Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRI COH consortium
Q&A: Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium

Questions on the aims, results and conclusions from the new study

What is this publication about?

This publication, “Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium” is the first report from the AGRICOH consortium on pesticide exposure and cancer. The paper reports on the possible association of exposure through professional application of various formulated pesticides with non-Hodgkin lymphoid cancers. The study included three cohorts, namely from France (‘Agriculture and Cancer’ (AGRICAN), covering 11 Departments in France), Norway (Cancer in the Norwegian Agricultural Population (CNAP), nationwide study) and the United States of America (Agricultural Health Study (AHS), covering two states in the USA), from the AGRICOH consortium.

Overall, the study combines data on 316 270 farmers/workers pooled from the three individual cohorts. The study evaluates the association of non-Hodgkin lymphoid malignancies (NHL) and four major subtypes of this cancer for potential association with the exposure to pesticides through professional pesticide application. This study involves already-published data (AHS) and new data (AGRICAN, CNAP), combined and analysed together in a new way.

What is the AGRICOH consortium?

AGRICOH ("A Consortium of Agricultural Cohort Studies"; http://agricoh.iarc.fr ) is an international group or network of 29 agricultural cohort studies from 12 countries in 5 continents. AGRICOH was formed in October of 2010 with the aim of pooling data from studies of farmers and farm workers. The Consortium is coordinated by a Steering Group chaired by the International Agency for Research on Cancer (IARC) and aims to study various health outcomes, including cancer, associated with exposure to pesticides and other agricultural exposures.

What are the main NHL subtypes?

NHL is a complex disease that includes several subtypes. The subtypes are defined by cell lineage (for instance B-cell or T-cell-related cancers), by the phase of development of the cells (for example precursor or mature) and by other attributes. The most frequent sub-types belong to mature NHL B-cell type including chronic/small lymphocytic leukaemia/lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and multiple myeloma. The chances of getting these sub-types may vary across countries but overall these are the most common sub-types within the three countries.

It is not known how much the causes of these cancers differ by sub-type but it is well established that the incidence of these sub-types varies by age, sex and ethnicity. To look at any reasons for increases in the chances of getting NHL sub-types, it is important to have a large enough study.
What is the aim of the study?

NHL is one of the cancers that has been shown in some reports to occur more often in farmers than among other groups. On the other hand, farmers show the same or even lower incidences of most other cancers compared with the general population. Therefore, it was suspected that exposures related to farm work – including use of pesticides – may be related to an increase in the chance of developing NHL in farmers.

Which pesticides have been studied?

We investigated occupational exposures to various pesticide formulations, which included 14 pesticide groups and 33 pesticide active ingredients selected at the outset of the study. We gave priority to pesticides that had not been previously studied in humans and to pesticides with some evidence for an association with NHL in other studies. To help select agents, we used the International Agency for Research on Cancer (IARC) Monograph evaluations, the US Environmental Protection Agency (EPA) assessments of carcinogenicity, and the published epidemiological literature.

The 14 pesticide groups included four groups of insecticides, seven groups of herbicides, two groups of fungicides, and one group of arsenical compounds.

The detailed list of the 33 pesticide active ingredients is as follows:
2,4-D, Alachlor, Aldicarb, Atrazine, Butylate, Captafol, Captan, Carbaryl, Carbofuran, Chlorpyrifos, DDT, Deltamethrin, Dichamba, Dichlorvos, EPCT, Esfenvalerate, Glyphosate, Isoproturon, Lindane, Linuron, Malathion, Mancozeb, MCPA, MCPP, Metolachlor, Metribuzin, Parathion, Permethrin, Primicarb, Simazine, Terbufos, Thiram, Trifluralin.

What are the results?

No association with NHL was found for the majority of the 14 pesticide groups and the 33 pesticide active ingredients investigated in this study. In other words, this means that NHL was not more common in farmers who had ever used a certain pesticide compared to farmers who never used this particular pesticide.

However, for three chemical active ingredients, the study showed that NHL or NHL subtypes were higher among those using these ingredients than among those who were not. Specifically, all NHL was higher in those farmers who had ever used terbufos. In addition, chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) was higher among those farmers who had ever used deltamethrin. Furthermore, diffuse large B-cell lymphoma (DLBCL) was higher in those farmers who had ever used glyphosate in this study. On the other hand, NHL was lower in those farmers who had ever used organochlorine insecticides or phenoxy herbicides in this study.

It is important to note that this study alone is not conclusive either way on whether professional use of a certain pesticide is associated with NHL or an NHL subtype. Thus the interpretation should be conservative and careful.

What are the strengths and limitations of the study?
The study has several strengths, including the large size of the study. The analysis is based on data gathered in large-size cohort studies which brings many advantages over smaller studies. The large total size, over 300,000 study participants and a large number of people experiencing NHL (N=2,430), enabled us to look into whether NHL sub-types were more common among farmers using specific pesticides than among farmers who were not. Another strength is that exposure information (whether the person used a given pesticide) was collected before the cancer (NHL or its sub-type) was diagnosed, which makes the information more reliable.

Yet, our study has several shortcomings. First, most farmers in the study used one or more pesticides, and it therefore wasn’t possible to make comparisons to farmers who didn’t use any pesticides. Second, the exact pesticides used by the farmers were not always clearly documented. These two main weaknesses raise concern that the study would overestimate or underestimate any potential association of professional pesticide use and cancer.

**Can we draw conclusions regarding the cancer risk of using pesticides for farmers?**

This study provides important scientific findings. However, it is important to note that this study alone is not conclusive either way on whether pesticide use is associated with cancer. A cancer hazard evaluation, such as done by the IARC Monographs, can help to identify carcinogenic hazards to farmers and other workers.

**Who is funding the study?**

This work was mainly supported by a grant from the Office National de l’Eau et des Milieux Aquatique (ONEMA), Plan d’action national ECOPHYTO 2018, in France. In addition, this work received some financial support from the International Agency for Research on Cancer in France, the Intramural Research Program of the National Cancer Institute, National Institutes of Health (Z01-CP010119) in the USA and the Ammodo van Gogh travel grant VGP.14/20, from a Dutch-French partnership.
Questions on the results of the new study in the context of the IARC Monographs on glyphosate

Glyphosate was among the pesticides investigated in the new study. What were the results of the study specifically on glyphosate?

Glyphosate was among the pesticides for which a specific type of NHL was more common among ever-users in this study. The increase was seen for one subtype of NHL, namely diffuse large B-cell lymphoma (DLBCL), but not for any other NHL subtype and not for overall NHL. It is important to note that this study alone is not conclusive either way on whether professional use of a certain pesticide is associated with NHL or an NHL subtype. This applies to the findings for glyphosate as well.

Would the results of the new study have changed the Monographs evaluation of glyphosate and why?

No, the results of the IARC Monographs are not changed by this one study. The classification of glyphosate in Group 2A remains valid.

The IARC Monograph classification reflects the consensus view of an independent expert Working Group and we cannot speculate how one new study would change that expert opinion. The classification of glyphosate was based on a systematic review of all publicly available studies at the time of the review. For the IARC Monograph on glyphosate, the total volume of publications and other information sources considered by the Working Group was about 1000 citations. Once published, the IARC Monograph on glyphosate cited 269 references.

The “Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium” study is one study with limitations, and the results are not in themselves conclusive.

In any future evaluation, the results of this one study would need to be considered in the context of all the other studies. In addition to the many studies available today, there are a number of ongoing studies of glyphosate relevant to understanding cancer hazard. In total, these studies cover a broad range of topics and include other studies of cancer in humans, studies of cancer in experimental animals, and studies of the mechanisms by which glyphosate may cause cancer.

Why are you evaluating the risk associated with exposure to certain pesticides?

IARC aims to research the causes of cancer and how to prevent cancer. It is important for the Agency to study if exposure to pesticides can cause cancer.

Pesticides, which include hazardous substances to human health, are common exposures in certain types of workers. It is therefore important to study if repeated exposure to pesticides in these workers has any health impact, including cancer.

The “Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium” compared the occurrence of NHL in farmers exposed to certain pesticides to the occurrence of NHL in farmers
never exposed to these pesticides. This study is different from a cancer hazard assessment, such as
are performed by the IARC Monographs Programme, or a “risk assessment”. Cancer hazard and risk
assessments consider the totality of studies on the subject, and are not based on one observational
study alone.