

Occupational exposure to organophosphate pesticides and hematologic neoplasms: a systematic review

Exposição ocupacional a agrotóxicos organofosforados e neoplasias hematológicas: uma revisão sistemática

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ABSTRACT: *Objective:* To update findings of observational analytical studies on the association between occupational exposure to organophosphates and hematologic malignancies. *Methodology:* Systematic literature review, including cohort and case-control studies, without limitation of publication time, in Portuguese and English. The articles were traced from June 2017 to July 2019 in PubMed, MEDLINE, LILACS, Web of Science, and Scopus databases. The qualitative bias risk assessment was performed using the Newcastle-Ottawa Scale and the Downs and Black Checklist. Results were presented according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). *Results:* Seventeen studies evaluated as good/high methodological quality were eligible. Exposure to diazinon (1 cohort), phosphos (1 cohort), dichlorvos, crotoxiophos and famphur (1 case control) was associated with leukemia, while exposure to organophosphate was associated to lymphomas (6 case control); the risk of non-Hodgkin's lymphoma was higher in those exposed to diazinon (1 control case) and malathion (3 control case) than non-exposed ones. Multiple myeloma occurred more commonly in organophosphate exposed than in non-exposed individuals (1 case-control). *Conclusion:* Occupational exposure to organophosphates increases the risk of hematologic malignancies, especially among individuals with longer exposure periods. Worker monitoring and exposure control measures are recommended.

Keywords: Hematologic neoplasms. Agrochemicals. Risk factors. Epidemiology. Review. Occupational health.

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RESUMO: *Objetivo:* Atualizar achados de estudos observacionais analíticos sobre a associação entre exposição ocupacional a organofosforados e neoplasias hematológicas. *Métodos:* Revisão sistemática de literatura, incluindo estudos de coorte e caso controle, sem limitação de tempo de publicação, nos idiomas português e inglês. O rastreamento de artigos foi feito no período de junho de 2017 a julho de 2019 nas bases de dados PubMed, MEDLINE, LILACS, Web of Science e Scopus. A avaliação qualitativa de risco de viés foi feita com a Escala Newcastle-Ottawa e com o Checklist Downs e Black. Os resultados foram apresentados segundo as recomendações da Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). *Resultados:* Foram elegíveis 17 estudos avaliados como de boa/alta qualidade metodológica. A exposição a diazinon (um coorte), fonofós (um coorte), diclorvós, crotoxióis e fanfur (um caso controle) associou-se à leucemia, enquanto a exposição a organofosforados associou-se aos linfomas (seis caso controle). O risco de linfoma não-Hodgkin foi maior para os indivíduos expostos a diazinon (um caso controle) e malation (três caso controle), em relação aos não expostos. O mieloma múltiplo ocorreu mais comumente em expostos a organofosforados do que entre os não expostos (um caso controle). *Conclusão:* A exposição ocupacional a organofosforados aumenta o risco de neoplasias hematológicas, sobretudo entre os indivíduos com maior período de exposição. Medidas de monitoramento de trabalhadores e de controle da exposição são recomendadas.

Palavras-chave: Neoplasias hematológicas. Agroquímicos. Fatores de risco. Epidemiologia. Revisão. Saúde do trabalhador.

INTRODUCTION

Occupational exposure to some types of chemical compounds used in pesticides is common. Among these compounds, those belonging to the chemical group of organophosphates (OP) are the most studied ones, consisted of insecticides widely used in agriculture, such as Acephate, the fourth most active ingredient commercialized in Brazil in 2017¹. Many studies have shown that OP associate with hematologic neoplasms (HN)²⁻¹⁰, when analyzing specific substances, as well as different types of HN. These analyses rely on a synthesis of the knowledge produced through systematic reviews of the findings.

In recent years, systematic reviews (SR) such as the one by Weichenthal et al.¹¹ have been published, focusing on exposure to chlorpyrifos, fonofos, and diazinon and the association of this exposure with leukemia and HN, in the studies of the Agricultural Healthy Study (AHS) cohort. Schinasi and Leon¹⁰ showed an increase in non-Hodgkin's lymphoma (NHL) through exposure to chlorpyrifos, diazinon, malathion, phorate, and terbufos. Hu et al.¹² reviewed the association between terbufos, malathion, diazinon, and NHL.

In addition, the International Agency for Research on Cancer (IARC) classified the OP tetrachlorvinphos and paration insecticides as possibly carcinogenic to humans (group 2B) and malathion and diazinon as probably carcinogenic to humans (group 2A), making it possible to associate malathion to NHL, and diazinon to NHL and leukemia¹³.

Analytical studies relate individual exposures to the occurrence of cancer and provide effect estimates (*odds ratio* or relative risk) as the main association measure. Therefore, investigating the association between HN and exposure to OP through these studies allows us

to understand the impact of exposure to these compounds on humans, especially on the agricultural worker, as potential risks can be assessed, as well as it is possible to subsidize implementing exposure reduction strategies in agricultural regions.

Thus, considering that the previously published SR described the association between OP and HN, leukemia and NHL, this study aims to update the findings of studies that estimated the association between occupational exposure to OP and HN, taking into account the publications after the SR of Hu et al.¹² and including the results of the association between OP and multiple myeloma (MM).

METHODS

Publications with results of cohort and case-control studies, with full text, in Portuguese and English, which presented estimates of the association between occupational exposure to some chemical compound in the OP and HN group (leukemias, lymphomas, and MM). No limits were set for publication time. Other eligibility criteria were those recommended in the PICO strategy (acronym for Patient or Problem, Intervention, Comparison and Outcomes)¹⁴:

- Participants/population: adults, of both genders, without restriction of region of origin
- Intervention/exposure: occupational exposure to pesticides of the OP chemical group reported by interview or measured in biological samples of plasma, urine or blood of the participants;
- Controls: comparison of outcomes between non-exposed and occupationally exposed individuals to OP;
- Results/outcomes: HN (leukemias, lymphomas, and MM) and ratio of neoplasms between exposed and unexposed individuals, calculated by *odds ratio* (OR) and relative risk (RR).

Exclusion criteria were:

- Ecological editorials, monographies and case studies, review, focusing on children and adolescents (0-19 years), and animal studies;
- There is no occupational exposure of participants to OP;
- Studies that did not present inclusion and exclusion criteria of participants in the sample;
- There is no description of the active ingredients or the chemical group of pesticides;
- Studies with association results only for specific subgroups diagnosed with any disease (asthmatics, HIV positive, etc.).

SEARCH STRATEGIES

The search for publications was carried out from June 14th, 2017 to July 23rd, 2019, in the databases of Public Medline (PubMed), Medical Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Literature in Health Sciences (LILACS),

Web of Science, and Scopus, using a combination of descriptors in English related to occupational exposure to pesticides (pesticides, pesticide exposure, organophosphorus compounds, organophosphate pesticides) and neoplasms (neoplasms, hematologic neoplasms, leukemia, lymphoma, multiple myeloma). An example of a search strategy was (“hematologic neoplasms” OR leukemia OR lymphoma OR multiple myeloma) AND (pesticides OR “organophosphate pesticides”).

Two reviewers performed the search independently, in cases of disagreement a third reviewer would evaluate the studies; however, there was no divergence in the selection process. An initial screening followed, after reading the article’s title and abstract, with elimination of duplications. After reading the full text, the eligible publications were identified and selected, from which the variables required for the analysis of this review were extracted.

The study variables were:

- Article:
 - a) authors’ names;
 - b) periodical;
 - c) date of publication;
- Study population:
 - a) gender;
 - b) age;
 - c) number of cases and references or controls;
 - d) if there was individual or frequency pairing;
 - e) form of recruitment;
 - e) country or region of origin;
 - f) inclusion and exclusion criteria;
- Exhibition:
 - a) name of the chemical compound of the OP group;
 - b) technique of investigation of perceived exposure (telephone interview, face-to-face, internet chat, etc.), or by quantitative measures in biological samples or exposure matrix, if any;
- Results:
 - a) types of HN (leukemias, lymphomas, and MM);
 - b) Gross and adjusted RR or OR;
 - c) alpha error of 0.005.

ANALYSIS

For the qualitative assessment of bias in the methodology of the studies, the Newcastle-Ottawa Scale (NOS)¹⁵ and the Downs and Black Checklist¹⁶ were employed, which are used in the analysis of systematic reviews of non-randomized studies included in SR¹⁷. NOS is a qualitative assessment tool for non-randomized studies that allows judgment in three

dimensions: the selection of groups (four items), the comparability of groups (one item), and the verification of exposure or outcome of interest (three items) adapted according to the type of study (case control or cohort). The scoring system is based on the quality of the selection and the exposure / outcome measure, whose scores range from zero to nine stars. The higher the score, the better the quality of the study¹⁵.

The Downs and Black Checklist is validated for qualitative assessment of randomized clinical trials and non-randomized studies. It comprises 27 questions based on the following domains: information or report (ten items), external validity (three items), internal validity / measurement bias (seven items), internal validity / selection bias (six items), and statistical power (one item). Answers are scored with a value of zero or one, except for a question in the “information or report” domain that can be scored from zero to two and the question in the “power” domain that can receive from zero to five points. The maximum score of the checklist is 32 points, there is a higher methodological quality when a higher score is reached¹⁶. It should be noted that only 19 questions are fully applicable to observational studies, while eight are specific to randomized controlled trials (questions 4, 8, 13, 14, 15, 19, 23, and 24). In this study, the adapted version of the Downs and Black Checklist was used (only with specific questions for cohort and case control studies) and a maximum score of 24 points¹⁸.

The protocol for this SR was registered on the International Prospective Register of Systematic Reviews Platform (PROSPERO). The presentation of the results followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁹.

RESULTS

823 articles published between 1986 and 2019 were identified, of which, after screening, 17 publications from 1990 to 2015 were eligible for analysis (Figure 1). The methods employed (population, sampling, exposure measurement, and adjustment variables) and the results of the studies (adjusted OR and RR) are described in Tables 1 and 2. Six cohort articles derived from the same study (Agricultural Health Study, United States) and 11 case-control articles with data from the United States, Canada, Australia, Czech Republic, Germany, France, Italy, Ireland, and Spain. Most of the articles were limited to the male population of pesticide applicators, and the exhibition comprised diazinon, phosphorus, malathion, terbufos, phorate, coumaphos, dichlorvos, tetrachlorvinphos, famphur, crotoxiphos, dimethoate, and methyl parathion.

Most studies ($n = 16:94.1\%$) were classified as having good/high methodological quality according to NOS and Downs and Black Checklist. NOS identified a selection bias due to the self-report on exposure in cohort studies²⁰⁻²⁵ and when the case definition was based only on records²⁶, without second confirmation, for example the review of the anatomopathological exam. There were gaps in the measurement of exposure, such as in the use

of unblinded interviews for cases and controls^{8,27-35}, in the written self-report on exposure²⁶ and in the proportion of different non-response or not described between the case and control groups^{8,26-29,32-35}.

Information and selection biases were observed, such as the omission of reference to losses²⁷, which compromises the understanding of external validity, for example the degree of representativeness of the sample^{8,28,29} according to the Downs and Black Checklist.

GROUPED HEMATOLOGIC NEOPLASMS

Six cohort studies investigated the pooled HN²⁰⁻²⁵, all derived from AHS, a study conducted with 89,658 people, 57,311 pesticide applicators, and 32,347 spouses³⁶, which is distinguished by the type of OP studied. Exposure to diazinon²⁰ was associated with HN

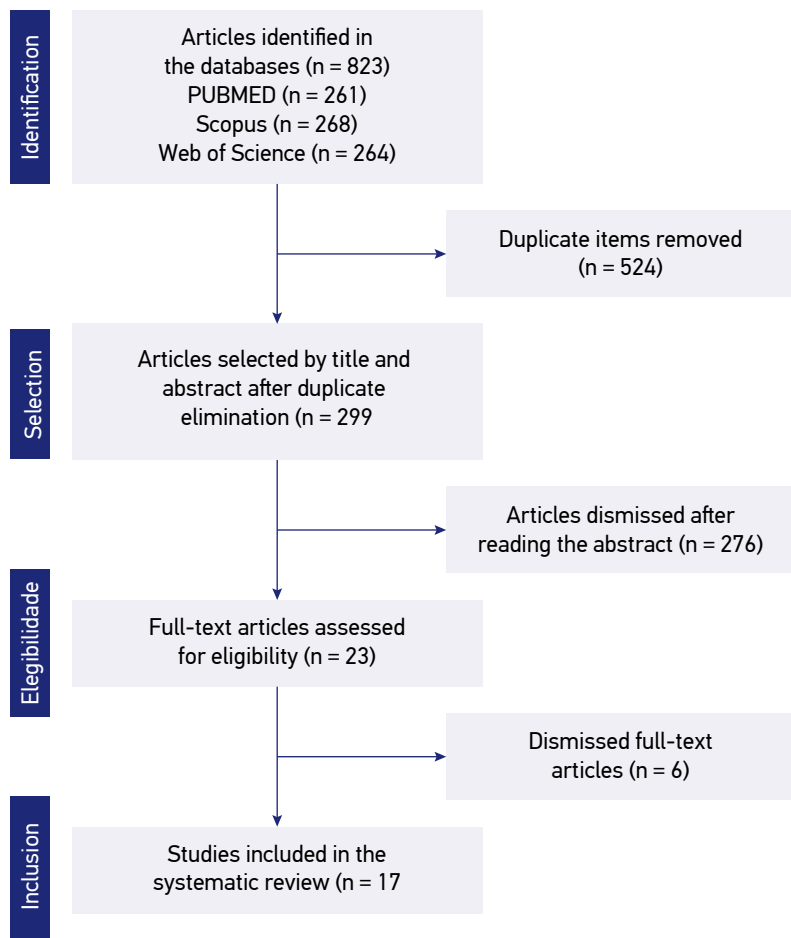


Figure 1. Flowchart with the screening and article selection process for systematic review.

(RR = 1.84; 95%CI 0.89 – 3.82) in general, however, among those with a greater number of days and greater intensity of exposure throughout their working lives (RR = 2.01; 95%CI 1.02 – 3.94) this association was more evident, with the risk being twice as high. Exposure to phorate²², phonophos²¹, malathion²³, dichlorvos²⁴, and terbufos²⁵ was not associated with HN.

LEUKEMIA

Two case-control studies^{26,30} and four cohort studies^{20,21,23,25} investigated the association between exposure to OP and leukemia. In one of these case control studies, there was an association between dichlorvos (OR = 2.0; 95%CI 1.2 – 3.5), crotoxiphos (OR = 11.1; 95%CI 2.2 – 55.0), and famphur (OR = 11.6; 95%CI 1.2 – 107.0) and leukemia in insecticide applicators in animals³⁰, although the strength of association found is limited by the small

Chart 1. Characteristics of cohort studies that associate exposure to organophosphates with hematologic neoplasms.

Authors/year/ country	Study population /sample	Exposure Measurement / outcome	Adjusted RR/OR (95%CI)
Beanne Freeman et al. 2005 USA ²⁰	23,106 pesticide applicators	Questionnaire HN, leukemia, and NHL	Diazinon: Leukemia RR = 3.36 (1.08 – 10.49). High intensity HN: RR = 2.01 (1.02 – 3.94); NHL RR = 1.7 (0.56 – 5.18); Leukemia RR = 2.88 (0.92 – 9.93)
Mahajan et al. 2006 USA ²¹	45,372 pesticide applicators	Questionnaire HN and leukemia	Phonophos: High intensity exposure/ days HN RR = 1.14 (0.64 – 2.02); Leukemia RR = 2.67 (1.06 – 6.70)
Mahajan et al. 2006 USA ²²	21,016 pesticide applicators	Questionnaire HN	Phorate: High exposure in number of days during life HN RR = 0.64 (0.52 – 2.17)
Bonner et al. 2007 USA ²³	19,717 pesticide applicators	Questionnaire HN, leukemia, and NHL	Malathion. High exposure in number of days during life HN RR = 1.27 (0.75 – 2.16); Leukemia RR = 1.65 (0.71 – 3.86); NHL RR = 0.81 (0.33 – 2.01)
Koutros et al. 2008 USA ²⁴	49,762 pesticide applicators	Questionnaire HN	Dichlorvos. High intensity exposure / days HN RR = 1.00 (0.51 – 1.96)
Bonner et al. 2010 USA ²⁵	44,624 pesticide applicators	Questionnaire HN, leukemia, and NHL	Terbufos. High intensity exposure HN OR = 1.25 (0.83 – 1.87); Leukemia OR = 1.37 (0.69 – 2.75); NHL OR = 1.22 (0.67 – 2.22)

RR: relative risk; OR: odds ratio; 95% CI: 95% confidence interval; USA: United States of America; NHL: non-Hodgkin's lymphoma; HN: hematologic neoplasms.

Chart 2. Characteristics of case-control studies that associate exposure to organophosphates with hematologic neoplasms.

Authors/ year/country	Study population / sample	Exposure Measurement / outcome	Adjusted OR (95%CI)
Kachuri et al. 2013 Canada ⁸	342 Cases/ 1,357 Controls	Questionnaire and interview MM	Use of 1 type of OP OR = 1.16 (0.75 – 1.1) Malation OR = 1,12 (0,71 – 1,74)
Mills et al. 2005 USA ²⁶	131 Cases/ Controls (5:1)	UFW membership form data Leukemia, NHL and MM	Leukemia diazinon: OR = 1.32 (0.65 – 2.65)/ malathion OR = 1.3 (0.91 – 3.67). NHL: diazinon OR = 1,39 (0,76 – 2,53)/ malation OR = 1,77 (0,99 – 3,17). MM sem associação
Waddell et al. 2001 USA ²⁷	748 Cases /2,236 Controls	Interview NHL	Malathion > 20 years of use OR = 1.7 (1.1 – 2.9)
Hohenadel et al. 2011 Canada ²⁸	513 Cases / 1,506 Controls	Questionnaire and interview NHL	Use of 1 type of OP: OR = 2.10 (1.5 – 2.94). Use of 2 or + types of OP OR = 1.69 (1.04 – 2.74)
Costas et al. 2015 6 European countries ²⁹	2,178 Cases / 2,457 Controls	Interview Lymphomas and MM	OP: Mature B-cell lymphoma OR = 1.10 (1.01 – 1.2) MM OR = 1.22 (1.06 – 1.41)
Brown et al. 1990 USA ³⁰	578 Cases /1,245 Controls	Interview Leukemia	Dichlorvos OR = 2.0 (1.2 – 3.5); crotoxiphos OR = 11.1 (2.2 – 55.0). Uso há > 20 anos: famphur OR = 11,6 (1,2 – 107,0)
Cantor et al. 1992 USA ³¹	622 Cases /1,245 Controls	Interview NHL	Use since 1965: diazinon OR = 2.6 (1.2 – 5.9); malathion OR = 2.9 (1.1 – 7.4); Phorate OR = 1.8 (0.7 – 4.5)
Nanni et al. 1996 Italy ³²	187 Cases /977 Controls	Interview NHL and CLL	OP: NHL and CLL: OR = 1.7 (0.94 – 3.09). LNH de baixo grau e LLC OR = 2,97(1,28 – 6,91)
McDuffie et al. 2001 Canada ³³	517 Cases /1,506 Controls	Questionnaire and interview NHL	OP OR = 1.73 (1.27 – 2.36). Malathion up to 2 days/year OR = 1.82 (1.25 – 2.68). Use > 2 days/year OR = 1.75 (1.02 – 3.03)
Fritschi et al. 2005 Australia ³⁴	694 Cases / 694 Controls	Questionnaire and interview NHL	OP: Follicular lymphoma OR = 4.28 (1.41 – 13.0)
Cocco et al. 2013 6 European countries ³⁵	2,348 Cases / 2,462 Controls	Interview Lymphomas	OP: Lymphoma: OR = 1.6 (0.9 – 2.8). CLL: OR = 2.7 (1.2 – 6.0)

OR: odds ratio; 95%CI: 95% confidence interval; USA: United States of America; MM: multiple myeloma; NHL: non-Hodgkin's lymphoma; CLL: chronic lymphocytic leukemia; OP: organophosphate; UFW: United Farm Workers of America.

number of participants in the study, which is evidenced by the ample confidence intervals for crotoxiphos and famphur.

Exposure to diazinon was analyzed in three studies: a cohort²⁰ that estimated the association with leukemia (RR = 3.36; 95%CI 1.08 – 10.49) exclusively among individuals with exposure time greater than 38 days during the working life. However, in two case-control studies, no association was found^{26,30}.

The phonophos was associated with leukemia only in the categories with the greatest number of days and the greatest intensity of exposure throughout a working life, according to the findings of the cohort of Mahajan et al.²¹ (RR = 2.67; 95%CI 1.06 – 6.70). Unlike Brown et al.³⁰ who found no association between this chemical agent and leukemia. There was also no association between exposure to malathion^{23,26,30}, methyl parathion²⁶, terbufos^{25,30}, phorate, coumaphos, tetrachlorinphos³⁰, and leukemia.

LYMPHOMAS

The association between exposure to OP and lymphomas has been the target of the largest number of publications, nine case control studies^{26-29,31-35} and three cohort studies^{20,23,25}. In general, OP have been associated with:

- NHL and chronic lymphocytic leukemia (CLL), assessed jointly by Nanni et al.³² (OR = 2.97; 95%CI 1.28 – 6.91);
- NHL in the studies by McDuffie et al.³³ (OR = 1.73; 95%CI 1.27 – 2.36) and Hohenadel et al.²⁸ (OR = 2.10; 95%CI 1.5 – 2.94 / p < 0.01);
- follicular lymphoma, according to Fritschi et al.³⁴ (OR = 4.28; 95%CI 1.41 – 13.0);
- CLL, in the study by Cocco et al.³⁵ (OR = 2.7; 95%CI 1.2 – 6.0);
- mature B-cell lymphoma, according to Costas et al.²⁹ (OR = 1.10; 95%CI 1.01 – 1.2).

There were five studies that found no association between OP and subtypes of lymphoma³⁵, NHL^{27,31,34}, and HL²⁹.

The findings for diazinon showed an association with NHL³¹ in those with more than 15 years of exposure (OR = 2.6; 95%CI 1.2 – 5.9), but no associations were found in three case-control studies^{26,27,33} and in one cohort one²⁰.

The measure of association between the time of exposure to malathion and NHL was greater in the studies by Cantor et al.³¹ (OR = 2.9; 95%CI 1.0 – 7.4), with more than 15 years of exposure, by McDuffie et al.³³ (OR = 1.75; 95%CI 1.02 – 3.03), with use greater than 2 days/year, and by Waddell et al.²⁷ (OR = 1.7/; 95%CI 1.1 – 2.9), with use for more than 20 years. However, other studies do not corroborate these results for malathion^{23,26}. Other OP such as phonophos, phorate^{27,31}, terbufos^{25,27,31}, coumaphos, dichlorvos, famphur³¹, dimethoate^{33,35}, and methyl parathion²⁶ were not associated with lymphoma.

MULTIPLE MYELOMA

Only three case control studies investigated exposure to OP and risk of MM. There was a higher risk of MM in those exposed to OP in general²⁹ compared to the references (OR = 1.22; 95%CI 1.06 – 1.41). This result differs from the findings by Kachuri et al.⁸, who found no association between OP and malathion and MM. As well as no association was found between exposure to diazinon, malathion, methyl parathion and MM²⁶.

DISCUSSION

The results of this SR show that in two cohort^{20,22} and four case control studies^{27,30,31,33} the findings were of a positive association between occupational exposure to OP and HN, in which the time of exposure to pesticides appeared as a modifying variable effect on these causal relationships.

Among the investigated OP, individuals exposed to diazinon for a longer period, compared to those not exposed, had a higher risk of HN, leukemia, and NHL. This association was estimated regardless of methodological differences in the measurement of time — in days of working life, days per year or years of exposure to pesticides.

Leukemia was the neoplasm associated with a greater diversity of OP, such as famphur, crotoxiphos, dichlorvos, diazinon, and phonophos among the studied compounds. The increased risk from exposure to diazinon and phonophos occurred among those who had the longest exposure time.

There were divergences in some results, which may be due to differences in design and methods of analysis. For example, only in the cohort studies was there a uniformity of the variables used for adjustment and of the strategies used to assess the intensity of occupational exposure. However, in most articles there was an adjustment for age, family history of cancer, exposure to other pesticides, smoking, among others; Regarding the exposure assessment, some studies considered time in days or years and others used matrices according to the toxicity of pesticides, methods of applying the substances, use of personal protective equipment (PPE), exposure time, among others. None of the studies had quantitative measures of exposure with biomonitoring of residues or enzymatic activity.

Measuring exposure to chemicals is a complex task and comprises:

- intensity, degree of concentration in external and environmental measures or dose of the agent in the body;
- exposure time or duration;
- frequency with which it occurs, daily or weekly, for example;
- cumulative exposure that corresponds to the sum of the exposure times weighted by the degree of intensity.

Other aspects to be considered are the windows of susceptibility and the time of metabolism or persistence in the body. To obtain measures of these dimensions in epidemiological studies, data from environmental or biological monitoring, records from workplaces or other sources, expert evaluations, exposure-work matrices and questionnaires or interviews with subjects or family members can be used³⁷. All of these secondary-based measures, obtained through access to company data records, can be biased.

The qualitative analysis of the articles showed selection bias such as: definition of cases based on registration of information systems and exposure assessment considering only the self-report of the participants. Specifically, the measurement of exposure based on self-report has a series of gaps linked to memory bias, since individuals may have difficulties in accurately reporting the types of chemicals used and the frequency of application throughout life³⁸.

COMPARISON WITH OTHER SR

The SR that summarized the results of studies from the AHS cohort estimated a higher risk of HN among those exposed to diazinon and chlorpyrifos in the categories with the highest exposure intensity, in addition to the association between diazinon, chlorpyrifos and phosphos and leukemia in individuals exposed for the longest time throughout working life¹¹.

In two SR with meta-analysis, it was observed that in the first, Schinasi and Leon¹⁰ reviewed 44 studies and found an association between OP in general, malathion and diazinon and NHL, while in the second, Hu et al.¹² demonstrated the association between diazinon and NHL after meta-analysis of ten observational studies.

The results of this SR, updated until July 2019, corroborate the findings of the previous SR for NHL and leukemia and include the results of the multicenter case study conducted in Europe by Costas et al.²⁹, which describes the association between OP and MM, not explored in the other SR. Such findings reinforce the evidence of the carcinogenicity of OP to HN.

ADVANCES AND LIMITS OF THE STUDY

In the NOS guidance manual, the distinction between the scores of good studies and those of low quality is not clear. Thus, in this review, the classification used in a meta-analysis¹² was adopted, which considered low from zero to three stars, moderate from four to six stars and high quality from seven to nine stars. The criticisms of NOS are directed to case definition, since there is no specification of the need for validation by two different examiners, and the difficulty of guaranteeing the interviewer's blindness to the case control status, as some diseases are visually identified, for example, signs of neurological damage³⁹. Nonetheless, NOS has been recommended to verify the methodological quality and the risk of bias in observational analytical studies⁴⁰.

It is important to highlight the role of epidemiological studies in the process of evaluating the carcinogenicity of pesticides. By integrating the results of observational studies with the findings of experimental animal studies and mutagenic tests, the OP insecticides tetrachlorynphos and paration were classified by the IARC as possibly carcinogenic to humans (group 2B), and malathion and diazinon as probably carcinogenic to humans (group 2A), with a possible association between malathion and NHL, and between diazinon and NHL and leukemia¹³. However, even with this classification, some of these products continue to be used in agriculture. The process of regulating active ingredients of pesticides is fundamental to reduce risks to human health and the environment resulting from the use of these substances, however the regulation occurs differently between regions of the world.

In Brazil, diazinon and malathion are authorized for use, paration was already banned in 2015, and there is no record of pesticides using tetrachlorynphos⁴¹. In the United States, all of these active ingredients are in use, but in the process of reevaluation⁴². While only malathion is allowed for use in agriculture in the European Union, the rest has been banned⁴³.

In 2017, the Human Rights Council of the United Nations issued a warning on the lack of standardization in the laws that regulate the use of pesticides worldwide, especially in developing countries, where the pressure to increase the production generated by the export of agricultural products has the consequence of increasing the use of agrochemicals without adequate security to control the risks associated with these products. Gaps in legislation in these countries may result in a higher risk of toxicity due to the permission to commercialize highly toxic products already banned in industrialized countries⁴⁴.

Considering the issue of increasing agricultural production in developing countries, the scarcity of studies from these regions discussing the risks of chronic exposure to these products to human health, particularly neoplasms, draws attention.

In relation to Brazil, the third largest producer of soybeans and corn in the world in 2016 and the second country with the highest proportion of pesticide use by planted area in 2014^{45,46}, the article screening process identified three studies, which were not selected in the review for being of ecological design^{7,47,48}.

The findings of this study coincide with those of other systematic reviews, but they must be evaluated with caution due to the number of selected studies, in addition to the small number of participants. It is noteworthy that diazinon is an OP that has been associated with HN, leukemia, and NHL. In addition, there is a relationship between the time of exposure to pesticides and the occurrence of HN. In this sense, future studies should analyze this exposure using standardized time measurement, in order to allow a more accurate comparison between the findings obtained in different populations.

The importance of increasing research that identifies health risks, especially in the most vulnerable groups, such as farmers and residents of developing countries with significant agricultural production, is emphasized.

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