Non-cancer health effects of pesticides

Systematic review and implications for family doctors

M. Sanborn MD CCFP FCFP **K.J. Kerr** MD DIP ENV HEALTH **L.H. Sanin** MD MPH ScD
D.C. Cole MD MSc FRCPC **K.L. Bassil** MSc **C. Vakil** MD CCFP FCFP

ABSTRACT

OBJECTIVE To investigate whether there are associations between exposure to pesticides and 4 chronic non-cancer health effects: dermatologic, neurologic, reproductive, and genotoxic effects.

DATA SOURCES We searched PreMedline, MEDLINE, and LILACS using the key word *pesticide* combined with the term for the specific health effect being searched. Reviewers scanned the references of all articles for additional relevant studies.

STUDY SELECTION Studies since 1992 were assessed using structured inclusion and quality-of-methods criteria. Studies scoring <4 on a 7-point global methodologic quality scale were excluded. In total, 124 studies were included. These studies had a mean quality score of 4.88 out of 7.

SYNTHESIS Strong evidence of association with pesticide exposure was found for all neurologic outcomes, genotoxicity, and 4 of 6 reproductive effects: birth defects, fetal death, altered growth, and other outcomes. Exposure to pesticides generally doubled the level of genetic damage as measured by chromosome aberrations in lymphocytes. Only a few high-quality studies focused on the dermatologic effects of pesticides. In some of these studies, rates of dermatitis were higher among those who had had high exposure to pesticides on the job.

CONCLUSION Evidence from research on humans consistently points to positive associations between pesticide exposure and 3 of the 4 non-cancer health outcomes studied. Physicians have a dual role in educating individual patients about the risks of exposure and in reducing exposure in the community by advocating for restrictions on use of pesticides.

EDITOR'S KEY POINTS

- Due to the unethical nature of cause-effect studies on pesticide exposure, the growing body of literature on pesticide health effects cannot be used to establish a cause-effect relationship between the use of pesticides and non-cancer health effects.
- However, there is consistent evidence in the literature that pesticide exposure does increase the risk of 3 non-cancer health effects (neurologic, reproductive, and genotoxic).

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Pesticides: effets sur la santé, outre le cancer

Revue systématique et implications pour le médecin de famille

M. Sanborn MD CCFP FCFP **K.J. Kerr** MD DIP ENV HEALTH **L.H. Sanin** MD MPH ScD
D.C. Cole MD MSc FRCPC **K.L. Bassil** MSc **C. Vakil** MD CCFP FCFP

RÉSUMÉ

OBJECTIF Déterminer s'il existe une association entre l'exposition à des pesticides et 4 types d'effets nocifs chroniques sur la santé, outre le cancer: effets d'ordre dermatologique, neurologique, reproducteur et génotoxique.

SOURCES DES DONNÉES On a consulté PreMedline, MEDLINE et LILACS à l'aide du mot-clé *pesticide* combiné à chacun des termes désignant les effets spécifiques à l'étude. Les analystes ont scruté la bibliographie de chaque article pour identifier toute autre étude pertinente.

CHOIX DES ÉTUDES Le choix des études publiées depuis 1992 était basé sur des critères d'inclusion structurés et des critères de qualité méthodologique. Les études obtenant un score inférieur à 4 sur une échelle de qualité méthodologique globale de 7 points ont été exclues. Au total, 124 études ont été retenues, avec un score de qualité moyen de 4,88 sur 7.

SYNTHÈSE On a trouvé des preuves convaincantes d'une association entre l'exposition aux pesticides et l'ensemble des issues neurologiques, la génotoxicité et 4 des 6 effets sur la reproduction: malformations congénitales, mort fœtale, anomalie de croissance et autres issues. De façon générale, l'exposition aux pesticides a doublé le niveau de dommage génétique tel que mesuré par les modifications chromosomiques dans les lymphocytes. Seules quelques études de bonne qualité ont porté sur les effets dermatologiques des pesticides. Dans certaines de ces études, on a observé un taux plus élevé de dermatites chez ceux qui avaient été fortement exposés en milieu de travail.

CONCLUSION La plupart des données tirées de la recherche chez l'humain indiquent que l'exposition à des pesticides est associée à 3 des 4 problèmes de santé étudiés. Le médecin a le double rôle de renseigner chaque patient sur les risques d'une telle exposition et de promouvoir un usage restreint des pesticides afin de réduire l'exposition dans la communauté.

POINTS DE REPÈRE DU RÉDACTEUR

- En raison de la nature non éthique des études de type cause-effets sur l'exposition aux pesticides, on ne peut utiliser les données de plus en plus nombreuses de la littérature dans ce domaine pour établir une relation de cause à effet entre l'utilisation des pesticides et les effets sur la santé autres que les cancers.
- Il existe toutefois dans la littérature des preuves abondantes confirmant que l'exposition aux pesticides augmente le risque de développer trois effets nocifs autres que cancéreux: effets sur le système nerveux, sur la reproduction et génotoxicité.

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Pesticides include all classes of chemicals used to kill or repel insects, fungi, vegetation, and rodents.[1,2] It is well accepted that acute poisonings cause health effects, such as seizures, rashes, and gastrointestinal illness.[1-4] Chronic effects, such as cancer and adverse reproductive outcomes, have also been studied extensively, and the results have been interpreted in various ways as evidence that pesticides are safe or are a cause for concern because they can be detrimental to human health. Bylaw debates across Canada have focused public attention on the cosmetic (non-commercial crop) uses of pesticides and the attendant potential risks of chronic low-level exposure.

Family physicians need evidence-based information on the health effects of pesticides to guide their advice to patients and their involvement in community decisions to restrict use of pesticides. A systematic review by the Ontario College of Family Physicians' Environmental Health Committee was done as a basis for informing family physicians' approach to disseminating information on pesticides to patients and communities.[5]

This article reports on a systematic review of articles published between 1992 and 2003 on 4 non-cancer chronic health effects thought to be associated with exposure to pesticides: dermatologic, neurologic, reproductive, and genotoxic effects. Cardiovascular, respiratory, and learning disability outcomes were not included in the review because of resource constraints. Findings on pesticides and cancer outcomes are reported in another article.[6]

DATA SOURCES

Primary peer-reviewed studies were located using PreMedline, MEDLINE, and LILACS (Spanish- and Portuguese-language articles) databases. All searches included the key MeSH heading "pesticides" combined with the MeSH heading for the health effects under study. Reviewers systematically scanned the references of all articles for additional relevant studies.

Dr Sanborn *is an Assistant Clinical Professor in the Department of Family Medicine at McMaster University in Hamilton, Ont.* **Dr Kerr** *is a lecturer in the Department of Family and Community Medicine at the University of Toronto in Ontario.* **Dr Sanin** *is a Professor in the Department of Public Health Sciences at the Universidad Autonoma de Chihuahua in Mexico.* **Dr Cole** *is an Associate Professor of Medicine and* **Ms Bassil** *is a doctoral candidate in the Department of Public Health Sciences at the University of Toronto.* **Dr Vakil** *is an Assistant Professor in the Department of Family Medicine at Queen's University in Kingston, Ont.*

Study selection

The 3 criteria for inclusion in the assessment were being peer reviewed, being a study of human health effects related to pesticide exposure, and being published between 1992 and 2003. A systematic review done in 1993 had covered pesticide health effect studies up to 1991.[7] A total of 150 studies were retrieved by the search for the 4 categories of health effects (**Table 1**). Two independent reviewers each filled out 5-page Data Extraction Forms for each study. A 7-point Likert-type Global Methodological Quality Assessment Scale was used to assess all papers; 26 papers scored <4 out of 7 and were excluded.

SYNTHESIS

Dermatologic effects

Skin is the primary route of exposure to pesticides for sprayers, handlers, and people using repellants. Excluding acute poisonings, contact dermatitis is thought to be the most common health effect of pesticides, through either irritant or allergic mechanisms.[8] Along with eye injuries, it is the health effect most likely to be seen in the office[2] and might be the only indicator of exposure.

In the 10 studies reviewed[9-18] (none from Canada), it was difficult to assess the prevalence of skin disorders attributable to pesticides. In agricultural workers with contact dermatitis, sensitization to both plant material and pesticides was documented,[9,16] but most study designs did not allow attribution of rashes specifically to pesticide exposure. One study that used a biomarker for pesticide exposure found a dose-response relationship between dermatitis and years of fungicide exposure or poor application practices[13]; 61% of pesticide-exposed agricultural workers and 31% of controls had dermatitis ($P<.001$).[13] Pet groomers who gave more than 75 pyrethrin flea treatments per year had more rashes (odds ratio [OR] 2.04, 95% confidence interval [CI] 1.02 to 4.09) and more eye symptoms (OR 4.75, 95% CI 1.14 to 18.23) than those who gave fewer treatments.[10]

Neurotoxicity

Long-term effects of pesticides on the nervous system include cognitive and psychomotor dysfunction, and neurodegenerative and neurodevelopmental effects. Pesticide poisonings result in well-described acute and chronic neurotoxic syndromes.[19] Chronic effects from low or moderate exposures have been less well documented.

Our systematic review began with 4 relevant studies, including a metanalysis on Parkinson disease (PD) and pesticide exposure[20]; 41 primary studies[21-62] were of adequate quality. Most studies analyzed covariates that might affect nervous system function. Differentiating between the effects of chronic or cumulative exposure and current

Table 1. Summary of studies reviewed

HEALTH EFFECT	NO. OF STUDIES FOUND	NO. OF STUDIES INCLUDED*	SUMMARY OF RESULTS	MEAN GLOBAL SCORE OF STUDIES INCLUDED*
Dermatologic effects	11	10	7/10 studies positive for dermatitis with pesticide exposure	4.50
Neurotoxicity	60	41	39/41 studies positive for increase in 1 or more neurologic abnormalities with pesticide exposure	4.99
Reproductive outcomes	64	59	Birth defects: 14/15 studies positive; time to pregnancy: 5/8 studies positive; fertility: 7/14 studies positive; altered growth: 7/10 studies positive; fetal death: 9/11 studies positive; other outcomes: 6/6 studies positive	4.83
Genotoxicity	15	14	11/14 studies positive for increased chromosome aberrations with pesticide exposure†	5.03

*Assessors scored each paper on a 7-point scale for methodologic quality from 1—very poor to 7—excellent. Papers scoring <4 were excluded.
†**Figure 1** aggregates results from all 14 genotoxicity studies.

intense exposure can be difficult. Unfortunately for many exposed populations (eg, Ecuadorian farm families[29,30]), mixed past poisoning, cumulative exposure, and current work and home exposures are overlaid.

Maternal, in-utero, and early childhood exposures are likely all involved in producing neurodevelopmental effects in preschool children in pervasive exposure situations, such as Mexican valley agriculture.[40] Only 2 studies of effects including children were found,[40,42] despite considerable concern about the effects of pesticide exposure on sensitive populations, such as inner-city children.[4]

Most studies documented mixed pesticide exposures. Cross-sectional studies often included exposure biomarkers, such as herbicide or alkyl phosphates in urine or acetylcholinesterase levels in blood. Some studies were exceptional in documenting specific exposures, for example, fumigants.[28]

General neurotoxic morbidity. General malaise and mild cognitive dysfunction might be the earliest neurotoxic responses to pesticide exposure.[62] Most studies using validated questionnaires and performance tests found an increased prevalence of symptoms or mood changes, as well as alterations in neurobehavioural performance and cognitive function.

Studies of the mental and emotional effects of pesticides found associations for current minor psychiatric morbidity,[27] depression,[55] suicide among Canadian farmers,[49] and death from mental disorders,[60] particularly neurotic disorders in women. Keifer et al[42] found substantially higher rates of mental and emotional symptoms in residents (including adolescents) exposed to spray-plane drift compared with those not exposed.

Associations between previous pesticide poisonings, particularly from organophosphates and carbamates, and decreases in current neurobehavioural function were most consistently positive. Those with greater exposures (eg, termiticide applicators[31] or farmers handling concentrates[50]) also showed more consistent decreases in function. Together, these studies provide important evidence of the subclinical effects of pesticides on the nervous system. These effects might become clinically manifest in a few cases.

Neurodegenerative disease. Most of these studies examined mixed occupational exposures. Some focused on herbicides. Health outcomes varied from PD on clinical examination through adjusted incidence of hospitalization for PD to deaths from PD. All found positive associations between exposure and PD. Combined with the earlier meta-analysis,[20] the results of 15 out of 26 studies were positive for associations between pesticide exposure and PD. These data provide remarkably consistent evidence of a relationship between PD and past exposure to pesticides on the job (OR 1.8 to 2.5).

Evidence of other neurodegenerative effects of pesticides is also accumulating. Of 2 studies on Alzheimer disease, 1[38] found no association and 1[24] found an association in men. A study on amyotrophic lateral sclerosis[46] found consistently elevated adjusted ORs associated with pesticide exposure in both men and women.

Reproductive outcomes

Six distinct groups of reproductive outcomes were chosen for study: birth defects, fecundability, fertility, altered growth, fetal death, and mixed outcomes.

Birth defects. Fifteen studies from 9 countries[63-77] examined associations between pesticides and birth defects. The studies consistently showed increased risk with pesticide exposure. Specific defects included

limb reductions,[64,67,73] urogenital anomalies,[68,73,75] central nervous system defects,[68,73] orofacial clefts,[74] heart defects,[66,67] and eye anomalies.[77] The rate of any birth defect was also increased by parental exposure to pesticides.[66-71,74,76] In many studies, there were multiple exposures. Two studies identified specific pesticides: glyphosate[64] and the pyridil derivatives.[69]

Time to pregnancy. Eight studies from 6 countries[78-85] analyzed associations between pesticide exposure and time to pregnancy. Data on pesticide exposures and outcome were collected retrospectively by self-report. Five studies showed positive associations, and 3 showed no association between pesticide exposure and time to pregnancy. All 3 papers showing no association collected exposure and outcome information from men only.[79-81]

Fertility. Fertility refers to the ability to become pregnant in 1 year and includes male and female factors, such as semen quality and infertility. Twelve studies from 7 countries were reviewed.[86-99] Results were mixed; several studies found no associations between pesticide exposure and sperm abnormalities. One study found an association between organophosphate metabolites and sperm sex aneuploidies[94]; another study found an association between erectile dysfunction and pesticide exposure.[95] One study found an increased risk of infertility among women who worked with herbicides in the 2 years before attempted conception.[98]

Altered growth. Low birth weight, prematurity, and intrauterine growth restriction are not only important determinants of health during the first year of life, but also of chronic diseases of adulthood.[100] Ten studies, mainly from Europe and North America,[76,77,101-108] examined pesticide effects on fetal growth. Seven of these showed positive associations between agricultural pesticide exposure and altered fetal growth. Two pesticides implicated in the positive studies were pyrethroids and chlorpyrifos, the latter a commonly used ant-killer now being phased out because of health effects.

Fetal death. Fetal death includes spontaneous abortion, fetal death, stillbirth, and neonatal death. Results were consistent across several study designs; 9 of 11 studies[64,76,77,109-116] found positive associations with pesticide exposure. The Ontario Farm Study results suggested critical windows when pesticide exposure is most harmful. Preconception exposure was associated with early first-trimester abortions, and post-conception exposure was associated with late spontaneous abortions.[110] In a study from the Philippines,[76] risk of spontaneous abortion was 6 times higher in farming households with heavy pesticide use than it was among those using integrated pest management (which results in reduced pesticide use).

Other reproductive outcomes. Seven studies examined other reproductive outcomes, such as sex ratio, placental quality, and developmental delay after in-utero exposure.[64,107,117-121] A Mexican study[115] found higher rates of placental infarction in rural women exposed to organophosphate insecticides; exposure was biomarker-documented with depressed red blood cell cholinesterase levels. Results on altered sex ratios were inconsistent.[64,114]

Genotoxicity

Genotoxicity is the ability of a pesticide to cause intracellular genetic damage. In all reported studies, it was measured as percent chromosome aberrations per 100 peripheral blood lymphocytes. Increased frequency of chromosome aberrations was a predictor of increased cancer rates in a large prospective cohort study (n=5271) with follow-up for 13 to 23 years.[122] Similar studies of associations with reproductive outcomes have not been done.

Important confounders are exposures that cause genetic damage: smoking, alcohol consumption, diet, caffeine intake, radiation, and mutagenic drugs. The latter are important since drugs such as methotrexate are now used widely for rheumatoid arthritis and Crohn disease. Few studies measured all confounders; most excluded smokers and subjects who had x-rays or took mutagenic drugs during the previous year.

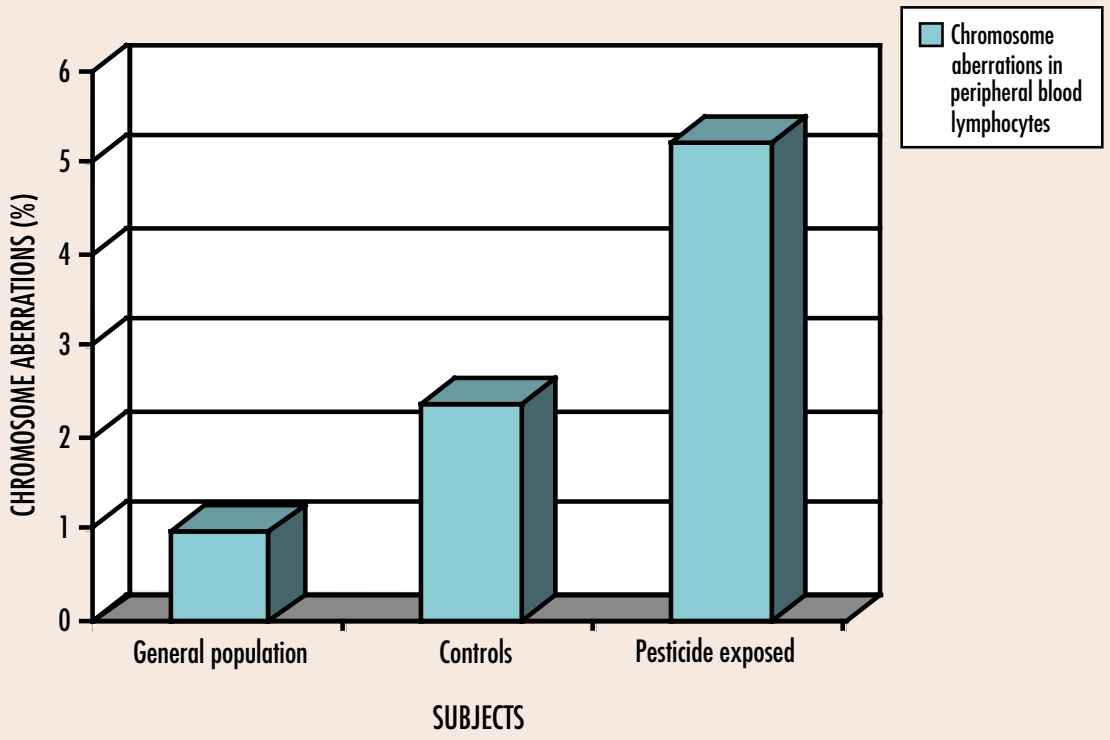
Positive associations between pesticide exposure and elevated percent chromosome aberrations were found in 11 of 14 studies.[123-136] Two studies showing no association had taken blood samples during low-exposure seasons.[128,129] Two studies pointed to synthetic pyrethrins[134] and organophosphates[135] as highly genotoxic. Aggregate results from all 14 studies are shown in **Figure 1**; pesticide exposure doubled the frequency of chromosome aberrations. In clinical practice, these aberrations could present as spontaneous abortion, birth defects, sperm abnormalities, or cancer risk.

DISCUSSION

For the 4 non-cancer effects reviewed, the strongest evidence of association with pesticide exposure was found for neurologic abnomalities, 4 out of 6 reproductive outcomes, and genotoxicity effects (**Table 1**).

The most striking feature of the results of this systematic review is the consistency of evidence showing that pesticide exposure increases the risk of 3 non-cancer health effects: neurologic, reproductive, and genotoxic effects. The results are consistent with those of other reviews published before[20] and since[137,138] this review was completed. Results of dermatologic studies are less consistent and of poorer quality and indicate the need for a primary care prevalence study of pesticide-related skin conditions.

Figure 1. Percent of chromosome aberrations for 500 control and 529 pesticide exposed subjects in 14 genotoxicity studies compared with the general population



Assessment of exposure remains a key problem that is being addressed in newer studies by enhanced biomonitoring. For example, a cohort of children now being followed longitudinally had cord-blood levels of several pesticides measured at birth[139] and by maternal air and blood sampling during pregnancy.[140] The role of genetics in the ability to metabolize pesticides, which varies widely among ethnic groups,[141] is being incorporated into more study designs[41,124,142] and should refine our knowledge and explain some inconsistencies in the international literature.

Limitations

The major limitation of studies of the health effects of pesticides is their inability to demonstrate cause-effect relationships. Study subjects cannot be deliberately exposed to potentially harmful toxins, and few exposure-reduction options are tested in randomized controlled trials. The evidence generated by well-constructed clinical and epidemiologic observational studies is the highest level of evidence we can ethically obtain.

The studies reviewed have methodologic problems, such as exposure misclassification and inadequate exposure assessment (causing mixed results) and recall bias (in retrospective case-control studies). Unpublished literature on health effects that was not accessed would be useful to determine whether there is a publication bias toward positive studies. The effect of unpublished positive or negative studies generated by chemical industry–funded research also cannot be assessed. Many good-quality studies were found in the review, however, and taken together, the results provide sufficient cause for family doctors to educate patients and to act to prevent unnecessary pesticide exposure.

Conclusion

This systematic review provides clear evidence that pesticide exposure increases risk to human health across a range of exposure situations and vulnerable populations. Public support for restrictions on pesticide use is growing; 71% of respondents supported provincewide restrictions in a recent Ontario poll.[143] The Canadian Association of Physicians for the Environment[144] and national pediatric and public health groups in Canada and the United States[145-8] have expressed concern about health effects from cosmetic use of pesticides and recommended that physicians participate in reduction efforts.

Family doctors have a dual role in reducing pesticide exposures. First, during individual encounters, we can educate patients about pesticide health effects,[149] monitor through exposure histories[150] and laboratory tests,[151] and advise when we believe the level of exposure poses a health threat. We should encourage harm reduction through use of protective equipment when pesticide exposure is necessary. Advice about use of protective

Practice tips based on the review

1. Advise patients to avoid pesticide exposure during critical reproductive periods. This includes occupational, indoor, lawn, and garden exposure to pesticides.
- For women, the critical period for early spontaneous abortion is before pregnancy, and for late spontaneous abortion, the first trimester.
- For men, the critical period is the 3 months of spermatogenesis before conception.

2. Take a pesticide-exposure history from patients who have adverse reproductive events, such as intrauterine growth restriction, prematurity, inability to conceive in 1 year, or birth defects.
- Birth defects are associated with both maternal and paternal exposure to pesticides before conception and during the first trimester.
- Most exposures are work related, but transposition of the great vessels is increased with household exposure.

3. Screen patients with a history of exposure to pesticides for neurologic conditions (which can be subtle).
- Occupationally exposed adults are at increased risk of neurologic symptoms, including neurobehavioural changes and Parkinson disease.

4. Use biomonitoring as an effective tool to reduce exposure. Biomonitoring for recent (within 3 months) organophosphate insecticide exposure is done by ordering red blood cell cholinesterase tests.[2] The test is covered by the Ontario Health Insurance Plan; in other provinces, it costs $25 to $100, but might be covered for exposed workers.

equipment is an important and neglected area of family practice,[152] although it is an effective intervention for reducing pesticide exposure.[133,153] Then, in our role as public and community health advocates, we need to educate the public about the health effects of pesticide use. We need to reinforce community efforts to reduce cosmetic use of pesticides that can disproportionally affect children, pregnant women, and elderly people.

Contributors

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

Competing interests

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Correspondence to: **Dr Margaret Sanborn**, *Chesley Medical Clinic, Box 459, Chesley, ON N0G 1L0; e-mail* **msanborn@sbghc.on.ca**

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