

Cancer health effects of pesticides

Systematic review

K.L. Bassil MSc C. Vakil MD CCFP FCFP M. Sanborn MD CCFP FCFP
D.C. Cole MD MSc FRCPC J.S. Kaur MD K.J. Kerr MD DIPENVHEALTH

ABSTRACT

OBJECTIVE To review literature documenting associations between pesticide use and cancer.

DATA SOURCES We searched MEDLINE, PreMedline, CancerLit, and LILACS to find studies published between 1992 and 2003 on non-Hodgkin lymphoma, leukemia, and 8 solid-tumour cancers: brain, breast, kidney, lung, ovarian, pancreatic, prostate, and stomach cancer.

STUDY SELECTION Each title and abstract was assessed for relevance; disagreements among reviewers were resolved by consensus. Studies were assessed by a team of 2 trained reviewers and rated based on methodologic quality according to a 5-page assessment tool and a global assessment scale. Studies rated below a global score of 4 out of 7 were excluded.

SYNTHESIS Most studies on non-Hodgkin lymphoma and leukemia showed positive associations with pesticide exposure. Some showed dose-response relationships, and a few were able to identify specific pesticides. Children's and pregnant women's exposure to pesticides was positively associated with the cancers studied in some studies, as was parents' exposure to pesticides at work. Many studies showed positive associations between pesticide exposure and solid tumours. The most consistent associations were found for brain and prostate cancer. An association was also found between kidney cancer in children and their parents' exposure to pesticides at work. These associations were most consistent for high and prolonged exposures. Specific weaknesses and inherent limitations in epidemiologic studies were noted, particularly around ascertaining whether and how much exposure had taken place.

CONCLUSION Our findings support attempts to reduce exposure to pesticides. Reductions are likely best achieved through decreasing pesticide use for cosmetic (non-commercial) purposes (where children might be exposed) and on the job.

EDITOR'S KEY POINTS

- There is increasing controversy over the use of pesticides in the community. Studies looking at pesticide use and cancer have shown a positive relationship between exposure to pesticides and the development of some cancers, particularly in children.
- Because most studies assessed use of multiple pesticides, the authors recommend that exposure to all pesticides be reduced.
- The quality of studies looking at the association between pesticide use and cancer is variable, consisting mainly of cohort and case-control methodologies.

This article has been peer reviewed.
Can Fam Physician 2007;53:1704-1711

Pesticides et cancer

Revue systématique

K.L. Bassil MSc C. Vakil MD CCFP FCFP M. Sanborn MD CCFP FCFP
D.C. Cole MD MSc FRCPC J.S. Kaur MD K.J. Kerr MD DIPENVHEALTH

RÉSUMÉ

OBJECTIF Faire une revue de la littérature portant sur l'association entre les pesticides et le cancer.

SOURCE DES DONNÉES On a repéré dans MEDLINE, Premedline, CancerLit et LILACS les études publiées entre 1992 et 2003 qui traitaient de lymphomes non hodgkiniens, de leucémies et de 8 tumeurs cancéreuses solides: cerveau, sein, rein, poumon, ovaire, pancréas, prostate et estomac.

CHOIX DES ÉTUDES La pertinence de chacun des titres et résumés a été évaluée : toute discordance entre réviseurs a été résolue par consensus. Une équipe de 2 réviseurs expérimentés a évalué la qualité de la méthodologie à l'aide d'un outil d'évaluation de 5 pages et d'une échelle d'évaluation globale. Les études obtenant un score global inférieur à 4 sur 7 ont été exclues.

SYNTHÈSE La plupart des études sur les lymphomes non hodgkiniens et sur les leucémies montraient une association positive avec l'exposition aux pesticides. Certaines montraient une relation dose-réponse et quelques-unes avaient pu identifier des pesticides spécifiques. Certaines études montraient que les cancers étudiés étaient plus fréquents chez les enfants et les femmes enceintes exposés à des pesticides, mais aussi chez les parents qui y étaient exposés au travail. Plusieurs travaux montraient une association positive entre l'exposition aux pesticides et certaines tumeurs solides. Les associations les plus fréquentes concernaient les cancers du cerveau et de la prostate. On a également observé une association entre le cancer rénal chez les enfants et l'exposition des parents aux pesticides au travail. Ces associations étaient plus fréquentes lors d'expositions fortes et prolongées. On a noté des faiblesses spécifiques et des limitations inhérentes dans les études épidémiologiques, en particulier dans la façon de déterminer s'il y avait eu exposition et à quel degré.

CONCLUSION Nos observations viennent à l'appui des efforts pour réduire l'usage des pesticides. La meilleure façon d'y arriver est probablement en réduisant l'exposition professionnelle ainsi que l'usage à des fins cosmétiques (non commerciales), qui risque davantage d'exposer les enfants.

POINTS DE REPÈRE DU RÉDACTEUR

- L'utilisation de pesticides dans la communauté est de plus en plus remise en question. Certaines études ont montré une relation positive entre l'exposition aux pesticides et le développement de certains cancers, notamment chez les enfants.
- Comme la plupart de ces études portaient sur l'utilisation de plusieurs pesticides, les auteurs recommandent qu'on réduise l'exposition à tous les pesticides.
- Les études examinant l'association entre les pesticides et le cancer sont de qualité variable, reposant surtout des cohortes ou des cas-témoins.

Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2007;53:1704-1711

In recent years, few environmental issues have aroused public concern as much as use of and exposure to pesticides, especially with respect to children's health. Despite many published studies on the relationships between exposure to pesticides and human health, deep controversy surrounds these associations. Since the Supreme Court ruling in 2001 allowing the municipality of Hudson, Que, to pass a bylaw restricting use of pesticides for cosmetic purposes (non-commercial use), many municipalities across the country have passed similar bylaws. Cosmetic use of pesticides remains a complex issue involving arguments about the rights of lawn-care companies and property owners, and increasingly, the effects of pesticides on health. Because randomized controlled trials on the health effects of potentially harmful chemicals cannot be conducted and because of the difficulty of measuring exposure to pesticides and the limitations innate in observational studies, we are still unsure about the effects of pesticides on human health.

As family physicians, cancer specialists, and epidemiologists, we initiated a systematic review of the literature on the effects of pesticide use on chronic health outcomes in order to assess the evidence currently available.

DATA SOURCES

Primary peer-reviewed studies were found by searching PreMedline, MEDLINE, CancerLit, and LILACS (Spanish and Portuguese-language articles) databases. These databases were selected as we considered them to be the most comprehensive for studies of causes of cancer among humans. The references lists of all studies were checked to identify papers not captured in our search. We included studies that were systematic in their approach; peer reviewed; and published in English, French, Spanish, or Portuguese. Decisions regarding language restrictions were based on the language capabilities of the reviewers. Studies on organochlorines were excluded, as most of these chemicals are no longer used as pesticides in Canada. Studies were collected

and organized according to health effect (Table 1) rather than specific pesticide exposure, because most of the literature considers mixed pesticide exposures.

Study selection

Our search strategy was designed to be comprehensive. To ensure this, all searches included the key MeSH heading "pesticides" and the MeSH headings for the cancers of interest. Our inclusion criteria were that studies be peer reviewed, that they looked at a cancer with an important burden in Canada, and that they were published between 1992 and 2003. The Canadian Cancer Statistics webpage¹ lists cancers in terms of greatest incidence and associated morbidity and mortality. From this list, 8 categories of solid tumours were selected for inclusion. No studies of acceptable quality were found for testicular cancer or colorectal cancer. We chose 1992 as the starting point for our search because a previous review had covered the period to 1991.²

A list of abstracts was produced from each search and distributed to reviewers for evaluation. Reviewer pairs read the abstracts and selected articles that met the inclusion criteria. When articles lacked abstracts or contained too little information on which to make a selection, the original primary studies were obtained for evaluation. Disagreements between reviewers concerning selection of articles for inclusion were resolved by discussion and input from a third reviewer. After abstract selections were agreed upon, the primary studies were collected and distributed back to the reviewer teams for evaluation.

Each study was evaluated by 2 independent reviewers using a quality-assessment and data-extraction tool designed to assess the methodologic quality of each study and developed through consultation with colleagues with experience in systematic reviews. All members of the reviewer team participated in a pilot exercise to test the tool, which was revised until we achieved high interrater reliability ($\kappa > 0.8$ on global assessment scores). A global assessment scale that integrated reviewers' judgment of various methodologic components was used to decide which studies would be included in the final report. This scale used a 7-point response format; all studies ranked below 4 were considered of insufficient methodologic quality to provide valid data to the review and were excluded.

Data extraction and synthesis

Data from the 104 studies included were transferred to tables by cancer type and study type. Reviewers tabulated the number of studies and calculated mean quality scores. Synthesis was based on number and quality of studies and aspects of heterogeneity relevant to the studies included. Tables by cancer type are available in the full report on the Ontario College of Family Physicians' website.³

Ms Bassil is a doctoral candidate in the Department of Public Health Sciences at the University of Toronto in Ontario. **Dr Vakil** is an Assistant Professor in the Department of Family Medicine at Queen's University in Kingston, Ont. **Dr Sanborn** is an Assistant Clinical Professor in the Department of Family Medicine at McMaster University in Hamilton, Ont. **Dr Cole** is an Associate Professor of Medicine in the Department of Public Health Sciences at the University of Toronto. **Dr Kaur** is an Associate Professor of Oncology at the Mayo Clinic College of Medicine in Rochester, Minn. **Dr Kerr** is a lecturer in the Department of Family and Community Medicine at the University of Toronto.

Table 1. Global quality score of studies included: *Studies are organized by type of cancer; 104 studies were found, and 83 were included.*

TYPE OF CANCER	NO. OF STUDIES FOUND	NO. OF STUDIES INCLUDED	SUMMARY OF RESULTS	AVERAGE GLOBAL QUALITY SCORE OF STUDIES INCLUDED
Lung	4	4	2/4 found positive associations	4.1
Breast	12	6	5/6 found positive associations; 1 found decreased risk with exposure	5.0
Pancreatic	3	3	All found positive associations	4.7
Non-Hodgkin lymphoma	32	27	23/27 found positive associations	4.5
Leukemia	23	16	14/16 found positive associations	4.5
Brain	11	11	All found positive associations	4.7
Prostate	10	8	All found positive associations	4.8
Stomach	1	1	Found a positive association	5.0
Ovarian	1	1	Failed to find an association	5.5
Kidney	7	6	All found positive associations	4.2

SYNTHESIS

Non-Hodgkin lymphoma

We reviewed 32 papers on non-Hodgkin lymphoma (NHL)⁴⁻³⁵; 27 met the quality criteria for inclusion.^{4-6,8,11-30,32,34,35}

Cohort studies looked at exposure to a variety of pesticides. Subjects were usually adult white males in occupational groups such as farmers, pesticide applicators, workers in pesticide factories, landscapers, lumberjacks, and golf course superintendents.

Results were positive in 10 of the 12 studies; results reached statistical significance in 4 studies. A large study of 155 000 farmers found an increased risk of NHL with exposure to pesticides (relative risk [RR] 2.11, 95% confidence interval [CI] 1.1 to 3.9) that increased with the number of acres sprayed.²⁵ Another study found an increased rate of NHL (proportionate mortality ratio 237, range 137 to 410) among golf course superintendents who had been exposed to pesticides as well as other chemicals, such as diesel fumes and fertilizers.²⁰

Results of 12 of the 14 case-control studies were positive; 8 reached statistical significance. The 1 study of children found elevated odds ratios (ORs) in children from homes where pesticides were used most days (OR 7.3, $P < .05$), where pesticides were used for professional home exterminations (OR 3.0, $P = .002$), when children had had direct postnatal exposure (OR 2.4, $P = .001$), and when parents had had occupational exposure (OR 1.74) (not statistically significant).⁸

Most studies revealed an elevated risk of NHL with several classes of pesticides. A well-designed Canadian study assessed risk, first with major classes of pesticides and then with individual compounds within these classes, including dicamba, mecoprop (both commonly used weed-killers available in hardware stores) and carbamate (an insecticide).²⁴ One pooled study found

elevated ORs for NHL and hairy cell leukemia, a rare form of NHL, for men exposed to herbicides, insecticides, fungicides, and impregnating agents (chemicals added to assist in applying pesticides). Elevated risk was also seen with some individual compounds, such as the herbicides glyphosate and MCPA (2-methyl-4-chlorophenoxyacetic acid). A dose-response effect was found with certain other pesticides and classes.¹⁶

Leukemia

This review assessed 23 studies on leukemia,³⁶⁻⁵⁸ 16 of which met the quality criteria for inclusion.^{36-39,43-50,52-54,58} Most of the 6 cohort studies looked at occupationally exposed adult white males. Exposure histories in most of the studies were estimated indirectly from information such as amount of money spent on pesticides, location of farm, type of crop, number of acres treated, and duration of employment. Two studies showed elevated rates of leukemia associated with live-stock farming.^{45,46} A study of golf course superintendents found an increased rate of leukemia, but it was not statistically significant.²⁰

Results of all 8 case-control studies were statistically significantly positive. One of the few studies that included women found an elevated OR of 4.4 (95% CI, 1.7 to 11.5) for chronic myelocytic leukemia and acute myelocytic leukemia, though specific pesticides were not named or quantified.³⁷

Several case-control studies analyzed rates of leukemia among children exposed to pesticides. Increased rates of all types of leukemia were found in children whose parents used insecticides in the garden and on indoor plants and whose mothers had been exposed while pregnant.⁴⁴ A case-only cytogenetic study within this study found that the presence of 1 of 3 "poor metabolizer" mutations increased the risk of all types of leukemia when subjects had been exposed to pesticides.⁴⁴

An excellent study showed increased rates of childhood leukemia with exposure to insecticides. Timing of exposure seemed to be critical (preconception, and both prenatal and postnatal periods).⁴⁸ The most crucial exposure period for later development of leukemia was during pregnancy.

An interesting laboratory study found a different pattern of chromosomal aberrations, cytologic features, peripheral blood and bone marrow indices, prognosis, and resistance to treatment in leukemia patients who were exposed to pesticides compared with patients who were not.³⁹ This pattern resembled the pattern found in patients with secondary leukemia, usually caused by radiation, chemotherapy, or other chemical exposure, suggesting that exposure to pesticides might be a precipitant to development of leukemia.

Solid tumours

Brain cancer. All 11 studies from the United States, Canada, and Europe examining the association between pesticide exposure and brain cancer showed increased risk.^{20,45,59-67} A large European study also found this relationship in the children of parents exposed to pesticides at work, particularly for non-astrocytic neuroepithelial tumours.⁴⁵ A strong association was also found for exposure to pesticides indoors at home.⁶³

Breast cancer. Six studies analyzed the association between pesticide exposure and breast cancer.⁶⁸⁻⁷³ Most of them supported an association. One exception was a study that found that women who farmed had a decreased risk of breast cancer.⁶⁹ This might have been due to the protective effect of physical activity against breast cancer, or exposure to sunlight, which might reduce risk by increasing vitamin D levels. Even within this group of farmers, however, those who reported being in the field during or shortly after pesticide application and those who reported not using protective clothing while applying pesticides had an increased risk of breast cancer. A study of female greenhouse workers in Crete found that exposure to pesticides for more than 4 hours daily for at least 10 years increased the risk of benign breast disease (as seen on mammography).⁷⁰

Although most of these studies considered a mix of pesticides, 1 study looked at exposure to triazine herbicides and atrazine (a corn herbicide) as a specific example. While the results did not support a positive association between atrazine and breast cancer, there was an increased risk of breast cancer with medium and high levels of exposure to triazine herbicides as a class.⁷³

Kidney cancer. Six papers evaluated the relationship between pesticide exposure and kidney cancer, and all found positive associations.⁷⁴⁻⁷⁹ The association was found not only in directly exposed populations, but also

in children of exposed parents, and was most consistent when people had had prolonged exposure.

Lung cancer. Four studies examined the association between lung cancer and pesticide exposure.^{20,61,80,81} Results of these studies are somewhat difficult to interpret as only 2 collected information regarding smoking status. One of these studies⁸⁰ found an elevated risk of lung cancer among women exposed to pesticides at work, and the other found an increased risk in a cohort of Florida pest-control workers who had been exposed to specifically named pesticides. The confidence intervals were extremely broad, however, making interpretation difficult.

Ovarian cancer. Few studies were found on pesticide exposure and ovarian cancer. One paper included ovarian cancer as a health effect of interest and evaluated its association with exposure to atrazine. No association was found.⁷²

Pancreatic cancer. Three studies evaluated the relationship between pancreatic cancer and pesticide exposure, and all 3 found positive associations.⁸²⁻⁸⁴

Prostate cancer. Eight papers examined the association between prostate cancer and pesticide exposure and consistently showed positive associations.^{20,85-91} One well-designed US study investigated more than 55 000 men who applied pesticides and found an increased risk of prostate cancer, especially among those with a family history of prostate cancer, and particularly with use of methyl bromide, a fumigant.⁸⁵

Stomach cancer. One study investigated the relationship between stomach cancer and nitrates and atrazine.⁹² A higher rate of stomach cancer was found in areas with high levels of atrazine contamination in the water.

DISCUSSION

The preponderance of evidence uncovered in our systematic review indicated a positive relationship between exposure to pesticides and development of some cancers, particularly brain, prostate, and kidney cancers, as well as NHL and leukemia. A number of the studies on children found increased risk of cancer associated with critical periods of exposure, both prenatal and postnatal, and with parental exposure at work. Most studies showed increased risk, and many showed dose-response relationships. Other reviews have suggested a possible link between pesticide exposure and certain cancers, and further studies have been recommended due to limitations innate in the design of cohort and case-control studies.^{2,93} The studies varied in terms of

number and types of subjects, types of pesticides studied, ways of measuring exposure, covariates examined, and follow-up times.

Limitations

In studying any potentially harmful substances, such as pesticides, where randomized controlled trials are not ethically possible to do, researchers rely mostly on cohort and case-control studies. Each of these designs have limitations, given the difficulty of measuring pesticide exposure. Cohort studies typically rely on indirect measures of exposure, such as type of occupation, duration of employment, and agricultural census data. Usually, specific pesticides are not named or quantified. Covariates, such as family history, smoking, and race, are not always available. Follow-up times are sometimes too short to account for the long latency period between exposure and onset of illness. Recall bias (relying on subjects' memories) is a limitation to case-control studies, as are low response rates and use of proxy respondents. Publication bias (lack of publication of negative studies) is also a potential limitation, as is incomplete collection of all relevant studies in any particular systematic review.

A promising newer method of studying the effects of pesticides is to examine chromosomal aberrations, and, therefore, future cancer risk,⁹⁴ in people exposed to pesticides. Looking at gene polymorphisms (the genetically determined ability to metabolize substances slowly or quickly) will also be a very exciting method of studying the health effects of pesticides.

Conclusion

We believe that there is enough evidence to recommend that patients reduce use of pesticides. Because most studies analyzed exposure to multiple rather than individual pesticides, our recommendation is to reduce exposure to all pesticides. The results of this systematic review have prompted the Ontario College of Family Physicians to recommend that everyone, especially children and pregnant women, reduce exposure to pesticides whenever possible, both at home and in the workplace. Bans on the cosmetic use of pesticides (used only for appearance and not for major infestations and risks to human health) are also supported by the Ontario College of Family Physicians, the Canadian Paediatric Society, the Canadian Cancer Society, the Canadian Nurses Association, the Registered Nurses' Association of Ontario, the Toronto Board of Health, both the Canadian and the Ontario Public Health Associations, and many other physician and health professional associations.

The public has expressed concern about the issue of pesticides, especially regarding the risk to children. More than 100 municipalities across the country have implemented bylaws restricting and banning cosmetic use of pesticides, including Toronto, Vancouver, Montreal, and Halifax, and these bylaws have been supported by the public.

Family doctors should consider asking about pesticide exposure during periodic health examinations and make recommendations about minimizing exposure. They should also encourage use of protective clothing and masks for patients who use pesticides on the job and encourage them to be attentive to the timing of re-entry into recently sprayed areas. Family doctors can also advocate for reductions in pesticide use in communities, schools, and hospitals, and to governments, and can educate patients about the potentially harmful effects of pesticides on health. ✱

Contributors

Ms Bassil, Dr Vakil, Dr Sanborn, Dr Cole, Dr Kaur, and Dr Kerr contributed to concept and design of the study, data analysis and interpretation, and preparing the article for submission.

Competing interests

The systematic review was completed with funding from the Laidlaw Foundation and the Ontario College of Family Physicians. **Dr Vakil** has received teaching honoraria from the Ontario College of Family Physicians and the International Joint Commission Health Professional Task Force. **Dr Sanborn** received honoraria for working on this project. **Dr Cole** has received funding from the International Development Research Centre and the Canadian Institutes for Health Research. **Dr Kerr** has received honoraria from the Ontario College of Family Physicians and from the Foundation for Science and Education.

Correspondence to: Dr Catherine Vakil, Family Medicine Centre, Queen's University, 220 Bagot St, Kingston, ON K7L 5E9; e-mail cv4@post.queensu.ca

References

1. Canadian Cancer Society. *Canadian cancer statistics*. Toronto, Ont: Canadian Cancer Society; 2007. Available from: http://www.cancer.ca/ccs/internet/standard/0,3182,3543_12851_langId-en,00.html. Accessed 2007 August 8.
2. Maroni M, Falt A. Health effects in man from long-term exposure to pesticides. A review of the 1975-1991 literature. *Toxicology* 1993;78(1-3):1-180.
3. Sanborn M, Cole D, Kerr K, Vakil C, Sanin LH, Bassil K. Pesticides literature review. Toronto, Ont: Ontario College of Family Physicians; 2004. Available from: <http://www.ocfp.on.ca/local/files/Communications/Current%20Issues/Pesticides/Final%20Paper%2023APR2004.pdf>. Accessed 2007 August 29.
4. Asp S, Riihimäki V, Hernberg S, Pukkala E. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. *Am J Ind Med* 1994;26:243-53.
5. Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, et al. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. *Cancer Causes Control* 1996;7:312-21.
6. Blair A, Cantor KP, Zahm SH. Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. *Am J Ind Med* 1998;33:82-7.
7. Bloemen LJ, Mandel JS, Bond GG, Pollock AF, Vitek RP, Cook RR. An update of mortality among chemical workers potentially exposed to the herbicide 2,4-dichlorophenoxyacetic acid and its derivatives. *J Occup Med* 1993;35:1208-12.
8. Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer* 2000;89:2315-21.
9. Bueno de Mesquita HB, Doornbos G, Van der Kuip DA, Kogevinas M, Winkelmann R. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in The Netherlands. *Am J Ind Med* 1993;23:289-300.
10. Burns CJ, Beard KK, Cartmill JB. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update. *Occup Environ Med* 2001;58:24-30.

11. Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;52:2447-55.
12. Costantini AS, Miligi L, Kriebel D, Ramazzotti V, Rodella S, Scarpi E, et al. A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. *Epidemiology* 2001;12:78-87.
13. Fontana A, Picoco C, Masala G, Prastaro C, Vineis P. Incidence rates of lymphomas and environmental measurements of phenoxy herbicides: ecological analysis and case-control study. *Arch Environ Health* 1998;53:384-7.
14. Hansen ES, Hasle H, Lander F. A cohort study on cancer incidence among Danish gardeners. *Am J Ind Med* 1992;21:651-60.
15. Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 1999;85:1353-60.
16. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma* 2002;43:1043-9.
17. Hoar ZS, Weisenburger DD, Cantor KP, Holmes FF, Blair A. Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma[comment]. *Scand J Work Environ Health* 1993;19:108-14.
18. Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG Jr, et al. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am J Epidemiol* 1998;147:891-901.
19. Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno-de-Mesquita HB, et al. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. *Epidemiology* 1995;6:396-402.
20. Kross B, Burmeister L, Ogilvie L, Fuortes L, Fu C. Proportionate mortality study of golf course superintendents. *Am J Ind Med* 1992;21:501-6.
21. Lynge E. Cancer incidence in Danish phenoxy herbicide workers, 1947-1993. *Environ Health Perspect* 1998;106(Suppl 2):683-8.
22. MacLennan PA, Delzell E, Sathiakumar N, Myers SL. Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A* 2003;66:501-17.
23. McDuffie HH, Pahwa P, Spinelli JJ, McLaughlin JR, Fincham S, Robson D, et al. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). *Am J Ind Med* 2002;Suppl 2:54-61.
24. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001;10:1155-63.
25. Morrison HI, Semenciw RM, Wilkins K, Mao Y, Wigle DT. Non-Hodgkin's lymphoma and agricultural practices in the prairie provinces of Canada. *Scand J Work Environ Health* 1994;20:42-7.
26. Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. *Cancer* 1993;72:1773-8.
27. Sathiakumar N, Delzell E, Cole P. Mortality among workers at two triazine herbicide manufacturing plants. *Am J Ind Med* 1996;29:143-51.
28. Schreinemachers DM, Creason JP, Garry VF. Cancer mortality in agricultural regions of Minnesota. *Environ Health Perspect* 1999;107:205-11.
29. Sperati A, Rapiti E, Settini L, Quercia A, Terenzoni B, Forastiere F. Mortality among male licensed pesticide users and their wives. *Am J Ind Med* 1999;36:142-6.
30. Thorn A, Gustavsson P, Sadigh J, Westerlund-Hannestrand B, Hogstedt C. Mortality and cancer incidence among Swedish lumberjacks exposed to phenoxy herbicides. *Occup Environ Med* 2000;57:718-20.
31. Viel JF, Richardson ST. Lymphoma, multiple myeloma and leukaemia among French farmers in relation to pesticide exposure. *Soc Sci Med* 1993;37:771-7.
32. Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes Control* 2001;12:509-17.
33. Zahm SH, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A. The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. *Arch Environ Health* 1993;48:353-8.
34. Zahm SH. Mortality study of pesticide applicators and other employees of a lawn care service company. *J Occup Environ Med* 1997;39:1055-67.
35. Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. *J Occup Environ Med* 2001;43:641-9.
36. Beard J, Sladden T, Morgan G, Berry G, Brooks L, McMichael A. Health impacts of pesticide exposure in a cohort of outdoor workers. *Environ Health Perspect* 2003;111(5):724-30.
37. Ciccone G, Mirabelli D, Levis A, Gavarotti P, Rege-Cambrin G, Davico L, et al. Myeloid leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case-control study. *Cancer Genet Cytogenet* 1993;68:135-9.
38. Clavel J, Hemon D, Mandereau L, Delemotte B, Severin F, Flandrin G. Farming, pesticide use and hairy-cell leukemia. *Scand J Work Environ Health* 1996;22:285-93.
39. Cuneo A, Fagioli F, Pazzi I, Tallarico A, Prevati R, Piva N, et al. Morphologic, immunologic and cytogenetic studies in acute myeloid leukemia following occupational exposure to pesticides and organic solvents. *Leuk Res* 1992;16:789-96.
40. Deschamps M, Band P. Study of a cluster of childhood leukemia. *Health Rep* 1993;5:81-5.
41. El Sadek WY, Hassan MH. Chronic lymphocytic leukaemia in Egyptian farm workers exposed to pesticides. *East Med Health J* 1999;5:960-6.
42. Fagioli F, Cuneo A, Piva N, Carli MG, Prevati R, Balboni M, et al. Distinct cytogenetic and clinicopathologic features in acute myeloid leukemia after occupational exposure to pesticides and organic solvents. *Cancer* 1992;70:77-85.
43. Heacock H, Hertzman C, Demers PA, Gallagher R, Hogg RS, Teschke K, et al. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenolate fungicides. *Environ Health Perspect* 2000;108:499-503.
44. Infante-Rivard C, Labuda D, Krajcinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 1999;10:481-7.
45. Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. *Int J Cancer* 1996;65(1):39-50.
46. Kristensen P, Andersen A, Irgens LM, Laake P, Bye AS. Incidence and risk factors of cancer among men and women in Norwegian agriculture. *Scand J Work Environ Health* 1996;22:14-26.
47. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. *Am J Public Health* 1995;85:249-52.
48. Ma X, Boffetta PA, Gunier RB, Dahl G, Smith MT, Reinier K, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspect* 2002;110:955-60.
49. Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. *Eur J Cancer* 1996;32A:1943-8.
50. Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *Am J Epidemiol* 2000;151:639-46.
51. Mulder YM, Drijver M, Kreis IA. Case-control study on the association between a cluster of childhood haematopoietic malignancies and local environmental factors in Aalsmeer, The Netherlands. *J Epidemiol Commun Health* 1994;48:161-5.
52. Nanni O, Amadori D, Lugaresi C, Falcini F, Scarpi E, Saragoni A, et al. Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on a priori exposure matrices. *Occup Environ Med* 1996;53:652-7.
53. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Harnly ME. Childhood cancer and agricultural pesticide use: an ecologic study in California. *Environ Health Perspect* 2002;110:319-24.
54. Richardson S, Zittoun R, Bastuji-Garin S, Lasserre V, Guihenneuc C, Cadiou M, et al. Occupational risk factors for acute leukaemia: a case-control study. *Int J Epidemiol* 1992;21:1063-73.
55. Safi JM. Association between chronic exposure to pesticides and recorded cases of human malignancy in Gaza Governorates (1990-1999). *Sci Total Environ* 2002;284:75-84.
56. Scheele J, Teufel M, Niessen KH. Chlorinated hydrocarbons in the bone marrow of children: studies on their association with leukaemia. *Eur J Pediatr* 1992;151:802-5.
57. Smith JG, Christophers AJ. Phenoxy herbicides and chlorophenols: a case control study on soft tissue sarcoma and malignant lymphoma. *Br J Cancer* 1992;65:442-8.
58. Waterhouse D, Carman WJ, Schottenfeld D, Gridley G, McLean S. Cancer incidence in the rural community of Tecumseh, Michigan: a pattern of increased lymphopoietic neoplasms. *Cancer* 1996;77:763-70.
59. Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. *Arch Environ Contam Toxicol* 1993;24:87-92.
60. Elfird JT, Holly EA, Preston-Martin S, Mueller BA, Lubin F, Filippini G, et al. Farm-related exposures and childhood brain tumours in seven countries: results from the SEARCH International Brain Tumour Study. *Paediatr Perinat Epidemiol* 2003;17(2):201-11.
61. Figa-Talamanca I, Mearelli I, Valente P, Bascherini S. Cancer mortality in a cohort of rural licensed pesticide users in the province of Rome. *Int J Epidemiol* 1993;22:579-83.
62. Littorin M, Attewell R, Skerfving S, Horstmann V, Moller T. Mortality and tumour morbidity among Swedish market gardeners and orchardists. *Int Arch Occup Environ Health* 1993;65:163-9.
63. Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environ Health Perspect* 1997;105:1214-20.
64. Rodvall Y, Ahlbom A, Spannare B, Nise G. Glioma and occupational exposure in Sweden, a case-control study. *Occup Environ Med* 1996;53:526-37.
65. Smith-Rooker JL, Garrett A, Hodges LC, Shue V. Prevalence of glioblastoma multiforme subjects with prior herbicide exposure. *J Neurosci Nurs* 1992;24:260-4.
66. Van Wijngaarden E, Stewart PA, Olshan AF, Savitz DA, Bunin GR. Parental occupational exposure to pesticides and childhood brain cancer. *Am J Epidemiol* 2003;157(11):989-97.

67. Viel JF, Challier B, Pitard A, Pobel D. Brain cancer mortality among French farmers: the vineyard pesticide hypothesis. *Arch Environ Health* 1998;53:65-70.
68. Abdalla MH, Gutierrez-Mohamed ML, Farah IO. Association of pesticide exposure and risk of breast cancer mortality in Mississippi. *Biomed Sci Instrum* 2003;39:397-401.
69. Band PR, Le ND, Fang R, Deschamps M, Gallagher RP, Yang P. Identification of occupational cancer risks in British Columbia. A population-based case-control study of 995 incident breast cancer cases by menopausal status, controlling for confounding factors. *J Occup Environ Med* 2000;42:284-310.
70. Dolapsakis G, Vlachonikolis IG, Varveris C, Tsatsakis AM. Mammographic findings and occupational exposure to pesticides currently in use on Crete. *Eur J Cancer* 2001;37:1531-6.
71. Duell EJ, Millikan RC, Savitz DA, Newman B, Smith JC, Schell MJ, et al. A population-based case-control study of farming and breast cancer in North Carolina. *Epidemiology* 2000;11:523-31.
72. Hopenhayn-Rich C, Stump ML, Browning SR. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Arch Environ Contam Toxicol* 2002;42:127-36.
73. Kettles MK, Browning SR, Prince TS, Horstman SW. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. *Environ Health Perspect* 1997;105:1222-7.
74. Buzio L, Tondel M, De Palma G, Buzio C, Franchini I, Mutti A, et al. Occupational risk factors for renal cell cancer. An Italian case-control study. *Medicina del Lavoro* 2002;93:303-9.
75. Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture: the role of pesticides. *Br J Cancer* 1998;77:825-9.
76. Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. *Occup Med (Oxf)* 2002;52:157-64.
77. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Occupational risk factors for renal-cell carcinoma in Denmark. *Scand J Work Environ Health* 1994;20:160-5.
78. Ramlow JM, Spadacene NW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940-1989. *Am J Ind Med* 1996;30:180-94.
79. Sharpe CR, Franco EL, de Camargo B, Lopes LF, Barreto JH, Johnsson RR, et al. Parental exposures to pesticides and risk of Wilms' tumor in Brazil. *Am J Epidemiol* 1995;141:210-7.
80. Brownson RC, Alavanja MC, Chang JC. Occupational risk factors for lung cancer among nonsmoking women: a case-control study in Missouri (United States). *Cancer Causes Control* 1993;4:449-54.
81. Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). *Cancer Causes Control* 1994;5:310-8.
82. Alguacil J, Kauppinen T, Porta M, Partanen T, Malats N, Kogevinas M, et al. Risk of pancreatic cancer and occupational exposures in Spain. PANKRAS II Study Group. *Ann Occup Hyg* 2000;44:391-403.
83. Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: follow-up from 1965-1988. *Am J Ind Med* 1999;36:239-47.
84. Ji BT, Silverman DT, Stewart PA, Blair A, Swanson GM, Baris D, et al. Occupational exposure to pesticides and pancreatic cancer. *Am J Ind Med* 2001;39:92-9. Erratum in: *Am J Ind Med* 2001;40(2):225-6.
85. Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, et al. Use of agricultural pesticides and prostate cancer risk in the agricultural health study cohort. *Am J Epidemiol* 2003;157(9):800-14.
86. Dich J, Wiklund K. Prostate cancer in pesticide applicators in Swedish agriculture. *Prostate* 1998;34:100-12.
87. Fleming LE, Bean JA, Rudolph M, Hamilton K. Cancer incidence in a cohort of licensed pesticide applicators in Florida. *J Occup Environ Med* 1999;41:279-88.
88. MacLennan PA, Delzell E, Sathiakumar N, Myers SL, Cheng H, Grizzle W, et al. Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med* 2002;44:1048-58.
89. Mills PK, Yang R. Prostate cancer risk in California farm workers. *J Occup Environ Med* 2003;45(3):249-58.
90. Settimi L, Masina A, Andriano A, Axelsson O. Prostate cancer and exposure to pesticides in agricultural settings. *Int J Cancer* 2003;104:458-61.
91. Sharma-Wagner S, Chokkalingam AP, Malker HS, Stone BJ, McLaughlin JK, Hsing AW. Occupation and prostate cancer risk in Sweden. *J Occup Environ Med* 2000;42:517-25.
92. Van Leeuwen JA, Waltner-Toews D, Abernathy T, Smit B, Shoukri M. Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991. *Int J Epidemiol* 1999;28:836-40.
93. Alavanja MCR, Hoppin JA, Kamel F. Health effects of chronic pesticide exposure: cancer and neurotoxicity. *Annu Rev Public Health* 2004;25:155-97.
94. Hagmar L, Bonassi S, Stromberg U, Brogger A, Knudsen LE, Norppa H, et al. Chromosomal aberrations in lymphocytes predict human cancer: a report from the European study group on cytogenetic biomarkers and health (ESCH). *Cancer Res* 1998;58:4117-21.

— * * * —