin, D., Flesch-Janys, D., Fingerhut, M., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Mathews, J.D., Neuberger, M., Pearce, N. & Saracci, R. (1997) Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: an expanded and updated International Cohort Study. *American Journal of Epidemiology*, **145,** 1061–1075.

Kogevinas, M., Sala, M., Boffetta, P., Kazerouni, N., Kromhout, H. & Zahm, S.H. (1998) Cancer risk in the rubber industry: a review of the recent epidemiological evidence. *Occupational and Environmental Medicine*, **55,** 1–12.

Lan, Q., Zhang, L.P., Li, G.L., Vermeulen, R., Weinberg, R.S., Dosemeci, M., Rappaport, S.M., Shen, M., Alter, B.P., Wu, Y.J., Kopp, W., Waldyanatha, S., Rabkin, C., Guo, W.H., Chanock, S., Hayes, R.B., Linet, M., Kim, S., Yin, S.N., Rothman, N. & Smith, M.T. (2004) Hematotoxicity in workers exposed to low levels of benzene. *Science*, **306,** 1774–1776.

Lander, B.F., Knudsen, L.E., Gamborg, M.O., Jarventaus, H. & Norppa, H. (2000) Chromosome aberrtions in pesticide-exposed greenhouse workers. *Scandinavian Journal of Work, Environment and Health*, **26,** 436–442.

Lebailly, P., Devaux, A., Pottier, D., De Meo, M., Andre, V., Baldi, I., Severin, F., Bernaud, J., Durand, B., Henry-Amar, M. & Gauduchon, P. (2003) Urine mutagenicity and lymphocyte DNA damage in fruit growers occupationally exposed to fungicide captan. *Occupational and Environmental Medicine*, **60,** 910–917.

Lee, W.J., Hoppin, J.A., Blair, A., Lubin, J.H., Dosemeci, M., Sandler, D.P. & Alavanja, M.C.R. (2004) Cancer incidence among pesticide applicators exposed to alachlor in the Agricultural Health Study. *American Journal of Epidemiology*, **159,** 373–380.

Lewis, R.J., Gamble, J.F. & Jorgensen, G. (2000) Mortality among three refinery/petrochemical plant cohorts. I. 1970 to 1982 active/terminated workers. *Journal of Occupational and Environmental Medicine*, **42,** 721–729.

Linet, M.S., Devesa, S.S. & Morgan, G.J. (2006) The leukemias. In: *Cancer Epidemiology and Prevention* (ed. by D. Schottenfeld & J.F. Fraumeni Jr), pp. 841–871. Oxford University Press, New York, NY.

Mahajan, R., Blair, A., Lynch, C.F., Schroeder, P., Hoppin, J.A., Sandler, D.P. & Alavanja, M.C.R. (2006) Fonofos exposure and cancer incidence in the Agricultural Health Study. *Environmental Health Perspectives*, **114,** 838–1842.

Malone, P.K., Koepsell, T.D., Daling, J.R., Weiss, N.S., Morris, P.D., Taylor, J.W., Swanson, G.M. & Lyon, J.L. (1989) Chronic lymphocytic leukemia in relation to chemical exposures. *American Journal of Epidemiology*, **130,** 1152–1158.

Miligi, L., Costantini, A.S., Bolejack, V., Veraldi, A., Benvenuti, A., Nanni, O., Ramazzotti, V., Tumino, R., Stagnoro, E., Rodella, S., Fontana, A., Vindigni, C. & Vineis, P. (2003) Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian Multicenter Case-Control Study. *Am J Indust Med*, **44,** 627–636.

Miligi, L., Costantini, A.S., Benvenuti, A., Kriebel, D., Bolejack, V., Tuminor, R., Ramazzotti, V., Rodella, S., Stagnaro, E., Corignani, P., Amadori, D., Mirabelli, D., Sommani, L., Belletti, I., Troschel, L., Romeo, L., Miceli, G., Tozzi, G.A., Medico, I. & Vineis, P. (2006) Occupational exposure to solvents and the risk of lymphoma. *Epidemiology*, **17,** 552–561.

Mills, P.K., Yang, R. & Riordan, D. (2005) Lymphohematopoietic cancers isn the United Farm Workers of America (UFW) 1988–2001. *Cancer Causes and Control*, **16,** 823–830.

Nanni, O., Amadori, D., Lugaresi, C., Falcini, F., Scarpi, E., Saragoni, A. & Buiatti, E. (1996) Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population cases-control study based on a priori exposure matrices. *Occupational and Environmental Medicine*, **53,** 652–657.

Palermo-Neto, J., Santos, F.A., Guerra, J.L., Santos, G.O. & Pinheiro, S.R. (2001) Glue solvent inhalation impairs host resistance to *Mycobacterium bovis*-induced infection in hamsters. *Veterinary and Human Toxicology*, **43,** 1–5.

Pasqualetti, P., Casale, R., Colantonio, D. & Collacciani, A. (1991) Occupational risk of hematological malignancies. *American Journal of Hematology*, **38,** 147–149.

Pearce, N., Reif, J. & Fraser, J. (1989) Case-control studies of cancer in New Zealand electrical workers. *International Journal of Epidemiology*, **18,** 55–59.

Pekarsky, Y., Zanesi, N., Aqeilan, R.I. & Croce, C.M. (2007) Animal models for chronic lymphocytic leukemia. *Journal of Cellular Biochemistry*, **100,** 110–119.

Pinkerton, L.E., Hein, M.J. & Stayner, L.T. (2004) Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occupational and Environmental Medicine*, **61,** 193–200.

Raabe, G.K. & Wong, O. (1996) Leukemia mortality by cell type in petroleum workers with potential exposure to benzene. *Environmental Health Perspectives*, **104**(Suppl. 6)**,** 1381–1392.

Schwartz, G.G. (1997) Multiple myeloma: clusters, clues and dioxins. *Cancer Epidemiology, Biomarkers and Prevention*, **6,** 49–56.

Seidler, A., Mohner, M., Berger, J., Mester, B., Deeg, E., Elsner, G., Nieters, A. & Becker, N. (2007) Solvent exposure and malignant lymphoma: a population-based case-control study in German. *Journal of Occupational Medicine and Toxicology* **2,** 2, doi:10.1186/1745-6673-2-2.

Siemiatycki, J., Richardson, L. & Boffetta, P. (2006) Occupation. In: *Cancer Epidemiology and Prevention* (ed. by D. Schottenfeld & J.F. Fraumeni Jr), pp. 322–354. Oxford University Press, New York, NY.

Smith, M.T., Jones, R.M. & Smith, A.H. (2007) Benzene exposure and risk of non-Hodgkin lymphoma. *Cancer Epidemiology, Biomarkers and Prevention*, **16,** 385–391.

Steenland, K., Piacitelli, L., Deddens, J., Fingerhut, M. & Chang, L.I. (1999) Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Journal of National Cancer Institute*, **91,** 779–861.

Steenland, K., Stayner, L. & Deddens, J. (2004) Mortality analyses in a cohort of 18235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occupational and Environmental Medicine*, **61,** 2–7.

Stilgenbauer, S., Bullinger, L., Lichter, P. & Dohner, H. (2002) Genetics of chronic lymphocytic leukemia: genomic aberrations and V(H) gene mutation status in pathogenesis and clinical course. *Leukemia*, **16,** 993–1007.

Svec, M.A., Ward, M.H., Dosemeci, M., Checkoway, H. & De Roos, A.J. (2005) Risk of lymphatic or hematopoietic cancer mortality with occupational exposures to animals or the public. *Occupational and Environmental Medicine*, **62,** 726–735.

Tatham, L., Tolbert, P. & Kjeldsberg, C. (1997) Occupational risk factors for subgroups of non-Hodgkin's lymphoma. *Epidemiology*, **8,** 551–558.

Turner, J.J., Hughes, A.M., Kricker, A., Milliken, S., Grulich, A., Kaldor, J. & Armstrong, B. (2004) Use of the WHO lymphoma classification in a population-based epidemiological study. *Annals of Oncology*, **15,** 631–637.

Vineis, P., Miligi, L. & Costantini, A.D. (2007) Exposure to solvents and risk of non-Hodgkin lymphoma: clues on putative mechanisms. *Cancer Epidemiology, Biomarkers and Prevention*, **16,** 381–385.

Waterhouse, D., Carman, W.J., Schottenfeld, D., Gridley, G. & McLean, S. (1996) Cancer incidence in the rural community of Tecumseh, Michigan. *Cancer*, **77,** 763–770.

Wolf, P.H., Andjelkovich, D., Smith, A. & Tyroler, H. (1981) A case-control study of leukemia in the U.S. rubber industry. *Journal of Occupational Medicine*, **23,** 103–108.

Zahm, S.H., Ward, M.H. & Blair, A. (1997) Pesticides and cancer. *Occupational Medicine*, **12,** 269–289.

Zheng, T., Blair, A., Zhang, Y., Weisenburger, D.D. & Zahm, S.H. (2002) Occupation and risk of non-Hodgkins's and chronic lymphocytic leukemia. *Journal of Occupational and Environmental Medicine*, **44,** 469–474.

