Occupational exposure and risk of lymphomas

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Les facteurs de risque d'exposition professionnelle dans les lymphomes

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Résumé

Les facteurs de risque et les causes des hémopathies, en particulier des hémopathies lymphoïdes, sont encore peu connus de nos jours. Si certains facteurs de risque ont été identifiés, tels que les infections par le VIH et par *Helicobacter pylori*, ceux liés aux expositions professionnelles font l'objet, depuis les années 1980, de nombreuses études épidémiologiques. Les pesticides et les solvants organiques ont été les plus étudiés jusqu'à maintenant, la profession d'agriculteur étant la plus touchée. Nous proposons dans cette mini-revue une synthèse des données de la littérature portant sur les facteurs de risque d'exposition professionnelle aux lymphomes. Nous détaillerons les principaux facteurs incriminés et étudiés. Comme nous le verrons, bon nombre de ces études comportent des limites et des biais, rendant parfois difficile leur interprétation et les conclusions. Enfin, nous ferons un rappel sur la reconnaissance en maladie professionnelle des lymphomes.

Abstract

Little is known about the risk factors and causes of haematological malignancies, in particular lymphomas. While certain risk factors have been identified, such as HIV and *Helicobacter pylori* infections, factors linked to occupational exposure have been the subject of numerous epidemiological studies since the 1980s. Pesticides and organic solvents have been the most studied to date, and farming has been identified as the most affected occupation. In this mini-review, we present a summary of data from the literature on occupational exposure and the risk of lymphomas. We set out the main factors that have been proposed and studied. Our review reveals that many of these studies have limitations and biases, sometimes making them difficult to interpret and conclusions hard to draw. Finally, we highlight the recognition of lymphomas in terms of occupational disease.

Approximately 12,000 new cases of lymphoma are diagnosed every year in France. Some risk factors for these haematological malignancies are well known, including HIV, Epstein-Bar (EBV) and human T-cell lymphotropic 1 (HTLV-1) viruses, and *Helicobacter pylori*. In the majority of cases, lymphoma occurs without a cause and without any identifiable factor. The annual incidence of lymphomas has increased significantly in France and around the world in recent decades, although this trend slowed down in the early 2000s. HIV infection alone cannot explain this increase, hence other contributing factors must be sought. Since the 1980s, numerous epidemiological studies have examined the risk factors for lymphoma in relation to occupational exposure, particularly with regards to pesticides [1-12]. This continues to be a topical issue, with the recent publication of the first results of the French AGRICAN cohort [3, 4]. Although statistical associations have been demonstrated, the various studies contain numerous methodological biases, and links with certain substances have yet to be proven. This is a brief review of the literature on the risk factors associated with occupational exposure with regards to lymphomas.

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General overview of occupational exposure and risk of lymphomas

Numerous risk factors have been analysed with regards to the development of Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) following occupational exposure; the major agents are presented in *Figure 1*. Studies on pesticides top the list of publications in this field. They are classified firstly on the basis of their principal target (insects, grasses, rodents, fungi), and secondly on their composition and chemical structure (*Table 1*).

Organic solvents are another highly varied group consisting of esters, ethers, glycol ethers, alcohols, ketones, petroleum solvents, halogenated hydrocarbons and aromatic hydrocarbons (including benzene).

Two classifications are frequently used to assess the degree of carcinogenicity of such substances and mixtures: the Classification, Labelling and Packaging of Substances and Mixtures (CLP) regulation, and the classification published by the International Agency for Research on Cancer (IARC).

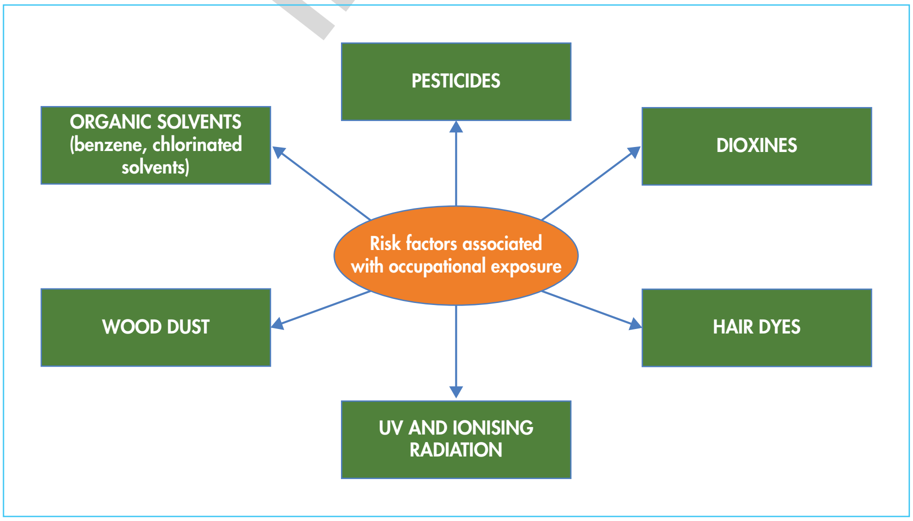
The CLP Regulation is the only European legislation on this subject and has been in force since 1st June 2015. It aims to apply, within the European Union, the recommendations of the United Nations, obliging companies to correctly label and package the substances and mixtures they produce, according to their level of carcinogenicity, in order to better identify and communicate the risks relating to these substances. The CLP categories, unlike those of the IARC, have legislative and regulatory value, and are as follows:

– 1A (formerly 1): substances known to have carcinogenic potential in humans;
– 1B (formerly 2): substances presumed to have carcinogenic potential in humans;
– 2 (formerly 3): suspected human carcinogens.

The IARC, a research agency of the World Health Organization based in the French city of Lyon, classifies substances according to the level of epidemiological evidence in humans and experimental evidence in animals as well as from the point of view of the pathophysiological mechanism. The IARC categories are as follows:

– 1: Carcinogenic to humans,
– 2A: Probably carcinogenic to humans,

Figure 1



Risk factors associated with occupational exposure for lymphomas.
Facteurs de risque d'exposition professionnelle pour les lymphomes.

Table 1

The main families of pesticides.

Classes	Groups	Products
Insecticides	Organochlorines	DDT
		Dieldrin
		Aldrin
		Heptachlor
		Lindane
		B-HCH
		Toxaphene
	Organophosphates	Malathion
		Methyl parathion
		Chlorpyrifos
	Pyrethroids	Permethrin
		Cypermethrin
		Deltamethrin
	Carbamates	Aldicarb
		Carbaryl propoxur
	Avermectins	Ivermectin
	Others	Nicotine
		Rotenoids
		Nitromethylene
		Chloronicotinyl
		Phenylpyrazole
Herbicides	Chlorophenoxy compounds	2,4-D
		MCPA
		MCPP
	Bipyridines	Paraquat
		Diquat
	Phosphomethyl amino acids	Glyphosate
	Chloroacetanilides	Alachlor

(*Continued*)

Table 1
(*Continued*)

Classes	Groups	Products
Fungicides	Dithiocarbamates	Asomate
		Amobam
		Vinclozolin
	Phthalamides	Captane
		Folpel
	Organomercurials	Methylmercury chloride
		Phenyl mercuric acetate
	Chlorophenols	Pentachlorophenols
		2,4,6-Trichlorophenol
	Others	Creosote
		Chlorothalonil
Rodenticides	Anticoagulants	Diphacinone
		Bromadiolone
	Fluoroacetic acid derivatives	
	Thiourea	Alpha-naphtyl thiourea
	Other	Zinc phosphide
Fumigants		Phosphine
	Ethylene dibromide	
	Formaldehyde	

DDT: dichlorodiphenyltrichloroethane; 2,4-D: 2,4-dichlorophenoxyacetate; β-HCH: β-hexachlorohexane; MCPA: methylchlorophenoxyacetic acid; MCPP: methylchlorophenoxypropionic acid.

– 2B: Possibly carcinogenic to humans,
– 3: Not classifiable as to its carcinogenicity to humans,
– 4: Probably not carcinogenic to humans.

It should also be noted that the substances in question may have a carcinogenic effect through one or more pathophysiological mechanisms; they may have a genotoxic and mutagenic effect, an immunotoxic and immunosuppressive effect, or a hormonal effect.
In this review, we present the main substances potentially involved in the occurrence of HL and NHL, starting with the most studied substances: pesticides.

Pesticides

Numerous studies have analysed the impact of occupational exposure to pesticides on the risk of lymphoma [1-12]. Many of them are case-control studies. Some of them use a job-exposure matrix. A job-exposure matrix is a tool used in epidemiological studies to assess and quantify exposure to potential health risks.

It includes a list of levels of exposure to potentially harmful agents for certain occupations. For example, in an Italian study including 158 cases of lymphoma and 76 controls, using a job-exposure matrix to quantify pesticide exposure, the occupation of farmer increases the risk of NHL, in particular diffuse large B cell lymphoma (DLBCL) (odds ratio [OR] = 10.9; CI95% [2.3–51.6]). The use of captafol is also associated with the risk of NHL and in particular DLBCL, and paraquat is associated with the risk of DLBCL and follicular lymphoma (FL).[1] A case-control study by the North American Pooled Project, investigating exposure to 11 organophosphates and two carbamates, showed, after adjusting for exposure to other pesticides, that malathion increases the risk of NHL, particularly FL and DLBCL. In addition, that risk increases with the duration of exposure to malathion.[2]

Large prospective cohorts have also looked for a statistical association between occupational exposure to pesticides and risk of lymphoma. Thus, the French AGRICAN (AGRIculture and CANcer) cohort brought together data on more than 180,000 men and women affiliated to the Mutualité Sociale Agricole (MSA) social protection scheme, both retired and currently working, and cross-referenced them against data from the French cancer registries. Although there was no statistically significant difference in overall cancer incidence between individuals in this cohort and the general population, there was an excess of prostate cancer (standardised incidence ratio [SIR] = 1.07; 95%CI: 1.03–1.11) and NHL (SIR = 1.09; 95% CI: 1.01–1.18) in men, melanoma in women (SIR = 1.23; 95% CI: 1.05–1.43), and myeloma in men (SIR = 1.38; 95%CI: 1.18–1.62) and women (SIR = 1.26; 95% CI: 1.02–1.54) [3]. Recently, the results of a meta-analysis by the AGRICOH consortium were published, combining data from three prospective cohorts (AGRICAN for France, Cancer in the Norwegian Agricultural Population [CNAP] for Norway, and the Agricultural Health Study [AHS] for the United States [Iowa and North Carolina]). This meta-analysis reported 2,430 cases of NHL diagnosed in 316,270 individuals. While the majority of substances studied did not increase the risk of NHL, some substances appeared to increase the risk of NHL very modestly: terbufos for NHL, deltamethrin for chronic lymphocytic leukaemia (CLL) and lymphocytic lymphoma, and glyphosate for DLBCL. In addition, there was an inverse association between exposure to certain substances and the risk of NHL, particularly for organochlorines and phenoxy herbicides. One of the weaknesses of these analyses was a lack of precise quantification of the different exposures. Furthermore, the risk of occurrence of NHLs appeared to vary among histological types, groups of pesticides and substances within pesticide groups.[4]

Other studies have looked at multiple exposures to pesticides (confounding factors). Goodman *et al.,* using data from the US prospective AHS cohort and updated data from a meta-analysis including the AHS, did not show a significant increase in NHL risk due to exposure to 2,4-dichlorophenoxyacetate (2,4-D) [5]. In contrast, the meta-analysis by Smith *et al.* of 12 observational studies (11 case-control studies and one cohort study) showed an excess of NHL in subjects exposed to 2,4-D (relative risk (RR) = 1.38; 95% CI: 1.07–1.77). Note that the RR increased to 1.73 (95% CI: 1.10–2.72) when only workers with the highest level of exposure [6] were considered.

Organochlorines are among the most carcinogenic substances in pesticides. Based on a meta-analysis of 13 case-control studies, Luo *et al.* demonstrated an increased risk of NHL when exposed to the main organochlorines (OR = 1.40; 95% CI: 1.27–1.56), without giving details of the histological types of NHL [7].

Organophosphates are also widely studied pesticides. A meta-analysis combining data from five cohorts and five case-control studies showed an association between exposure to three organophosphates (malathion, diazinon, terbufos) and NHL. When considered alone, only one of these pesticides, diazinon, increased the risk of NHL, via a suspected immunotoxic mechanism.[8]

On the other hand, the association between exposure to glyphosate and lymphoma remains moderate and debated. Based on a meta-analysis by Chang *et al*, which included a majority of case-control studies with numerous biases, the authors concluded that there was a significant but small excess of risk associated with glyphosate for NHL of all histological types (including even myeloma), but which was not significant for NHL and leukaemia. Due to the small number of studies, inconsistency with some of the data in the literature, confounding factors, lack of dose-response relationships, and lack of validation of Bradford Hill's criteria for causation, the authors did not find an established causal relationship between glyphosate exposure and the development of lymphomas [9]. A recent publication from the North American Pooled Project (a case-control study in the United States and Canada, analysing 1,690 cases and 5,131 controls) reported an increased risk of NHL with glyphosate exposure (OR = 1.43; 95% CI: 1.11–1.83), particularly for DLBCL and lymphocytic lymphomas. This risk, however, remained moderate, especially after adjustment for exposure to other pesticides [10]. These results reveal the magnitude and frequency of occupational exposure to multiple pesticides and other substances, and the difficulty of considering all exposures in a population when considering the risk of developing lymphoma.

From a pathophysiological point of view, pesticides can promote the development of lymphomas via various mechanisms. Thus, pesticides are associated with the occurrence of chromosomal translocations, such as t(14;18), which is characteristic of FLs. In a case-control study, an association between the occupation of farming and the occurrence of NHL with t(14;18) was found. However, in the same study, there was no significant association between the occupation of farming and NHL without t(14;18). The authors also noted an increased risk of NHL with t (14;18) with increasing duration of exposure to some of the pesticides [11].

Interestingly, a French study showed that exposure to pesticides was also a factor of poor prognosis of NHL. Indeed, a study involving 244 patients treated for DLBCL with first-line chemotherapy containing anthracyclines, in six hospitals in the Languedoc Roussillon region, revealed significantly more treatment failures (22.4% versus 11.3%, p = 0.03) and lower event-free survival at two years (70% versus 82%, p = 0.04) in patients exposed to pesticides (67/244, measured according to a job-exposure matrix) compared to patients who were not exposed. There was, however, no difference in clinical or biological characteristics between the lymphomas of exposed and unexposed patients. The physiopathological hypothesis put forward by the authors is that genotoxic pesticides may promote the development of resistance mechanisms to chemotherapy, which are themselves genotoxic.[12]

Having explained the role of the main pesticides in the development of lymphomas, we will go on to discuss the role of organic solvents, which have also been studied extensively.

Organic solvents

Although the association between exposure to benzene and the risk of leukaemia is well established, the causal link between benzene or other organic solvents and lymphomas remains controversial. In a case-control study by Wang *et al.* which included women in Connecticut who were diagnosed with NHL between 1996 and 2000 (601 cases and 717 controls), exposure to organic solvents was measured using a job-exposure matrix. The results showed an excess of NHL with exposure to organic solvents (OR = 1.3; 95% CI: 1.0–1.6) with a dose-response relationship, particularly for exposure to chlorinated solvents, formaldehyde, dichloromethane and carbon tetrachloride. Based on histological subgroup analyses, the risk was increased for DLBCL, but not for CLL/lymphocytic lymphomas or FL [13]. Similarly, in a 2007 French case-control study of NHL, HL, myeloma and lymphoproliferative

syndromes, which measured exposures based on interviews and questionnaires, there was an association between the occupation of farmer and the risk of NHL, which increased with the length of exposure. Exposure to pesticides was associated with risk of NHL and HL, which was not the case for organic solvents [14]. A study published in 2009 demonstrated the association between organic solvents and lymphomas, but only marginally for NHL (OR = 1.4; 95% CI: 1.0–2.0). The association was not significant for NHL, myeloma or lymphoproliferative syndromes and only high exposure to benzene was associated with risk of DLBCL (OR = 2.1; 95% CI: 1.0–4.6) [15].
Having addressed the impact of occupational exposure to pesticides and organic solvents on the risk of lymphoma, we will go on to discuss the impact of hair dyes, ultraviolet rays (UV) and ionising radiation.

Hair dyes

Hair dyes contain mutagenic and carcinogenic substances. Some studies showed an excess of lymphoma in workers and individuals using this type of dye. Thus, based on a meta-analysis including studies on the link between the domestic use of hair dyes and the occurrence of cancers (including 40 studies on haematological malignancies, mainly cohort and case-control studies), an excess risk was observed only for NHL, myeloma and leukaemia, but not for the various solid cancers or for NHL [16]. The results of a European multi-centre case-control study including 2,302 cases of lymphomas, diagnosed between 1998 and 2003, and 2,417 controls showed a moderate excess of lymphomas in women who used hair dyes. Furthermore, the risk increased with frequency of use and their use prior to 1980. In terms of histological subgroups, the risk was only significant for CLL [17].

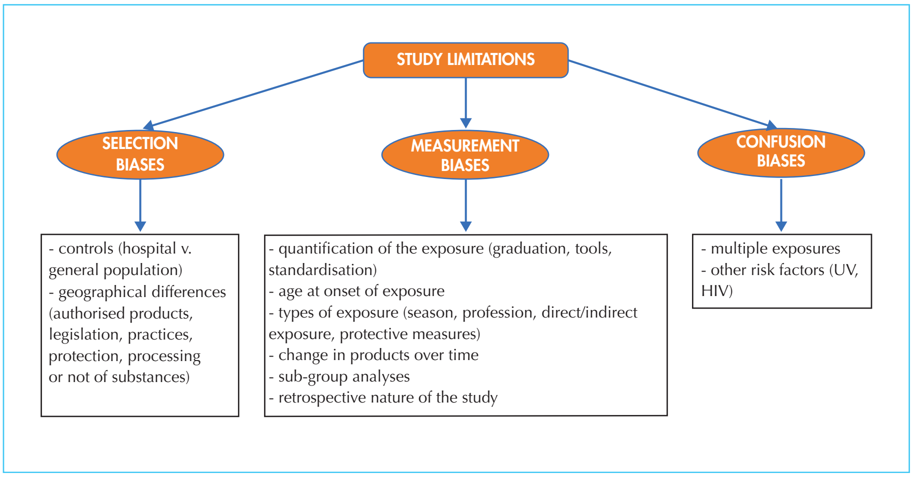
Ultraviolet and ionising radiation

Exposure to UV radiation in some individuals, whether during the course of work (farmers in particular) or in leisure settings, is suspected to be associated with a risk of lymphoma. A French case-control study (813 cases with NHL, HL, myeloma or lymphoproliferative syndrome versus 748 controls) demonstrated an association between the fairest phenotypes (UV-sensitive phototypes) and risk of NHL and HL [18].
An association between exposure to ionising radiation (occupational and non-occupational) and the occurrence of lymphomas has also been demonstrated. For example, in a study of two cohorts (a Japanese cohort of survivors of the Hiroshima and Nagasaki bombings and an American cohort of nuclear weapons workers), a positive relationship was demonstrated between the dose of radiation and mortality from lymphoma, including NHL [19].

Limitations of the studies carried out

Although reports of a few prospective cohort studies, such as the AGRICAN cohort study, exist in the literature, the vast majority of the studies mentioned above are case-control studies (based on the general population or inpatient populations). There are many biases in these studies which are summarised in *Figure 2*.
First of all, there are selection biases. Some studies used hospitalised patients as a control group. Cases and controls also vary between studies due to differences in legislation between countries: differences in authorised products, differences in use, protective measures, and whether or not the products used are processed, *etc.*
Measurement biases are by far the most significant biases in these studies. Problems have been observed in quantifying exposure to the agents studied: lack of quantification (yes/no exposure study), lack of graduation, not taking into account either the frequency or the duration of exposure, lack of quantification tools, lack of standardisation of measurements, *etc*. Similarly, the exact type of exposure is not

Figure 2



Limitations of epidemiological studies on risk factors associated with occupational exposure for lymphomas Most of these studies are case-control studies.
Limites des études épidémiologiques portant sur les facteurs de risque d'exposition professionnelle dans les lymphomes La plupart de ces études sont des enquêtes cas-témoins.

always provided, partly due to the retrospective nature of these studies: direct or indirect exposure, continuous, occasional or seasonal exposure, application of pesticides compared to harvesting crops, the use of protective measures (yes or no, if yes, which ones?), *etc*. Moreover, age at the onset of exposure is rarely provided, which may be an important element in the risk of developing haematological malignancies. Furthermore, exposures inevitably change according to the periods studied: changes in chemistry, processes, legislation, *etc*. Thus, the products used and the methods employed 30 years ago are not the same as today. Furthermore, the size of these studies do not always allow subgroup analyses to be carried out in an optimal way, and it is essential to be able to study the different types of molecules within the same class of toxic agents and to study their effects on the occurrence of the different histological types of lymphomas.
A lot of confusion bias also exists. There is often a wide variety of exposures within the same profession. For example, farmers are often exposed to several types of pesticides, organic solvents and UV radiation during their work. Finally, this type of analysis must also take into account non-occupational risks and susceptibility factors, such as HIV infection or the practice of extra-professional activities leading to exposure.

Recognition as an occupational disease

The occurrence of NHL in the context of occupational exposure to pesticides is recognised as an occupational disease according to Table 59 of the French agricultural social protection system, subject to a duration of exposure of at least 10 years and is covered for 10 years (*table 2*). Some lymphomas may not meet the definition of disease in this table. However, a case-by-case study of the disease contracted (type of haematological malignancy), including the type of exposure (toxic agent[s], duration of exposure), may still allow it to be recognised as an occupational disease based on the advice of the Regional Committee for the Recognition of Occupational Diseases (*Comité Régional de Reconnaissance en Maladie Professionnelle*; CRRMP), in accordance with Article L461-1, paragraph 4 of the French Social Security Code.

An analysis of the data extracted from the *Réseau National de Vigilance et de Prévention des Pathologies Professionnelles* (RnV3P, which includes data from all French occupational disease consultation centres), over the period from 2001 to 2016, identified 111 cases of DLBCL [20]. Of these 111 cases, 42 were considered to be work-related with a causal link that was estimated to be "moderate" or "strong". The most frequently mentioned exposures were to pesticides, trichloroethylene and benzene. The sector of activity most often concerned was agriculture and 34 cases were put forward as cases caused by an occupational disease.

On the basis of RnV3P data over the same period, 165 cases of FL were identified. Of these, 46 were considered to be of occupational origin with a causal link that was estimated to be "medium" or "strong". The most frequently encountered exposures were to pesticides and benzene. The most at-risk occupation was farming and 34 cases were put forward as cases caused by an occupational disease [20].

Conclusion

Many risk factors for the development of lymphomas related to occupational exposure have been explored. In most cases, these risks concern NHL. Pesticides continue to be the subject most often studied and only some of them have been shown to play a role in the occurrence of these haematological malignancies. Only studies involving multi-centre cohorts, with large numbers of people, will improve our knowledge. These studies will need to distinguish between different classes of pesticides and different substances used, but should also distinguish between different histological types of lymphomas in order to obtain more robust results. Exposure must also be accurately measured, using standardised quantification methods to improve the comparability of studies. Information on different types of professional activities, the way in which toxic agents are used and the means of protection put in place must also be provided. A more precise identification of these risk factors would make it possible to develop legislation, to avoid or recommend the use of certain substances and improve knowledge, with the aim of recognising occupational diseases. Haematologists should also routinely refer any patient who is exposed to such products for consultation regarding occupational disease.

Conflicts of interest: None of the authors have any conflicts of interest to disclose.]

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