Pesticides Literature Review

Project Team Members:

Margaret Sanborn, MD, CCFP, FCFP
McMaster University

Donald Cole, MD, FRCP(C)
University of Toronto

Kathleen Kerr, MD, Dip. Env. Health
Environmental Health Clinic, Sunnybrook & Women's College Health Sciences Centre

Cathy Vakil, MD, CCFP
Queen's University

Luz Helena Sanin, MD, MPH, ScD
University of Toronto
Autonomous University of Chihuahua, Mexico

Kate Bassil, MSc, PhD(c)
University of Toronto

CONTACT:

The Ontario College of Family Physicians
357 Bay Street, Mezzanine
Toronto, Ontario M5H 2T7
Tel: (416) 867-9646 ▪ Fax: (416) 867-9990
Email: ocfp@cfpc.ca ▪ Website: www.ocfp.on.ca

April 23, 2004

Systematic Review of Pesticide Human Health Effects

Table of Contents

Acknowledgements 1

Chapter 1 Introduction 2
References 5

Chapter 2 Methods 6

Chapter 3 Solid Tumours 12
References 17
Tables 22

Chapter 4 Non-Hodgkin's Lymphoma 36
References 39
Tables 42

Chapter 5 Leukemia 49
References 52
Tables 55

Chapter 6 Genotoxicity 61
Immunotoxicity 63
Genetic Susceptiblity to Pesticide Health Effects Mediated by Genetic Polymorphisms 64
References 66
Figure 1: N-weighted frequency of chromosome aberrations in exposed and non-exposed subjects 69
Tables 70

Chapter 7 Dermatologic Health Effects of Pesticides 79
References 81
Tables 82

Chapter 8 Chronic Neurologic and Mental Health Effects 86
References 89
Tables 94

Chapter 9 Reproductive Outcomes
Congenital Malformations 111
Fecundability or Time to Pregnancy 112
Fertility 113
Altered Growth 114
Fetal Death 114
Mixed Outcomes 116
References 118
Tables 126

Chapter 10 Pesticide Health Effects and Children 167
References 169

Chapter 11 Implications for Family Doctors 172
References 176

Appendix 1: Assessment Form for Review Papers 178

Appendix 2: Data Extraction Form 181

Acknowledgements

This project, which was initiated by the Environmental Health Committee of the Ontario College of Family Physicians, would not have been possible without funding provided by the Laidlaw Foundation. The Ontario College of Family Physicians contributed in-kind administrative assistance and support for completion of the project. Special thanks to the College's environmental health staff liaison, Helen Kwan, for many hours of cheerful organizational and administrative assistance to the project group.

We would like to thank Kelly Martin, McGill University for her work during the proposal and other initial stages of the project; and Kathleen Cooper of CELA for providing data to assist with scoping the project.

For locating studies, we appreciated access to the reference libraries of Loren Vanderlinden, Toronto Public Health, Jason Garay, North Toronto Public Health and University of Toronto, and the Institute for Work and Health.

Andrea Furlan of the Institute for Work and Health, Toronto, was very generous with her time over several meetings in providing expert guidance on steps for the systematic review, design of assessment tools, and structure and content of the summary tables.

Gladys Faba Beaumont, Institute of Public Health, Mexico kindly assisted with access to the LILACS database and finding Spanish papers. Jeff Kwong and Yves Leger, University of Toronto, and Mandy Weselak, University of Ottawa assisted our project team with the assessment of primary studies. Mandy Weselak also assisted the project team with writing and release of the report.

Finally, we are deeply indebted to those who volunteered their time to provide reviews and editing of reference lists or chapters of the report. Our peer and expert reviewers and editors provided important comments and suggestions and new perspectives during writing of the report. Peer reviewers were Alan Abelsohn, Neil Arya and Kathleen Finlay. Expert reviewers were Tye Arbuckle from Health Canada, Patricia Harper from Sick Childrens' Hospital Toronto, Linn Holness from University of Toronto and Judith Kaur from the Mayo Clinic, Rochester.

The Project Team:

Margaret Sanborn, MD, CCFP, FCFP, McMaster University

Donald Cole, MD, FRCP(C), University of Toronto

Kathleen Kerr, MD, Dip. Env. Health, Environmental Health Clinic, Sunnybrook & Women's College Health Sciences Centre

Cathy Vakil, MD, CCFP, Queen's University

Luz Helena Sanin, MD, MPH, ScD, University of Toronto, and Autonomous University of Chihuahua, Mexico

Kate Bassil, MSc, PhD(c), University of Toronto

Chapter 1 — Introduction

History

In recent years, few environmental issues have aroused the concern of the public as much as pesticides, especially in relation to the health of children. In spite of the many published studies on the subject of pesticides and human health, there remains deep controversy surrounding this issue. This report will try to elucidate the results of the many studies of pesticides and health, and draw conclusions as to the true health effects of pesticides.

To understand this controversial issue it is helpful to look at the history of pesticide use. Prior to World War II, the pesticides that we use now did not yet exist. Some pesticides currently in use were in fact developed during the World War II for use in warfare. The organophosphate insecticides were developed as nerve gases, and the phenoxy herbicides, including 2,4-D (the most commonly used herbicide in Canada), were created to eradicate the Japanese rice crop, and later used as a component of Agent Orange to defoliate large areas in jungle warfare. After World War II, these chemicals began to be used as pesticides in agricultural production, for environmental spraying of neighbourhoods for mosquito eradication, and for individual home and garden use.

During the 1960s and 1970s, epidemiologists in the USA noted a rise in the incidence of non-Hodgkin's lymphoma (NHL). When plotted on a map of the USA these cases were clearly clustered in agricultural areas. This increase in NHL incidence paralleled the rise in pesticide use, prompting some epidemiologists to theorize that there was a causal link. Rachel Carson's revolutionary book, *Silent Spring* (1), first published in 1962, started the slow process of raising political and public awareness of the hazards posed to wildlife, humans, and the ecosystem by the use of pesticides. This process continued with *Our Stolen Future* (2), described by then Vice-President Al Gore as the sequel to *Silent Spring*, which documented the health effects of endocrine-disrupting chemicals. Since then there have been hundreds of scientific studies done on all continents to determine if there is a relationship between pesticide use and human health problems.

Laws in Canada

Since 1990, when the municipality of Hudson, Quebec passed a by-law restricting the use of cosmetic pesticides on public and private property, pesticides have received considerable media attention in Canada. In 1991, two lawn-care companies challenged the Hudson by-law on the grounds that pesticide use was not within municipal jurisdiction. The court affirmed that municipalities do indeed have the power to pass by-laws regarding pesticide use, so the lawn-care companies appealed the ruling. In 2001, the Supreme Court of Canada upheld the municipality's right to pass the by-law. Interestingly, although the health effects of pesticides were not argued during the Supreme Court challenge, the judgement implied that this had been an important factor in the Court's decision (3). Since then, many municipalities across Canada, including Toronto and Halifax, have passed by-laws restricting the cosmetic use of pesticides. Cosmetic use of pesticides remains a complicated issue involving arguments about the rights of lawn-care and pesticide companies, property owners' rights, and increasingly, the health effects of pesticides.

Issues in Design of Pesticide Studies

So why, with so many studies available, is there still such controversy surrounding the issue of the health effects of pesticides? For ethical reasons, randomized controlled trials, which are the most conclusive studies of cause and effect, are not done with potentially harmful chemicals, so we rely on other types of studies that have marked limitations. Most of the studies done examine farmers, pesticide applicators, gardeners, and other occupational groups with higher exposures to pesticides than those of the general population. The subjects are mostly adult males, subject to multiple exposures to various pesticides and other toxins and carcinogens such as diesel fumes, animal viruses, and cadmium. If evaluated at all, the exposure history is often indirect and may be determined by a surrogate measure such as type of crop grown, annual expenditure on pesticides, or job description, rather than by direct evaluation of the exposed persons. Confounding factors and covariates are often incompletely assessed, and information such as cause of death from death certificates may be inaccurate or incomplete. In addition, the harmful health effects of the so-called inert substances used in pesticide products to potentiate the active ingredients can be difficult to separate from those of the active pesticide ingredients.

Some studies use case-control designs, which do provide good exposure histories, but are marred by the problems of recall bias, low participation rates, and loss to follow-up. The other main study type is ecological, which neither considers exposure at the individual level nor measures pesticide exposure directly. For example, an ecological study may use as an exposure measure the number of tons of pesticide applied annually in a particular county.

Finally, because all humans have some degree of background environmental pesticide exposure (4), there is never a true control group for any study design.

Routes of Exposure

There are many sources of exposure to pesticides. The three routes of exposure for pesticides are oral ingestion, dermal absorption, and inhalation. Lawn and garden pesticides are used in homes and gardens, on golf courses, along highways and hydro rights-of-way, and in public parks, exposing people by all three routes. Pesticides can be tracked into homes, or brought home from work on clothing and in vehicles, exposing family members as well. Pesticides are used in pet flea collars, in treatments for scabies and lice, and for home infestations of wasps, cockroaches, and ants. Agricultural pesticides are used on farms, greenhouses, and orchards, and consumers eating produce and other food products ingest them. Pesticides used domestically or in agriculture run off into ground and surface water, exposing entire populations.

Prevalence of Use

According to a 1997 inventory performed by the Quebec government described in *Lawn and Garden Pesticides: A Review of Human Exposure and Health Effects Research* (5), over 80% of pesticides sold in Quebec are for agricultural purposes, 8.5% are for domestic use (indoor and outdoor), and 3.0% for ornamental horticulture. Although herbicides are the most commonly used pesticide for lawn and garden care, homeowners purchase 3.7 times the amount of insecticides recorded for use in ornamental horticulture. According to a survey done by Toronto Public Health, “approximately 45% of Toronto homeowners with lawns had treated their yards with pesticides in the past two years. This figure reflects both homeowner application and those performed by a professional lawn care company” (5).

Children are particularly vulnerable to the effects of pesticides. Children eat and drink more per kilogram of body weight than adults. Their skin is more permeable and their livers do not excrete as efficiently as adults'. Their hand-to-mouth behaviour increases the chance of ingestion and their dermal contact is increased because of a proportionally larger skin surface, and because they play on the ground outdoors and on the floor indoors. Parents track pesticides indoors on their shoes, inadvertently exposing their children (6). Some pesticides that degrade outdoors in sunlight are more persistent once they are present indoors.

Rationale for Study

Acute effects of pesticides are well documented in the literature, especially with respect to organophosphate poisoning. However, the *chronic* effects of pesticide exposure are much more difficult to assess. Hundreds of studies done in the past few decades have attempted to establish whether chronic exposure to pesticides has adverse effects.

This systematic review of pesticide health effects was initiated in response to a complaint to the Ontario College of Family Physicians by a pesticide lobby group about the College's pesticide education brochure. This information pamphlet, produced in 1998, was designed to educate health professionals. The lobby group claimed that information describing harmful effects of pesticides was inaccurate. This complaint is typical of the confrontations between health advocates and pesticide lobby groups about the true health effects of pesticides, reflecting the difficulties we have in interpreting the studies available, and the dearth of systematic literature reviews on the subject. It may also reflect the fundamentally different interests and perspectives of the two groups.

Description of Study

This project is a systematic review of studies done since 1992, and was conducted with financial support from the Laidlaw Foundation. Chapter 2 details the methods used in the study, and Chapters 3–9 describe the findings of the review regarding major health effects, including nine types of solid tumours, non-Hodgkins lymphoma, leukemia, genotoxic effects, skin diseases, neurological diseases, and reproductive effects. The report also discusses findings specific to children (Chapter 10), and concludes with a chapter on implications for practising family physicians. We hope the report will contribute to a better understanding of this controversial topic, inform those who produce professional and patient educational materials, and aid various levels of government to direct policy on this important health issue.

Chapter 1 — Introduction

References

1. Carson R. *Silent Spring*. 40th anniversary ed. New York: Houghton Mifflin; 2002.
2. Colborn T, Dumanoski D, and Myers JP. *Our Stolen Future*. Toronto: Dutton; 1996.
3. Supreme Court of Canada. Decision regarding 114957 Canada Ltée (Spraytech, Société d'arrosage) *v*. Hudson (Town). Montreal: University of Montreal, Faculty of Law; 2001 [cited 29 March 2004]. Available from: http://www.lexum.umontreal.ca/csc-scc/en/pub/2001/vol2/html/2001scr2_0241.html
4. Hill RH, Head SL, Baker S, Gregg M, Shealy DB, Bailey SL, et al. Pesticide residues in urine of adults living in the United States: reference range concentrations. *Environ Res* 1995;71(2):99–108.
5. *Lawn and Garden Pesticides: A review of human exposure and health effects research*. Toronto: Toronto Public Health; April 2002.
6. Bradman MA Harnly ME Draper W Seidel S Teran S Wakeham D Neutra R. Pesticide exposures to children from California's Central Valley: results of a pilot study. *J Exp Anal Env Epi* 1997;7(2):217–34.

Chapter 2 — Methods

This project began in February 2003 with meetings between Dr. Cole and Dr. Sanborn to hire research assistants and approach physicians with experience and training in environmental health to act as reviewers. The project team was completed in mid-March, and since then, project group meetings have been held twice monthly by teleconference, with project decisions made by e-mail between teleconferences. In March 2003, discussions began regarding the general framework and direction for proceeding with the literature review. We agreed to begin by examining review articles to gauge the state of the current literature and identify any gaps that we would like to address in the review project. Details of the inclusion and exclusion criteria were also decided on at this time.

We decided to include all peer-reviewed studies published between 1992 and 2003 that investigated the human health effects of pesticides. These studies had to be systematic in their approach, and be written in English, French, Spanish, or Portuguese. The searches were done using the PreMedline, Medline, CancerLit, and LILACS (Spanish-language) databases. This review excluded the organochlorine literature, as most of these chemicals are no longer in use as pesticides in Canada and have been reclassified as persistent organic pollutants.

Phase 1 — Review of review papers

Selection of health effects for study

In the search for review papers, the inclusion criteria were expanded to include reviews conducted between 1990 and 2003. The initial search, using the term "pesticides," yielded 12,061 papers. For the second selection stage, the term "pesticides" was combined with "systematic review," "meta-analysis," and "review" to select those studies that apply a systematic approach. When the papers were limited to review articles only, 1684 articles were found. However, these papers had a number of limitations, and although many were categorized as reviews, most did not describe a systematic approach. In addition, a number of the papers were primarily reviews dealing with organochlorines that had been picked up in the search because they were classified broadly as dealing with pesticides. As a result, many of the papers did not meet our inclusion criteria. From this list of 1684 articles, 49 relevant review papers were selected. Two members of the pesticide review group evaluated these review paper abstracts to determine their relevance to the current project. Of the 49 identified reviews, 30 were selected for further assessment using the quality and relevance criteria.

The review articles were collected and categorized according to health effect. We decided to organize the papers according to health effect rather than specific pesticide exposure, since most of the human health effect literature considers people exposed to cumulative or aggregate pesticide mixtures. To ensure that all possible health effects were included, a comprehensive search of medical subject headings (MeSH) in Medline was done early in the review process. This ensured that all relevant terms were included in the search process, and minimized the exclusion of relevant studies.

The health effect categories included in Phase 1 included: cancer, genotoxic, immunologic, neurotoxic, reproductive, and other. Four members of the group reviewed these review articles: two focused on the cancer papers and two reviewed the non-cancer papers. To standardize this process all reviewers used a common assessment tool in an effort to ensure consistent application of the evaluation criteria. After this step, a full project team meeting was held in Toronto on May

5, 2003 to introduce project members, conduct in-depth assessments of the review papers, and formulate the next phase of the project. This process allowed the group to determine gaps in the literature, and decide on the focus and limits of the review. The group decided to apply the following guidelines in choosing the health effects for review:

1. For the health effect, absence of a current, methodologically excellent review paper;
2. For cancers, data on incidence, premature loss of life, and increasing incidence were used to select specific tumour types for review; as well, a chosen cancer had to account for a substantial portion of total cancer incidence.

Using these guidelines, the following health effects were chosen for review, and categorized broadly as "cancer" or "non-cancer":

A) Cancer

1. Lung
2. Breast
3. Colorectal
4. Pancreas
5. Non-Hodgkin's lymphoma
6. Leukemia
7. Brain
8. Prostate
9. Stomach
10. Ovary
11. Kidney
12. Testicular

B) Non-Cancer

1. Reproductive effects
2. Genotoxic/immunotoxic
3. Dermatologic
4. Neurotoxic

Over the next month, work proceeded on the quality assessment tool for reviewing the primary studies. This tool, referred to as the data extraction form, was designed through extensive consultation with Andrea Furlan, the Evidence Based Practice Coordinator at the Institute for Work and Health. In addition, all members of the pesticide group took part in a pilot exercise, using the data extraction tool to assess the same article. All ratings of the article used in the pilot exercise were within one point of each other on the global rating scale. This exercise also led to some minor changes that made the form easier to use for the primary studies.

Phase 2 — Assessment of Primary Studies

During June and July 2003, relevant primary studies for each of the health effects were retrieved using a number of search strategies that incorporated the above criteria. The main strategy used in the review article search was repeated with modifications for each health effect using relevant MeSH terms. All searches began by using the term "pesticides," limiting the search to human studies published between 1992 and 2003. For the search concerning non-Hodgkin's lymphoma, the following terms were also included to capture all relevant articles: "lymphoma, non-Hodgkin," "non Hodgkin lymphoma," "NHL," and "lymphoma." A list of abstracts was produced from each search and distributed to the appropriate reviewers.

Of the Spanish papers, 723 abstracts were identified from the LILACS database and 79 of these selected on the basis of relevance. Based on the abstracts, 21 papers were selected for assessment, eight of which met the quality criteria and were included in the review. Two more Spanish papers were selected via Medline for assessment and were included.

The teams read the abstracts and selected those articles that met the inclusion criteria. Case reports and small case series were excluded. When articles lacked abstracts or contained too little information on which to make a selection, the original primary studies were obtained for evaluation. The same reviewer teams who read the review articles for a health effect also assessed the primary studies, as they were already familiar with the background literature. In addition, three new reviewers joined the group at this point: two assisted in reviewing the neurotoxicology papers and one reviewed the reproductive papers. Disagreements between reviewers concerning selection of articles for inclusion were resolved by discussion and input from a third reviewer. After the abstract selections were agreed on, the primary studies were retrieved from hospital and university libraries, the Internet, and, in some cases, ordered from other external sources through the library document delivery service. A total of 109 cancer papers and 156 non-cancer papers met the criteria for review and were distributed to the reviewing teams.

Over a three-month period, the primary articles were assessed using the data extraction form (Appendix 1). This form contains detailed questions regarding the study design, exposure assessment measures, outcome assessment measures, analysis, and methodological quality assessment. These categories were reviewed and discussed at group meetings in July, August, and September to ensure consistency within the group in the approach to evaluating these study characteristics. After a detailed assessment of methodology, each reviewer ranked each paper according to a global assessment scale on a range from 1–7, where 1 represented a paper with clearly unacceptable methodology, 4 an adequate study, and 7 an excellent one. This global assessment scale covered all aspects of study methodology, and was used as a general guideline to decide which studies would be included in the summary tables and report. All studies ranked below a global score of 4 were excluded, as these were considered of insufficient methodological quality to provide reliable data.

The reviewer pairs met to resolve disagreements about global ratings (defined as a difference of two or more points) by first discussing elements of their assessment of the study. If the difference in ratings could not be resolved, a third reviewer acted as a tiebreaker to decide whether to include the paper.

In August, the project group presented the project methodology and preliminary results concerning two health effects to the University of Toronto community medicine residents, and received helpful critique and suggestions.

Phase 3 — Analysis, external review, and report

As assessments of the primary articles were completed, summary tables were made showing the studies included for each health effect category. These tables include information on the study population, design, pesticide type, exposure and outcome measurements, covariates, analysis, and specific measures of association and values. The full review group met November 6–7 to discuss these tables and the written summaries for each health effect category. At this time, the results of the papers were discussed in detail, questions about methodology resolved, and controversial papers discussed in detail. Some methodological issues were common across all health effects, and some, such as the use of measures of incidence versus mortality, were specific to cancer. At these meetings we also developed guidelines for writing chapters for the final report.

The report was written over the following three months, reviewing and editing being done by peer and expert reviewers.

Sources of bias

The group also discussed potential sources of bias in the selection of articles for the review. One of these involved potential bias in the search strategy. The search strategies look for relevant terms in the title or abstract of the primary study. However, if the selected term is not mentioned in these sections, this type of search will pass over the study. Another possibility is that those papers showing positive associations are more likely to mention these terms in the abstract and thus be collected in the search. This is particularly true in the case of cohort studies that examine a wide range of health outcomes. Also, a bias may exist toward publication of papers with positive results. To expand our search for articles we examined the reference lists of each paper and added relevant articles missed by the initial search. We also consulted experts on specific health effects at several stages of the review to solicit comments on the selection of articles and analysis, and reduce the possibility of missing important studies.

Another concern was that some of the cancer and reproductive studies reported the outcomes for many health effects and levels of exposure. As a result, there was sometimes a lack of analysis specific to each health effect; more information was included when results were statistically significant. The large number of statistically significant results in these papers made it difficult to develop summary tables for them.

Two studies revealed that the authors had paid to have them published. Also, two studies were funded by pesticide-producing corporations, introducing the potential for a bias toward publication of negative findings.

Types of studies and methodological issues

The papers reviewed were cohort, case-control, or ecological studies. There are several methodological issues specific to each of these designs.

Cohort studies

There are several limitations and advantages innate to the design of cohort studies. One advantage of cohort studies is the large number of subjects that can be included, which increases their ability to find elevated rates of rare illnesses. However, when large numbers of subjects are studied, it is usually impossible to attain detailed pesticide exposure histories. For instance, instead of measurements of direct exposure and specific pesticide use, surrogate measurements are often used to describe exposure. These could be indirect measurements such as the job description of an occupation involving high exposure to pesticides, length of time employed in an exposed environment, length of membership in a union of occupationally exposed workers, or location of residence or workplace. For farmers, exposure is often estimated by type of crop grown, number of acres farmed, or expenditure on pesticides. Usually specific pesticides are not identified and sometimes results are confounded because the study dates back to an exposure period when organochlorines or other chemicals now banned were still in use. For example, some older studies of 2,4-D occurred during the period when this chemical was heavily contaminated with dioxins. Some studies use follow-up times that are too short to show up higher incidence rates when there is a long latency period between exposure and illness onset (some latency periods are as long as 30 years). In addition, sometimes subjects are lost to follow-

up because of migration. Often standardized mortality rates (SMR) are used instead of standardized incidence rates (SIR), which underestimates the actual occurrence of curable and treatable cancers. Mortality information is usually derived from death certificates, and these are not always accurate. For instance, death certificates do not always describe subtypes of cancers; when pesticide exposure causes one subtype and not another, the lack of subtyping could mask the true association between an exposure and the cancer. A histological diagnosis, the most accurate way to diagnose cancer, is not always available, and this lack makes a study less reliable. Important covariates such as smoking, family history, and race are usually not included in cohort studies because of the large numbers of subjects involved.

Cohort studies are confounded by the "healthy worker effect." Ill people are less likely to hold down jobs or are more likely to be absent when the study is conducted. Hence, they will not be included in a group of workers studied, and the group will be pre-selected for healthy people. Also groups that possibly experience higher pesticide exposure, such as farmers, gardeners, and foresters, are known to be healthier than other workers in the population because they smoke less, exercise more, and are exposed to less air pollution. This makes them a pre-selected group within the larger working population. Another major limitation of these cohort studies and other studies is their lack of data on women.

Case-control studies

There are major limitations of case-control studies, the main one being that of recall bias: people who agree to participate may comprise a preselected group that is more likely to remember or exaggerate exposures in an effort to explain their own illness or that of a loved one. Some authors attempt to minimize recall bias by using a control group derived from hospital patients with other illnesses; however, these patients may also have illnesses related to exposures and are therefore not always valid controls.

Response rates vary with case-control studies, and low rates may introduce bias. In addition, random-digit dialing as a means of finding controls, can lead to controls with higher socioeconomic backgrounds that tend to be healthier than the general population, making them less appropriate controls. Another possible source of bias in case-control studies is a lack of interviewee blinding and data quality control. Also sometimes the case involved has died so a proxy respondent (usually a family member) must give information on exposure and other matters. Often the information available from these people is less accurate. However, because case-control studies offer the ability to interview or use questionnaires to obtain detailed exposure histories, details of covariates (such as smoking, family history, and race) can be determined.

Ecological Studies

Ecological studies consider groups rather than individuals as the unit of analysis. For example, such a study in the pesticides literature may compare mortality rates from national cancer registries to sales of pesticides by region. Others link disease cases from other national registries to employment information from national censuses to assess the relationship between pesticide exposure and adverse health effects. Ecological studies can be useful for detecting associations between exposure distributions and cases of disease, and are typically more easily and inexpensively conducted than are other study designs. However, because the data are measurements averaged over many individuals, the degree of association does not reflect individual-level associations. The failure of the effect estimate at the ecological level to reflect

the effect at the individual level is the primary limitation of this study design. Nevertheless, these studies are useful for generating hypotheses and suggesting future directions for observational studies.

The following Chapters (3–9) detail the findings for each health effect, and are accompanied by reference lists and summary tables.

Chapter 3 — Solid Tumours

Brief Methodology

Nine solid tumours were chosen for study in this review, using data from the Canadian Cancer Statistics webpage on cancer incidence, potential years of life lost and percent change in age-standardized incidence for selected cancer sites. (See Chapter2 – Methods for a detailed description). From these lists the following solid tumours were selected to be included in this review: lung cancer, breast cancer, pancreatic cancer, brain cancer, prostate cancer, stomach cancer, ovarian cancer, and kidney cancer. Testicular cancer was also selected, but the one retrieved article was of such poor methodological quality that it was excluded from the review. Colorectal cancer was also a tumour of interest, but despite numerous searches, no primary studies of pesticide exposure and bowel cancer were found.

General Strengths and Weaknesses in Study Design

Most of the solid tumour primary studies share common methodological strengths and weaknesses. There are several well-designed studies that include large sample sizes with an extensive follow-up period. Although the majority of the studies in this area are cohort or case-control, there are a few ecological studies, and they have also been included in this review.

The studies investigated a variety of populations including farmers, aerial pesticide applicators, children of pesticide applicators and employees of pesticide production plants. A small number of studies look at household and garden pesticide exposure. The exposures under study vary from pesticides as a general exposure category, to sub-categories of pesticides (i.e. fungicides, herbicides, insecticides), to specific pesticides. For the case-control studies, exposure was typically assessed through questionnaires regarding occupational and/or home exposure. Usually an industrial hygienist assigned categories of exposure based on the questionnaire answers. The cohort studies relied on agricultural census data and pesticide application licenses to assess exposure. However, the major drawback to most of the poorer quality papers is that the proxy measure of exposure is poor, introducing the possibility that the study results may be biased. In addition, several of the weaker papers do not sufficiently consider the broad range of potential confounders that are necessary to investigate (particularly in the breast cancer papers where several ignore important covariates like age at menarche, menopause, reproductive history, history of breast cancer in the family, etc). However, for the most part, the solid tumour studies evaluated in this review are of moderate to good quality, and present interesting and clinically relevant findings regarding the relationship between pesticide exposure and solid tumour cancers.

Brain Cancer

This review included eleven papers (14–24) that investigated the association between pesticide exposure and the risk of brain cancer. Of these studies, seven looked specifically at brain cancer as an outcome; one at intracranial gliomas, and another at astrocytoma and PNET (primitive neuroectodermal tumours) while the other four considered all cancers in general. Of the eleven studies, five were case-control, five cohort, and one ecological. The studies include populations in the US, Canada, and Europe and all were considered of good methodological quality, with global rankings of four or above.

The cohort studies all found significant positive associations between pesticide exposure and brain cancer. One study included a large sample size of 323,292 offspring of Norwegian farmholders and used census data to develop an exposure proxy through pesticide and spray equipment purchase (17). Increased risk was found for brain tumours, in particular non-astrocytic neuroepithelial tumours. In addition, there was a dose-response relationship with the magnitude of the effect strongest in children aged 0 to 14 years. The case-control studies found similar results. With regards to household pesticide use, another good quality study found a significant positive association between risk of pediatric brain tumours and prenatal use of flea-tick products (OR 1.7, CI 1.1-2.6) (20).

Breast Cancer

For the breast cancer group, twelve articles were found using the search strategy. Of these, four were excluded because they were lab studies rather than studies about human populations, and two others were excluded on quality scores. The remaining six papers include one cohort study with non-exposed controls, two case-controls, and three ecological studies. The cohort study (27) followed a group of women with at least ten years' work in greenhouses for more than four hours daily. Mammographic findings were compared between exposed women and matched, non-exposed women who were residents of large towns with non-agricultural occupations. The exposed women were found to be at a higher risk of having mammographic findings that are risk markers for the development of breast cancer. However, there was not a statistically significant difference between the groups in findings of malignancies following biopsy and histological confirmation.

Of the two case-control studies, two present positive associations, and the other two (excluded) found no association. One population-based study interviewed 1018 women with incident breast cancer, identified from the British Columbia Cancer Registry (26). Using interview information, occupations were coded in an effort to assess exposure to a variety of chemicals, one of which included pesticides. Excess risk of breast cancer was found in crop farmers and in the fruit and vegetable industries. Another case-control study focused specifically on farming and incident breast cancer (28). After controlling for a large number of potential confounders, this study concludes that among women who farmed, ORs were elevated for those who reported being present in fields during or shortly after pesticide application (OR 1.8, 95% CI 1.1-2.8) and for those who reported not using protective clothing while applying pesticides (OR 2.0, 95% CI 1.0-4.3). Interestingly, an increased duration of farming was associated inversely with breast cancer risk. Possible mechanisms for this may include a protective effect of physical activity against breast cancer, exposure to sunlight, which may increase vitamin D levels and thus decrease breast cancer risk, or the possibility that some pesticides or contaminants (like TCDD) may possess antiestrogenic activity.

Of the three ecological studies of breast cancer, one examined a mixed pesticide exposure, and the other two looked at herbicides only. The former study used National Cancer Institute data and focused on the whole population of Mississippi (25). The total number of acres planted during 1997–2000 for each Statistical Economic Area and by type of crop was used as a proxy measure for pesticide exposure. The total number of acres planted was positively and statistically significantly associated with breast cancer mortality rate. Specifically, the strongest correlations were associated with rice crops and catfish crops. The authors suggest that this may be due to pesticide bioaccumulation through the food chain. The other two ecological studies consider exposure to herbicides, specifically atrazine and triazine. Both of these study populations are the residents of the state of Kentucky and are part of the same research group, so it is likely that

these papers present information about the same study population (29, 30). While the results did not support a relationship between exposure to atrazine and breast cancer incidence (29), there was a statistically significant positive association with triazine exposure (30); specifically, there was an increased breast cancer incidence with medium and high levels of triazine herbicide exposure (OR 1.14, $p<0.0001$ and OR 1.2, $p<0.0001$ respectively).

Kidney Cancer

Seven papers evaluated the relationship between kidney cancer and pesticide exposure. However, one of these was excluded due to its poor methodological quality. Of the remaining six studies, four are case-control, and two are cohort studies. One of the cohort studies looked at kidney cancer mortality in a large retrospective cohort of 167,703 children (32). A statistically significant excess of kidney cancer was found among the offspring of men with potential occupational exposure to pesticides (PMR 1.59, 95% CI 1.18–2.15). The other cohort study assessed the relationship between occupational exposure to pentachlorophenol and cause of mortality at a chemical company that produced this pesticide (35). It also found a statistically significant positive association between exposure and death from kidney cancer (SMR 502, 95% CI 101–1468). Unfortunately, the confidence intervals are quite broad in this latter study due to the small numbers in the group.

The four case-control studies all found statistically significant positive associations between pesticide exposure and kidney cancer (31, 33, 34, 36). This effect was seen most consistently for longer duration of exposure, and found in the cases of children whose parents were occupationally exposed to pesticides.

Lung Cancer

Four studies examined the association between lung cancer and pesticide exposure. Of these, two looked specifically at lung cancer mortality and incidence, and two considered all types of cancer mortality. One of the latter two is a retrospective cohort study of male farm workers in Italy who obtained a license to handle pesticides during the period 1973–1979 (38). The authors conclude that this cohort actually had a lower risk of mortality due to lung cancer when compared to provincial and national mortality data. This lowered risk was attributed to the 'healthy worker effect,' or the possibility that smoking is less common among farmers. Smoking status was not measured in the study. Given the clear relationship between smoking and lung cancer, the absence of information on this important covariate limits the usefulness of the study's findings. The other cohort paper considered all causes of mortality in a cohort of golf superintendents (39). Conversely, they found an elevated PMR (proportionate mortality ratio) of lung cancer in the exposed cohort. However, they also failed to control for smoking or passive smoking exposure and thus it is difficult to assess any potential causal relationship between the two.

The other two papers, case-control studies, included smoking as an important covariate in the analysis. One examined the occupationally related risk of lung cancer among non-smoking women for several occupations (37). Of these occupations, pesticide exposure was considered as a specific exposure in the workplace. An elevated incidence of lung cancer was found for women exposed to pesticides when compared to a population-based sample of controls (OR 2.4, 95% CI 1.1-5.6). A dose-response relationship was also found where the higher exposure range had a higher risk of lung cancer when compared to the lower exposure range. The other case-control study was nested within a retrospective cohort of Florida pest control workers (40), and considered specific types of pesticides, rather than the broad category as in the other two studies.

This study looked at lung cancer mortality, rather than incidence, as the outcome of interest. Information regarding specific pesticide use was collected from proxy interviews of next-of-kin and included information regarding use of organophosphates, organochlorines, carbamates, inorganics, organobromides, natural products, and phenoxy herbicides. Results were provided for comparisons between cases and dead controls and cases and living controls. Of these results, there was a statistically significant increased risk of lung cancer mortality for carbamate use in cases versus dead controls (OR 16.3, 95% CI 2.2–122.5) and for phenoxyacetic acid use in cases versus living controls (OR 22.4, 95% CI 1.8–276.2). Unfortunately, the confidence interval ranges for these values are quite broad, making it difficult to assess the precision of this value. Although increased risks were also found for the use of organophosphate, organochlorine, and inorganics, these findings were not statistically significant.

The results from these studies suggest that there may be a relationship between some pesticide exposures and risk of lung cancer. However, there is a need for further studies in this area that consider smoking and passive smoking exposure as important covariates before any causal associations can be concluded.

Ovarian Cancer

The current literature review failed to find any studies that looked exclusively at ovarian cancer. Rather, there was a selection of papers that considered ovarian cancer in addition to several other solid tumour cancers. One of these actually found a negative association between ovarian cancer and atrazine exposure (41). However, this suggested protective effect on incident ovarian cancer was not statistically significant, and determined in the context of an ecological study. Thus, its findings are limited in making associations between ovarian cancer risk and atrazine exposure.

Pancreatic Cancer

The risk of pancreatic cancer and exposure to pesticides was evaluated in three studies; two case-control, and one cohort. All the papers found a positive association, particularly for high intensity exposure, and exposure to herbicides and fungicides.

The retrospective cohort study followed male aerial pesticide applicators for their cause of death (43). This large study found a statistically significant positive association of pancreatic cancer in the applicator group when compared to non-exposed individuals (SMR 2.71, 95% CI 1.4–5.3). Unfortunately, the study did not consider smoking as a potential covariate.

The two case-control studies also found positive significant associations, and one of these included smoking habits as an important covariate. One Spanish study (42) compared incident cases of pancreatic cancer with hospital controls. Occupational history was obtained through interview and exposures evaluated by industrial hygienists. Moderately increased ORs were found in the high-intensity category of pesticides, highest for arsenical pesticides (OR 3.4, 95% CI 0.9–12.0) and ‘other pesticides’ (OR 3.17, 95% CI 1.1–9.2). The other case-control study, conducted in the United States (44, 45) compared pancreatic cancer cases with a random sample from the population. Occupational information was also collected through interviews, and then a job-exposure matrix was used to estimate the level of occupational risk for pesticide exposure. Excess risks were found for occupational exposure to fungicides (OR 1.5, 95% CI 0.3–7.6) and herbicides (OR 1.6, 95% CI 0.7–3.4).

Prostate Cancer

Ten papers looked at the risk of prostate cancer with exposure to pesticides. However, two were excluded due to poor methodological quality. Of the remaining eight papers, five are cohort studies, two case-controls, and one ecological (46–53). An excellent study (46) investigated a cohort of 55,332 male pesticide applicators and found a positive statistically significant association between exposure to pesticides and prostate cancer when compared to the rest of the population. This increase was also evident with the use of methyl bromide and use of chlorinated pesticides among applicators over 50 years of age (OR up to 3.75, $p<0.004$) (46). The other studies present a similar trend, suggesting that pesticide exposure, particularly at high levels of exposure, is a risk factor for the development of prostate cancer.

Stomach Cancer

One paper from Ontario investigated the relationship between exposure to nitrate and atrazine and stomach cancer (54). Although they found a positive significant association between atrazine contamination levels and stomach cancer ($p<0.05$), this study was an ecological design, and therefore it is difficult to make any conclusions from this about causality. Nevertheless, it is interesting for forming hypotheses about this new and yet to be studied area.

General Conclusions

In summary, there are many studies showing positive associations between solid tumours and pesticide exposure. In particular, the large well-designed cohort studies consistently show statistically significant positive associations. The relationships are most consistent for high exposure levels such as those found in occupational settings. The results frequently show dose-response relationships, and quality of studies was generally good. Overall, these findings strongly support a reduction of pesticide use, particularly for those individuals with occupational exposure (agriculture, pesticide applicators) at high doses. Future work targeted at non-occupational exposures, in addition to further work on some of the less studied solid tumours is warranted and will provide continued direction for clinical practice.

Chapter 3 — Solid Tumors

References

Review Articles:

1. Acquavella J, Olsen G , Cole P, Ireland B, Kaneene J, Schuman S, Holden L. Cancer among farmers: a meta-analysis. *Annals of Epidemiology.* 1998; **8:** 64-74.
2. Baldi I, Mohammed-Brahim B, Brochard P, Dartigues JF, Salamon R. Delayed health effects of pesticides: review of current epidemiological knowledge. *Revue d Epidemiologie et de Sante Publique.* 1998; **46:** 134–142.
3. Bohnen NI, Kurland LT. Brain tumor and exposure to pesticides in humans: a review of the epidemiologic data. *Journal of the Neurological Sciences*. 1995**; 132:** 110**–**121.
4. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. *Environmental Health Perspectives.* 1997; **105:** 1068–1077.
5. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer. *Cancer Causes & Control.* 1997; **8:** 420–443.
6. Johnson CC, Feingold M, Tilley B. A meta-analysis of exposure to phenoxy acid herbicides and chlorophenols in relation to risk of soft tissue sarcoma. *International Archives of Occupational & Environmental Health.* 1990; **62:** 513–520.
7. Keller-Byrne JE, Khuder SA, Schaub EA. Meta-analyses of prostate cancer and farming. *American Journal of Industrial Medicine.* 1997; **31:** 580–586.
8. Khuder SA, Mutgi AB, Schaub EA. Meta-analyses of brain cancer and farming. *American Journal of Industrial Medicine.* 1998; **34:** 252–260.
9. Khuder SA, Mutgi AB. Meta-analyses of multiple myeloma and farming. *American Journal of Industrial Medicine.* 1997; **32:** 510–516.
10. Maroni M, Fait A. Health effects in man from long-term exposure to pesticides. A review of the 1975-1991 literature. *Toxicology.* 1993; **78:** 1–180.
11. Sathiakumar N, Delzell E. A review of epidemiologic studies of triazine herbicides and cancer. *Critical Reviews in Toxicology.* 1997; **27:** 599–612.
12. Zahm SH, Blair A. Cancer among migrant and seasonal farmworkers: an epidemiologic review and research agenda. *American Journal of Industrial Medicine* 1993 Dec;**24**(6):753–66.
13. Zahm SH, Ward MH. Pesticides and childhood cancer. *Environmental Health Perspectives.* 1998; **106:** Suppl-908.

Primary Studies:

Brain Cancer

14. Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer [comment]. *Archives of Environmental Contamination & Toxicology.* 1993; **24:** 87–92.
15. Efird JT, Holly EA, Preston-Martin S, Mueller BA, Lubin F, Filippini G, Peris-Bonet R, McCredie M, Cordier S, Arslan A, Bracci PM. Farm-related exposures and childhood brain

tumours in seven countries: results from the SEARCH International Brain Tumour Study. *Paediatric and Perinatal Epidemiology.* 2003; **17**(2):201–11.

16. Figa-Talamanca I, Mearelli I, Valente P, Bascherini S. Cancer mortality in a cohort of rural licensed pesticide users in the province of Rome.[comment]. *International Journal of Epidemiology.* 1993; **22:** 579–583.
17. 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. *International Journal of Cancer.* 1996; **65:** 39–50.
18. Kross,B.C., Burmeister,L.F., Ogilvie,L.K., Fuortes,L.J., Fu,C.M. 1996. Proportionate mortality study of golf course superintendents. *American Journal of Industrial Medicine.* **29,** 501–506.
19. Littorin M, Attewell R, Skerfving S, Horstmann V, Moller T. Mortality and tumour morbidity among Swedish market gardeners and orchardists. *International Archives of Occupational & Environmental Health.* 1993; **65:** 163–169.
20. Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environmental Health Perspectives.* 1997; **105:** 1214–1220.
21. Rodvall Y, Ahlbom A, Spannare B, Nise G. Glioma and occupational exposure in Sweden, a case-control study. *Occupational & Environmental Medicine.* 1996; **53:** 526–537.
22. Smith-Rooker JL, Garrett A, Hodges LC, Shue V. Prevalence of glioblastoma multiforme subjects with prior herbicide exposure. *Journal of Neuroscience Nursing.* 1992; **24:** 260–264.
23. Van Wijngaarden E, Stewart PA, Olshan AF, Savitz DA, Bunin GR. Parental occupational exposure to pesticides and childhood brain cancer. *American Journal of Epidemiology.* 2003; **157**(11):989–97.
24. Viel JF, Challier B, Pitard A, Pobel D. Brain cancer mortality among French farmers: the vineyard pesticide hypothesis. *Archives of Environmental Health.* 1998; **53:** 65–70.

Breast Cancer

25. Abdalla MH, Gutierrez-Mohamed ML, Farah IO. Association of pesticide exposure and risk of breast cancer mortality in Mississippi. *Biomedical Sciences Instrumentation.* 2003; **39:** 397–01.
26. 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. *Journal of Occupational & Environmental Medicine.* 2000; **42:** 284–310.
27. Dolapsakis G, Vlachonikolis IG, Varveris C, Tsatsakis AM. Mammographic findings and occupational exposure to pesticides currently in use on Crete. *European Journal of Cancer.* 2001; **37:** 1531–1536.
28. Duell EJ, Millikan RC, Savitz DA, Newman B, Smith JC, Schell MJ, Sandler DP. A population-based case-control study of farming and breast cancer in North Carolina. *Epidemiology.* 2000; **11:** 523–531.
29. Hopenhayn-Rich C, Stump ML, Browning SR. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Archives of Environmental Contamination & Toxicology.* 2002; **42:** 127–136.

30. Kettles MK, Browning SR, Prince TS, Horstman SW. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. *Environmental Health Perspectives.* 1997; **105:** 1222–1227.

Kidney Cancer

31. Buzio L, Tondel M, De Palma G, Buzio C, Franchini I, Mutti A, Axelson O. Occupational risk factors for renal cell cancer. An Italian case-control study. *Medicina del Lavoro.* 2002; **93:** 303–309.

32. Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture: the role of pesticides. *British Journal of Cancer.* 1998; **77:** 825–829.

33. Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. *Occupational Medicine (Oxford).* 2002; **52:** 157–164.

34. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Occupational risk factors for renal-cell carcinoma in Denmark. *Scandinavian Journal of Work, Environment & Health.* 1994; **20:** 160–165.

35 Ramlow JM, Spadacene NW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940–1989. *American Journal of Industrial Medicine.* 1996; **30:** 180–194.

36. Sharpe CR, Franco EL, de Camargo B, Lopes LF, Barreto JH, Johnsson RR, Mauad MA. Parental exposures to pesticides and risk of Wilms' tumor in Brazil. *American Journal of Epidemiology.* 1995; **141:** 210–217.

Lung Cancer

37. 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:** 449–454.

38. Figa-Talamanca I, Mearelli I, Valente P, Bascherini S. Cancer mortality in a cohort of rural licensed pesticide users in the province of Rome.[comment]. *International Journal of Epidemiology.* 1993; **22:** 579–583.

39. Kross BC, Burmeister LF, Ogilvie LK, Fuortes LJ, Fu CM. Proportionate mortality study of golf course superintendents. *American Journal of Industrial Medicine.* 1996; **29:** 501–506.

40.Pesatori AC, Sontag JM, Lubin JH, Consonni D, BlairA. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). *Cancer Causes & Control.* 1994; **5:** 310–318.

Ovarian Cancer

41. Hopenhayn-Rich C, Stump ML, Browning SR. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Archives of Environmental Contamination & Toxicology.* 2002; **42:** 127–136.

** This paper is also found in the breast cancer list **

Pancreatic Cancer

42. Alguacil J, Kauppinen T, Porta M, Partanen T, Malats N, Kogevinas M, Benavides FG, Obiols J, Bernal F, Rifa J, Carrato A. Risk of pancreatic cancer and occupational exposures in Spain. PANKRAS II Study Group. *Annals of Occupational Hygiene.* 2000; **44:** 391–403.

43. Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: follow-up from 1965–1988. *American Journal of Industrial Medicine.* 1999; **36:** 239–247.

44. Ji BT, Silverman DT, Stewart PA, Blair A, Swanson GM, Baris D, Greenberg RS, Hayes RB, Brown LM, Lillemoe KD, Schoenberg JB, Pottern LM, Schwartz AG, Hoover RN.Occupational exposure to pesticides and pancreatic cancer.[erratum appears in Am J Ind Med 2001 Aug;40(2):225–6]. *American Journal of Industrial Medicine.* 2001; **39:** 92–99.

45. Ji BT, Silverman DT, Stewart PA, Blair A, Hoover R. Re: Occupational exposure to pesticides and pancreatic cancer. 2001. Ji BT, Silverman DT, Stewart PA, Blair A, Swanson GM, Baris D, Greenberg RS, Hayes RB, Brown LM, Lillemoe KD, Schoenberg JB, Pottern LM, Schwartz AG, Hoover RN. *Am. J. Ind. Med*. 2001; **39**:92–99. *American Journal of Industrial Medicine.* 2001; **40**(2):225–6.

Prostate Cancer

46. Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J, Coble J, Sandler DP, Blair A. Use of agricultural pesticides and prostate cancer risk in the agricultural health study cohort. *American Journal of Epidemiology.* 2003**; 157**(9):800–14.

47. Dich J, Wiklund K. Prostate cancer in pesticide applicators in Swedish agriculture. *Prostate.* 1998; **34:** 100–112.

48. Fleming LE, Bean JA, Rudolph M, Hamilton K. Cancer incidence in a cohort of licensed pesticide applicators in Florida. *Journal of Occupational & Environmental Medicine.* 1999; **41:** 279–288.

49. Kross BC, Burmeister LF, Ogilvie LK, Fuortes LJ, Fu CM. Proportionate mortality study of golf course superintendents. *American Journal of Industrial Medicine.* 1996; **29:** 501–506. (This paper is also found in the lung and brain cancer lists.)

50. MacLennan PA, Delzell E, Sathiakumar N, Myers SL, Cheng H, Grizzle W, Chen VW, Wu XC. Cancer incidence among triazine herbicide manufacturing workers. *Journal of Occupational & Environmental Medicine.* 2002; **44:** 1048–1058.

51. Mills PK, Yang R. Prostate cancer risk in California farm workers. *Journal of Occupational & Environmental Medicine.* 2003; **45**:(3):249–58.

52. Settimi L, Masina A, Andrion A, Axelson O. Prostate cancer and exposure to pesticides in agricultural settings. *International Journal of Cancer.* 2003; **104:** 458–461.

53. Sharma-Wagner S, Chokkalingam AP, Malker HS, Stone BJ, McLaughlin JK, Hsing AW. Occupation and prostate cancer risk in Sweden. *Journal of Occupational & Environmental Medicine.* 2000; **42:** 517–525.

Stomach Cancer

54. 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. *International Journal of Epidemiology.* 1999; **28:** 836–840.

Excluded Papers:

Breast Cancer

55. Cabello G, Juarranz A, Botella LM, Calaf GM. Organophosphorous pesticides in breast cancer progression. *Journal of Submicroscopic Cytology & Pathology.* 2003;**35**(1):1–9.

56. Chen H, Xiao J, Hu G, Zhou J, Xiao H, Wang X. Estrogenicity of organophosphorus and pyrethroid pesticides. *Journal of Toxicology & Environmental Health Part A.* 2002; **65:** 1419–1435.

57. Garey J, Wolff MS. Estrogenic and antiprogestagenic activities of pyrethoid insecticides. *Biochemical & Biophysical Research Communications*. 1998; **251**: 855–859.

58. Lopez-Carrillo L, Lopez-Cervantes M, Torres-Sanchez L, Blair A, Cebrian ME, Garcia RM. Serum levels of beta-hexachlorocyclohexane, hexachlorobenzene and polychlorinated biphenyls and breast cancer in Mexican women. *European Journal of Cancer Prevention.* 2002; **11:** 129–135.

59. Martinez Vidal JL, Moreno FM, Garrido FA, Olea-Serrano F, Olea N. Determination of endocrine-disrupting pesticides and polychlorinated biphenyls in human serum by GC-ECD and GC-MS-MS and evaluation of contributions to the uncertainty of the results. *Analytical & Bioanalytical Chemistry.* 2002; **372:** 766–775.

60. Zheng T, Holford TR, Mayne ST, Owens PH, Ward B, Carter D, Dubrow R, Zahm SH, Boyle P, Tessari J. Beta-benzene hexachloride in breast adipose tissue and risk of breast carcinoma. *Cancer.* 1999; **85:** 2212–2218.

Kidney Cancer

61. Forastiere F, Quercia A, Miceli M, Settimi L, Terenzoni B, Rapiti E, Faustini A, Borgia P, Cavariani F, Perucci CA. Cancer among farmers in central Italy. *Scandinavian Journal of Work, Environment & Health.* 1993; **19:** 382–389.

Prostate Cancer

62. Janssens JP, Van Hecke E, Geys H, Bruckers L, Renard D, Molenberghs G. Pesticides and mortality from hormone-dependent cancers. *European Journal of Cancer Prevention.* 2001; **10:** 459–467.

63. Koifman S, Koifman RJ, Meyer A. Human reproductive system disturbances and pesticide exposure in Brazil. *Cadernos de Saude Publica.* 2002; **18:** 435–445.

Testicular Cancer

64. Koifman S, Koifman RJ, Meyer A. Human reproductive system disturbances and pesticide exposure in Brazil. *Cadernos de Saude Publica.* 2002; **18:** 435–445.

** This paper is also found in the prostate cancer list **

Chapter 3 — Solid Tumors

Tables

Table 1 Brain Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Figa-Talamanca 1993	Retrospective cohort study of a group of 2310 male farm workers (over the age of 15 yrs) who were licensed to handle pesticides in Italy; included those issued pesticides licenses between 1973–1979.	Mixed pesticide exposure; mostly assessed through license information – a small group filled out a questionnaire (but did not have info on quantity or type of pesticide – just use or not).	Age	SMR, Poisson	There was a statistically significant excess for brain cancer in the exposed group (SMR 270, CI 108.6–556.9); no other ORs for brain cancer provided.	4,4
Kross 1996	Retrospective cohort study of a group of 686 deceased white male members of the Golf Superintendents Association of America; compared to white male US population; included subjects from across the US	Mixed pesticide exposure; could not provide specific exposure information as data source was death certificates; exposure assumed through membership in association.	None	PMR	The cohort experienced higher mortality for all cancers (PMR 136, CI 121, 152), PMR lung cancer 117 (CI 93, 148), PMR brain 234 (CI 121, 454), PMR NHL 237 (CI 137, 410), PMR prostate 293 (CI 187, 460).	4,4
Kristensen 1996	Retrospective cohort study of 323, 292 offspring of parents identified as farm holders in Norway born between 1952–1991.	Mixed pesticide exposure; assessed from Agricultural Censuses that had info re: pesticide purchases and pesticide spraying equipment.	Age, gender, period of follow-up, geographical region, type of agricultural work done by parent.	RR, Poisson	Positive association between brain tumours and pesticide purchase (RR 1.71, CI 1.11–2.63) and non-astrocytic neuroepithelial tumours (RR 3.37, CI 1.63–6.94); RRs for brain tumours ranged between 1.29–1.59 for various types of farming.	6,6
Littorin 1993	Retrospective cohort study of 2370 subjects who had been members of a	Mixed pesticide exposure; assessed through membership lists and	Gender, age	SMR,	This population had an increased rate of brain	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	horticulturists' trade association between 1965-1982 in Sweden; men and women.	association records.		Poisson	tumours (SMR 3.2, CI 1.6-5.7) for young and middle-aged horticulturists; no dose response relationship.	
Smith-Rooker 1992	Descriptive cohort study (retrospective chart review) of patients enrolled in a brain tumour treatment program in Arkansas between 1984–1991 (n=100).	Herbicide exposure assessed by residence proximity to rice and cotton crops;	Age, gender, residence, occupation	% of total cases who live in areas of high rice acreage, cotton acreage; also % of cases with certain occupations	More than one third of cases came from 3 counties (these counties are high producers of cotton, rice, and wood which is associated with high herbicide use).	4,4
Case-Control Studies						
Davis 1993	Case-control study to examine the relationship between childhood brain cancer and household pesticide use in Missouri; 45 cases (from age 0-10) diagnosed between 1985-1989, 85 friend controls, 108 other cancer controls; study limited to white children.	Pesticides for 'nuisance' pests (roaches, ants, spiders, termites, lice, fleas, ticks, garden or orchard pests, weeds in garden); assessed through a questionnaire administered to mother; composite variable of exposure developed for use up to age of diagnosis and # of times used during pregnancy and up to age of diagnosis.	Age, gender, child's age at diagnosis, child's exposure to environmental tobacco smoke, during birth to six months and 7 months to diagnosis, family income, fathers education, mothers education, family member in construction industry.	OR, Mantel-Hanzel	There were several positive associations of brain cancer and certain pesticides: Overall OR 3.4 (CI 1.1–10.6) for pesticide use in general during the 7 months of age to diagnosis period; other significant positive findings for use of no-pests strips, pesticides to control termites, Kwell shampoo, flea collars on pets, herbicides where ORs ranged between 0.6–6.2.	5,5
Efird 2003	International case-control study to examine farm-related exposure and childhood brain cancer; seven countries; cases under 20 yrs age at	Pesticides classified as a general term; assessed through a questionnaire administered to the birth mother about farm exposures (lots of	Age, gender, centre, race, mother's	OR, logistic regression.	Increased OR for brain tumours in children and specific farm-related exposures; pesticides OR	5,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	diagnosis, diagnosed between 1976–1994; 1218 cases and 2223 controls.	info collected about different animal exposures).	education.		2.0, (CI 1.2, 3.2); no other ORs for pesticides provided.	
Pogoda 1997	Case control study of paediatric brain tumours in LA, California (age 19 or under at diagnosis); 224 cases and 218 controls.	Mixed pesticide exposure; a variety of 'nuisance' pesticides investigated; detailed questions regarding exposure during pregnancy and childhood.	Gender, age, race, mother's education, SES	OR, logistic regression	Significant positive association between brain tumours and prenatal use of flea-tick products (OR 1.7, CI 1.1–2.6); other prenatal pesticide exposures non signif, but ORs ranged between 0.9-2.7; none of the pesticide exposures were significant for childhood exposure.	5,5
Rodvall 1996	Case control study of all newly diagnosed intracranial gliomas in 25-74 yr old people living in Sweden; 192 cases and 192 controls.	Mixed pesticides exposure; questionnaire; questions about job title, industrial exposures, how many days, weeks, months, yrs, came into contact.	Gender, age, parish, social status, education	RR, logistic regression	Pesticide use in any occupation resulted in increased risk of gliomas (RR 1.8, CI 0.6-5.1 for men and RR 2.2, CI 0.5–10.5 for women).	4,4
Van Wijngaarden 2003	Case control study of to determine risk of brain cancer in relation to parental occupation; 154 astrocytoma, 158 PNET, and 312 controls in Canada and the US diagnosed between 1986–1989; cases diagnosed before the age of 6 yrs.	Four broad classes of pesticides: insecticides, herbicides, agricultural and nonagricultural fungicides; exposure assessed through a questionnaire; detailed questions about occupation and then industrial hygienist assigned exposure intensity, probability, and frequency to each parent.	Mother's education, SES, maternal age at birth	OR, logistic regression	Slightly elevated risk of astrocytoma for all four classes of pesticides (OR 1.4-1.6); for mothers elevated risk with insecticides (OR 1.9, CI 1.1–3.3), herbicides (OR 1.3, CI 0.5–3.7), and nonagricultural fungicides (OR 1.6, CI 0.9–2.7).	5,5
Ecological Studies						
Viel 1998	Ecological study; included the total population of certain areas of France (close to 600 000); male farmers and	Mixed pesticide exposure; assessed through the Pesticide Exposure Index that assesses farmers exposure at a geographical level by using agricultural	Age, income	SMR, RR, Poisson	Mortality from brain cancer among farmers was significantly higher then mortality for the overall pop	5,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	farm laborers aged 35–74.	and national census data.			(SMR 1.25, p<0.01); significantly link between pesticide exposure in vineyards (RR 1.1, CI 1.03–1.18)	

Table 2: Breast Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Dolapsakis 2001	Cohort study of 1062 women in Crete who had a mammogram for the first time between 1988-1993; all women re-evaluated every 1 or 2 yrs until 1998; 2 groups - exposed (522) who had at least 10 yrs work in greenhouses, and non-exposed (540), who had non-agricultural occupations.	Mixed occupational exposure, but pesticides associated with agriculture (mainly organophosphates and organocarbamates); exposed women had worked for 10 yrs or more on a farm for at least 4 hrs/day.	age, family history of breast cancer, age at menopause and menarche, parity, contraceptive and estrogen use.	detection rates expressed as proportions, chi square; some RR's	Exposed women had a significantly higher risk ($p<0.05$) than non-exposed for fibroadenoma (RR 4.86, CI 1.4–16.7), ductal hyperplasia (RR 1.87, CI 1.1–3.13), sclerotic adenosis (RR 1.88, CI 1.1–3.1), fibrohyperplastic disease (RR 1.85, CI 1.3–2.6), cystic disease (RR 1.44, CI 1.1–2.0) and inflammatory mastitis (RR 2.21, CI 1.2–4.0) in mammographic findings. There were no significant differences in malignant changes.	5,5
Case-Control Studies						
Band 2000	Case control study of 1018 women with incident breast cancer compared to 1020 population controls in BC; all under the age of 75 yrs and dx between 1988–1989.	Mixed pesticide exposure assessed through qestionnaires about occupation; jobs coded and classified according to exposure; 'ever'/'never' categories for being in a given occupation.	smoking, alcohol consumption, ethnicity, marital status, education, age at menarche, age at menopause, family history of breast cancer, BMI, use of birth control pills, HRT, reproductive history, breast feeding, history of breast biopsy	OR, logistic regression	Increased risk of breast cancer for pre-and post-menopausal group combined for occupation with fruit and other vegetable farms (OR 3.11, CI 1.24-7.81); fruit farms only (OR 2.94, CI 0.90-9.60), and other vegetable farms (OR 7.33, CI 1.16-46.2).	5,4
Duell 2000	Case control study in North Carolina; 862 cases with breast cancer diagnosed	Pesticides classified as insecticides, herbicides, and fungicides;	age at dx, age at menarche, parity, age at first birth, smoking	OR, unconditional logistic regression	Increasing duration of farming was inversely associated with breast cancer risk; Also	5,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	between 1993–1996; 790 controls	exposure assessed through a questionnaire administered within 4 months of diagnosis; detailed questions on farm-specific exposures; categorized as never, 1–16 yrs, or >16 yrs exposed.	history, alcohol, education, history of lactation, oral contraceptive use, family history of breast cancer, BMI, duration of washing laundry for pesticide users, benign breast biopsy, HRT, menopausal status.		increased risk associated with being present in fields during or shortly after pesticide application (OR 1.8, CI 1.1–2.8) and for those reported not using protective clothing while applying pestcides (OR 2.0, CI 1.0–4.3)	
Ecological Studies						
Abdalla 2003	Ecological study; used breast cancer mortality data from the National Cancer Institute website and looked at the entire population of Mississippi; considered mortality in different regions of the state which have different pesticide use rates.	Mixed pesticide exposure; Proxy for pesticide exposure - total # of acres planted during 1997-2000 for each Statistical Economic Area and by type of crop.	Age, race	SMR, Spearman correlation coefficient	In some areas of heavy pesticide use the rate of breast cancer was elevated; strongest correlation between white women and rice crops planted in one region (ρ=0.674, p<0.03).	4,4
Hopenhayn-Rich 2002	Ecological study; used the Kentucky cancer registry for information about breast cancer incidence and compared to exposure indices to atrazine; included population of Kentucky (3 mill)	Atrazine; exposure index developed based on public water measurements, acres of corn planted, and pounds of atrazine sold.	age, county, race, education, degree of urbanisation, ses, use of public water	RR, Poisson	The breast cancer effect estimates indicate a null association with increasing exposure to atrazine.	5,6
Kettles 1997	Ecological study; used the Kentucky cancer registry for information about breast cancer incidence and compared to exposure indices for triazine	Triazine herbicides; exposure index developed based on water contamination data, corn crop production, and	age, race, age at first live birth, income, level of education, county	OR, Poisson	An increase in breast cancer risk with medium and high levels of triazine exposure (OR 1.14, p<0.0001 and OR 1.2, p<0.0001); for low exposure OR	5,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	herbicides; included population of Kenucky.	pesticide use data (from a 1979 survey); countied then classified into low, medium, or high exposure levels.			1.0.	

Table 3 Kidney Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Fear 1998	Retrospective cohort; 167, 703 childhood deaths in Wales and England during 1959-1963, 1970-1978, and 1979-1990; looked at cause of mortality for these children.	Agricultural and/or horticultural pesticides; exposure to these determined by paternal occupation as a farmer, agricultural workers, agricultural machine driver, gardener, and forester; exposure assumed if father had one of these jobs.	age, year of death, paternal social class	PMR, Poisson	There was a statistically significant increase in death from kidney cancer in those children with paternal occupational exposure to pesticides (PMR 1.59, CI 1.18–2.15)	4,4
Ramlow 1996	Retrospective cohort study of 770 employees of the Dow Chemical Company in Michigan.	Exposure to PCP assessed by job description, wipe samples, area exposure monitoring, personal breathing zone data, duration of exposure - this gave a cumulative exposure category between 1-3; exposure assessed for the period 1940–1989.	age, period of employment, general employment status (hourly vs salaried)	SMR, Mantel-Hanzel	There were no elevated levels of any cancer that was significant; when cumulative exposure was considered, kidney cancer was significantly elevated (SMR 502, CI 101–1468)	4,4
Case-Control Studies						
Buzio 2002	Case control study in Italy; 100 renal cell cancer cases and 200 controls.	Mixed pesticide exposure assessed by an interview; subjects asked questions about occupation and then an industrial hygenists coded according to level of exposure: labelled short or	age, smoking habits, gender, use of drugs, BMI, use of well water	OR, logistic multiple regression	Renal cell cancer was increased with prolonged pesticide exposure (OR 2.0, CI 0.8–4.7); for short exposure (OR 1.1, CI 0.2–5.9); these were the only ORs for pesticides provided.	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
		long exposure (greater or less than 10 yrs).				
Hu 2002	Case control study in eight Canadian provinces; 1279 cases included subjects with kidney cancer from provincial cancer registries; 5370 population controls.	Mixed pesticide exposure; assessed by a questionnaire; detailed questions about occupation and exposure to benzene, herbicides, pesticides, and other variables.	age, sex, province, ses, smoking habits, diet, BMI, physical activity, use of vitamins, alcohol	OR, logistic regression	Exposure to pesticides associated with increased risk of kidney cancer (OR 1.8, CI 1.4–2.3); higher OR if males exposed to herbicides in a dose response relationship (greater than 16 yrs exposure OR 2.0, CI 1.4–2.7); for women (OR 1.3, CI 0.9–1.8).	5,5
Mellemgaard 1994	Case control study in Denmark; 365 cases identified by cancer registry, between the ages of 20-79, born and living in Denmark; 396 controls	Insecticides and herbicides; exposure assessed with interviews w/questions about occupation and exposure; occ coded based on exposure, but occupation must have lasted at least one yr, and occurred at least 10 yrs prior to interview.	gender, age, smoking habits, BMI, ses	OR, logistic regression	Increased risk for RCC in men with over 20 yrs exposure to insecticides and herbicides (OR 3.9, CI 1.0–15); less than 20 yrs (OR 1.3, CI 0.4–4.1).	4,4
Sharpe 1995	Case control study in Brazil; 109 cases and 218 controls; hospital-based, multicentre; looked specifically at Wilms' tumour.	Mixed pesticide exposure assessed by questions about parents occupation, and agriculture practices of family; interview; for relevant occupations must have been employed at least 6 mos.	income, parental education, age, sex	OR, conditional logistic regression	Consistently elevated risks were seen for farm work involving frequent use of pesticides by both the father (OR 3.24, CI 1.2–9.0) and the mother (OR 128.6, CI 6.4–2569).	4, 4

Table 4 Lung Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Figa-Talamanca 1993	Retrospective cohort study of a group of 2310 male farm workers (over age 15 yrs) who were licensed to handle pesticides in Italy; included those issued pesticides licenses between 1973–1979.	Mixed pesticide exposure; mostly assessed through license information – a small group filled out a questionnaire (but did not have information on quantity or type of pesticide – just use or not).	age	SMR, Poisson	The cohort experienced statistically significant lower mortality for lung cancer (SMR 57, CI 35.6–80.0); this was confirmed in the two age groups considered where the SMR for ages 15–64 was 32 and that for ages 65 and over was 89.	4,4
Kross 1996	Retrospective cohort study of a group of 686 deceased white male members of the Golf Superintendents Association of America; compared to white male US population; included subjects from across the US	Mixed pesticide exposure; could not provide specific exposure information as data source was death certificates; exposure assumed through membership in association.	None	PMR	The cohort experienced higher mortality for all cancers (PMR 136, CI 121, 152), PMR lung cancer 117 (CI 93, 148), PMR brain 234 (CI 121, 454), PMR NHL 237 (CI 137, 410), PMR prostate 293 (CI 187, 460).	4,4
Case-Control Studies						
Brownson 1993	Case-control study to determine occupational risk factors for lung cancer and women; Missouri; 429 cases (294 nonsmokers, 135 ex-smokers), 1021 controls; 1986-1991; actually part of a larger study with a different study question.	Mixed pesticide exposure; assessed through a questionnaire and personal interview regarding questions about occupational exposure.	smoking habits, age, diet, history of previous lung disease	OR, logistic regression	Increased risk of lung cancer in exposed group for all subjects (OR 2.4, CI 1.1–5.6) and lifetime nonsmokers (OR 3.1, CI 1.3–7.5); the risk at 17.5 years or less was an OR of 1.5 (CI 0.4–6.5) and for more than 17.5 years OR 2.4 (CI 0.8–7.0).	5,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Pesatori 1994	Nested case control study (retrospective) from cohort of 4411 individuals from 1965-66 licensing applications submitted by pest control firms in Florida; 65 lung cancer cases, 122 deceased controls, 172 living controls; pest control workers.	Mixed pesticide exposure questionnaire with questions about occupation, work practices, and specific chemicals used; completed by next-of-kin as cases were deceased.	age, smoking, diet, other occupations	OR, logistic regression	Statististically significant increased risk of lung cancer for use of carbamates (OR 16.3, CI 2.2-122.5) when cases compared to dead controls, phenoxyacetic acids (OR 22.4, CI 1.8–122.5) when compared to living controls; overall range of OR's between 0.5–22.4.	4,4

Table 5 Ovarian Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Ecological Studies						
Hopenhayn-Rich 2002	Ecological study; used the Kentucky cancer registry for information about ovarian cancer incidence and compared to exposure indices to atrazine; included population of Kentucky (3 mill)	Atrazine; exposure index developed based on public water measurements, acres of corn planted, and pounds of atrazine sold.	Age, county, race, education, degree of urbanization, ses, use of public water	RR, Poisson	For ovarian cancer, the data suggests an inverse association with increasing exposure linked to decreasing incidence rates.	5,6

Table 6 Pancreatic Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Cantor 1999	Retrospective cohort study to compare the causes of death of aerial pesticide applicators and flight instructors; 9961 pesticide applicators and 9969 control flight instructors; US; all men	Mixed pesticide exposure; an index for exposure was estimated based on the number of flight hours.	age	RR, SMR, chi-square	Rates of pancreatic cancer were elevated in the applicator group compared to the instructor group (RR 2.71, CI 1.4–5.3); other RR's were all for other cancers and causes of mortality	5,5
Case-Control Studies						
Alguacil 2000	Case control study for cases of pancreatic cancer diagnosed in one of 5 hospitals in Spain; 164 cases and 238 controls (controls from hospitals, diagnosed with other cancers, and people with suspect pancreatic cancer).	Mixed pesticide exposure; assessed through a series of interviews with detailed questions about occupation, and specific activities related to pesticide exposure; industrial hygienist evaluated these exposure and coded them as high, low, unknown, or none.	age, gender, hospital, smoking, alcohol use, schooling, coffee, diabetes	OR, unconditional logistic regression	Increased risk of pancreatic cancer in the high intensity category for arsenical pesticides (OR 3.4, CI 0.9–12.0) and 'other pesticides' (OR 3.17, CI 1.1–9.2); other OR's ranged between 1 and 3.57).	5,4
Ji 2001	Case control study; 484 cases aged 30-79 yrs, dx b/t 1986-1989; 2095 population controls; Atlanta, Detroit, New Jersey	Insecticides, fungicides, and herbicides; exposure assessed through an interview; job exposure matrix then used to assign a level of exposure by an industrial hygienist (0–3 scale – none, low, mod/high)	age, race, gender	OR, unconditional logistic regression	Excess risks for pancreatic cancer for occupational exposure to fungicides (OR 1.5, CI 0.3–7.6) and herbicides (OR 1.6, CI 0.7–3.4); an increased risk for insecticide exposure disappeared after adjustment for fungicide and herbicide exposure.	5,4

Table 7 Prostate Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Alavanja 2003	Prospective cohort study of 55, 332 male pesticide applicators; commercial and farmer applicators in Iowa, and private applicators in North Carolina; those with a previous history of prostate cancer were excluded; recruited from a pesticide certification testing session.	45 common agricultural pesticides; questionnaire at enrollment; some pesticides asked 'ever'/'never' use, others asked for more detailed info about duration of use and frequency; info also collected about protective equip use, occurrence of spills, application method.	age, race, state of residence, license type, education, smoking, alcohol use, red meat consumption, vitamin use, fruit and veg intake, BMI, family history of prostate cancer,	SIR, unconditional logistic regression analysis	Increase in prostate cancer in participants compared to the rest of the population (SIR 1.14, CI 1.05–1.24), increase in prostate cancer linearly with the use of methyl bromide (up to OR 3.47, p<0.004); increase in prostate cancer in those with a family history of prostate cancer with use of several insecticides and butylate (OR 2.58).	7,7
Dich 1998	Retrospective cohort study of male pesticide applicators in Sweden (20,025)	Exposure assessment was only done on a subsample of the group (n=268); 92% of them had been exposed for at least one day.	age	SIR by year of birth	Elevated risk of prostate cancer, higher in younger applicators (SIR 1.13 all age groups, SIR 2.03 for younger pesticide applicators)	4,4
Fleming 1999	Retrospective cohort study of licensed pesticide applicators in Florida; 33, 658 members; 1975-1993; compared to general pop of Florida; mainly men in the cohort, but some women.	Mixed pesticide exposure assessed by pesticide license info; number of yrs of licensure is a proxy for the length of pesticide exposure.	age, calendar time	SIR, Breslow and Day	Among males, prostate cancer and testicular cancer were significantly elevated (SIR 1.91, CI 1.72–2.13 and SIR 2.48, CI 1.57–3.72); this incidence had an SIR 1.98 (CI 1.75–2.24) in 1975-1979, SIR 1.86 (CI 1.44–2.38) in 1980-1984, SIR 1.79 (CI 1.20–2.57) in 1985-1989, and SIR 0.71 (CI 0.14–2.07) in 1990–1994.	6,5
Kross 1996	Retrospective cohort study of a group of 686 deceased white male members of the Golf Superintendents Association of America; compared to white male US population; included	Mixed pesticide exposure; could not provide specific exposure information as data source was death certificates; exposure assumed through	None	PMR	The cohort experienced higher mortality for all cancers (PMR 136, CI 121, 152), PMR lung cancer 117 (CI 93, 148), PMR brain 234 (CI 121, 454), PMR NHL 237 (CI 137, 410), PMR prostate 293 (CI 187,	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	subjects from across the US	membership in association.			460).	
MacLennan 2002	Retrospective cohort of 2045 subjects who worked at a plant in Louisiana that made pesticides; subjects had to have worked there for at least 6 mos by the end of 1992, had worked in jobs involving potential contact with triazines or precursor chemicals.	Triazine herbicides; proxy exposure according to area of the plant employed and work history, job description; assessed from work records.	age, race, gender, years worked, years since hire, employee group	SIR, Poisson	There was an increased incidence of prostate cancer in this group: SIR 175 (CI 83–312) in all types of employees, SIR 394 (CI 128–920) in actively working employees, SIR 119 (CI 44–260) in inactively working or contract employees.	5,5
Case-Control Studies						
Mills 2003	Nested case control study within a cohort of predominantly Hispanic labor union in California - United Farm Workers of America; 222 cases and 1110 controls	Several pesticide exposures evaluated; assessed by using California's pesticide use reporting system - proxy measurement based on total number of pounds of pesticide active ingredient applied in a given county in a given year.	age, home use of pesticides and other toxins, lifestyle factors such as smoking	OR, Mantel-Hanzel, conditional logistic regression	Prostate cancer risk increased with exposure to several chemicals: dichlorvos, early dx OR 1.2, late dx OR 1.56; heptochlor, early dx OR 1.33, late dx OR 1.4, lindane, early dx OR 1.04, late dx OR 1.85, simazine, early dx OR 1.2, late dx OR 2.16	4,4
Settimi 2003	Case control study in Italy of men with cancer b/t ages 20-75; 124 cases and 659 controls (individ with other type of cancer).	Several pesticide exposures evaluated by a questionnaire; also included 10 crop-specific forms; assigned an exposure of probably exposed or not exposed.	age, family history of prostate cancer, smoking, education, interview (direct vs indirect)	OR, unconditional logistic regression	Increased risks among farmers exposed to organochlorine insecticides and acaricides (OR 2.5, CI 1.4-4.2).	5,5
Ecological Studies						
Sharma-Wagner 2000	Ecological study; in Sweden; linked 36,269 prostate cancer cases with employment info from the National Census (1961-1979).	National census database provided info about occupation which was used as a proxy measurement for exposure.	age, occupation	SIR, Poisson	Certain occupations have increased rates of pc, including those with pesticide exposure.	4,4

Table 8 Stomach Cancer

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Ecological Studies						
Van Leeuwen 1999	Ecological study; age standardized cancer incidence ratios for 1987–1991 from the Ontario Cancer Registry; compared with levels of contamination of drinking water and related agricultural practices; 40 ecodistricts in Ontario.	Atrazine and nitrate were measured from the drinking and ground water; Ontario Landscape Resource Unit provided information about pesticide use.	alcohol consumption, smoking, education level, income, occupational exposures, age, sex	least squares regression analysis	Atrazine contamination levels were positively associated with stomach cancer incidence ($p<0.05$), and nitrate was negatively associated with stomach cancer incidence; no other values provided.	5,5

Chapter 4 — Non-Hodgkin's Lymphoma

In contrast to leukemia, which is declining, the incidence of non-Hodgkin's lymphoma (NHL) continues to rise in Canada at the rate of 1–1.5% per year. The disease has an age-standardized incidence of 19.3/100,000 per year, and for Canadians the lifelong probability of getting any form of lymphoma is 2.5% for women and 2.9% for men.

Thirty-two papers on NHL were included in the assessment process and 27 met the quality criteria for inclusion. The study designs were as follows:

- Cohort studies: 11 (9 positive association, 3 with statistical significance, 2 negative)
- Case-control studies: 14 (12 positive association, 8 with statistical significance, 2 negative)
- Ecological: 2 (2 positive association).

Five studies were excluded on quality criteria (4 positive association, 1 with statistical significance, 1 negative). The remaining 27 studies were given 4 or 5 out of 7 by both readers, with only 2 studies receiving 6, both positive studies (24, 32).

Cohort Studies

There were 12 cohort studies. Asp et al. (10) did not find an increase in NHL incidence in a group of Finnish chlorphenoxy herbicide applicators, however the low number of deaths (384 in total) did not allow any conclusions to be drawn. Becher et al. (11) found an SMR of 326 (CI 119–710) for NHL in a group of workers in phenoxy herbicide plants in Germany, the excess occurring in the groups with higher exposure to dioxins and other contaminants of phenoxy acids (including pesticides now banned in Canada, such as 2,4,5-T). Hansen et al. (12) found an SMR of 200 (CI 86–393), though not statistically significant, in a cohort of Danish gardeners. Hooiveld et al. (13) found an RR of 1.7 (CI 0.2–16.5) with RR increasing parallel to serum levels of TCDD (a dioxin contaminant of phenoxy herbicides) indicating an exposure-related risk. However the main product of the factory was 2,4,5-T, which is banned in Canada, though the dioxin contaminant, TCDD, occurred previously in 2,4-D production. Kross et al. (14) looked at golf course superintendents, a group who experiences increased exposure to a number of environmental hazards such as pesticides, fertilizers, and diesel fumes. The PMR for NHL was 237 (CI 137–410) though the total number of NHL deaths was only 12.

Lynge et al. (15) did not find an elevated risk of NHL among a group of Danish phenoxy herbicide factory workers exposed to the herbicide MCPA. MacLennan et al. (16) found an SMR of 372 (101–952) for NHL among workers at a triazine herbicide factory. The authors, however, conclude that the almost fourfold increase was likely not due to triazine exposure, because the increase was not concentrated in the subgroup who had been long-term employees of the factory. Morrison et al. (17) conducted a large study of 155,000 farmers in Canada and found a statistically significant increase in NHL (RR 2.11, CI 1.1–3.9), the risk increasing with the number of acres sprayed. Sathiakumar et al. (18) found an SMR of 385 (CI 79–1134) for NHL and triazine exposure though the numbers were small (only 3 NHL deaths with 1.78 expected). The study group was young (only 13% were over 45 years old) and had been employed a relatively short time. Sperati et al. (19) looked at the mortality of pesticide users and their wives and found a not statistically significant increase in NHL among the female (SMR 2.29, CI 0.62–5.86) but not among the male pesticide users. The small numbers and poor exposure history, however, make it difficult to interpret this result. Thorn et al. (20) did not find elevated rates of NHL among Swedish lumberjacks exposed to phenoxy herbicides. Zahm (21) found a slight

excess of NHL (SMR 1.14, CI 0.31–2.91) among employees of a lawn-care company. However, the cohort was young, with short-duration employment (with more than half having been employed less than 6 months) and a short follow-up period (averaging 7.8 years), making conclusions difficult to draw, as lag time between exposure and illness can be decades.

Case-Control studies

There were 14 case-control studies. The pooled data study of Blair et al. (22) found an OR of 1.5 (CI 1.1–2.0) for farmers who had ever used lindane, though this was reduced by adjusting for exposure to other pesticides and was greater among proxy respondents. Buckley et al. (23) found elevated ORs in children from homes where pesticides were used a majority of days (OR 7.3, $p < 0.05$), for professional home exterminations (OR 3.0, $p = 0.002$), and for postnatal exposure (OR 2.4, $p = 0.001$). There was an elevated but not significant OR (1.74) for parental occupational exposure. Cantor et al. (24), one of the studies that received a rating of 6, showed a slightly increased OR (1.2, CI 1.0–1.5) of NHL in farmers in Iowa and Minnesota. The study by Costantini et al. (26) did show excess small-cell lymphoma (a subtype of NHL) in male agricultural workers, OR 1.4 (1.0–1.9). However such a study which groups occupations in categories may be less reliable, as the "agricultural worker" category may be too crude to enable assessment of pesticide exposure.

Hardell et al. (27, 28) reported on two case-control studies. The first (27) found elevated risks in males over 25 years old for exposure to herbicides (OR 1.6, CI 1.0–25), fungicides (OR 3.7, CI 1.1–132.0), and, specifically, phenoxy acids (OR 1.5, CI 0.9–2.4). The more recent study (28) described two case-control studies, one on NHL alone and one specifically on hairy-cell leukemia, a rare form of NHL, with respect to pesticide exposure (with many different pesticides and exposure levels tested). A pooled analysis (done in order to increase numbers) revealed elevated ORs with statistical significance for herbicides in general, phenoxyacetic acids, glyphosate, and MCPA. Also there were dose–response effects in these pesticide groups, most with statistical significance.

The study by Clavel et al. (25) showed an OR of 7.5 (CI 0.9–61.5) for hairy-cell leukemia in farmers exposed to organophosphate insecticides. Lack of quantitative data for 50% of the farmers prevented testing for a dose–response relationship.

Hoar et al. (29) pooled data from three case-control studies and concluded that there is little evidence to suggest a causal role of atrazine in the development of NHL. Kogevinas et al. (30) did not reveal an elevated NHL risk in connection with several phenoxy herbicides, though small excesses were found with some herbicides not used in Canada and with TCDD, a contaminant. MacDuffie et al. (31) showed elevated ORs (adjusting for many variables) for NHL with exposure to fungicides, organophosphate and carbamate insecticides, and dicamba herbicides, but without statistical significance. Specifics of pesticide exposure history were not discussed. MacDuffie et al. (32) found increased ORs for NHL with exposure to decamba, mecoprop, and aldrin (1.96, 2.22, and 3.42, respectively). This was a well-designed study that received a rating of 6, which began by assessing risks of exposure first to major classes of pesticides and then by individual compounds within those classes; the study stratified by days per year of exposure, and included many potential confounders.

Persson et al. (33) found an OR of 2.3 (CI 0.7–7.2) for NHL with occupational exposure to phenoxy herbicides, though the exposure was not quantified. Waddell et al. (34) was a pooled data study that showed a statistically significant 50% increase in NHL with exposure to

organophosphate insecticides; however, proxy respondents indicated a much higher risk (OR 3.0) than did direct interviews (OR 1.2), making interpretation difficult.

Zheng et al. (35) found elevated ORs for NHL with carbaryl exposure, which persisted after adjusting for other major classes of pesticide, some with statistical significance.

Ecological Studies

The two ecological studies were both positive. Fontana et al. (36) found higher rates of NHL in rice-growing areas of Italy where concentrations of 2,4-D (common in Canada) and 2,4,5-T (banned in Canada) were high in soil and water. In men, NHL rates were increased 50–60% in the most polluted areas. A nested case-control study showed elevated risk of NHL for women in rice-growing jobs (OR 1.9, CI 0.6–6.0). The other ecological study by Schreinemachers et al. (37) found higher rates of NHL for women (SRR 1.35, CI 1.09–1.66) in agricultural regions of Minnesota.

Excluded Studies

Five studies were excluded. The study by Zahm et al. (42) was one of the few studies on women and pesticides and it found a statistically significant 4–5-fold increase in NHL with the handling of organophosphates. However, it sampled only a very small number of women who handled pesticides, so the study was excluded.

Two studies (39, 41) were excluded on the basis of poor methodology (small sample size, few confounders measured, and poor exposure histories), and though their findings were positive, they were not statistically significant. Burns et al. (40) and Bloeman et al. (38) showed a not statistically significant increase in NHL. Both were excluded for methodological reasons; moreover, Dow Chemical funded both studies.

Summary

The etiology of NHL is considered to combine immunological and environmental factors. Predisposing immunodefective conditions, such as immunosuppressive medication after organ transplantation and HIV infection, are known risk factors, and viral infections such as EBV have also been implicated. Previous studies have pointed to certain pesticides, such as 2,4-D, as possible precipitants of NHL, and the findings of this review are clearly consistent with this. Out of 27 studies, 23 show associations between pesticide exposure and NHL, many with statistical significance. Exposure misclassification, a perpetual problem with cohort studies, tends to skew results towards the null, so in fact the associations in these studies may be underestimated. This review uncovered compelling evidence of the link between pesticide exposure and the development of NHL. This warrants further investigation, particularly in the area of cytogenetics, and also political action to address this public health issue. In addition, the public should try to minimize occupational and environmental exposure to pesticides. Ways to do this would include: avoiding use at home, on pets, and in the garden; avoiding—if possible—exposure via purchased food; and wearing protective gear if pesticide use is deemed necessary.

Chapter 4 — Non-Hodgkin's Lymphoma

References

Review Studies:

1. Acquavella J, Olsen G , Cole P, Ireland B, Kaneene J, Schuman S, Holden L. Cancer among farmers: a meta-analysis. *Ann Epidemiol* 1998;8:64–74.
2. Baldi I, Mohammed-Brahim B, Brochard P, Dartigues JF, Salamon R. Delayed health effects of pesticides: review of current epidemiological knowledge. *Rev Epidemiol Sante Publique* 1998;46:134–142.
3. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. *Environ Health Perspect* 1997;105:1068–1077.
4. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer. *Cancer Causes Control* 1997;8:420–443.
5. Ferris TJ, Garcia CJ, Berbel TO, Clar GS [Risk factors for non-Hodgkin's lymphomas] [Review] [Spanish]. *An Pediatr (Barc)* 2001;55:230–238.
6. Maroni M, Fait A. Health effects in man from long-term exposure to pesticides. A review of the 1975–1991 literature. *Toxicology* 1993;78:1–180.
7. Sathiakumar N, Delzell E. A review of epidemiologic studies of triazine herbicides and cancer. *Crit Rev Toxicol* 1997;27:599–612.
8. Zahm SH, Blair A. Cancer among migrant and seasonal farmworkers: an epidemiologic review and research agenda. *Am J Ind Med* 1993 Dec;24(6):753–766.
9. Zahm SH, Ward MH. Pesticides and childhood cancer. *Environ Health Perspec* 1998;106 Suppl 3:893–908.

Cohort Studies:

10. Asp S, Riihimaki 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;26:243–253.
11. Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, Wahrendorf J. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins [comment]. *Cancer Causes Control* 1996;7:312–321.
12. Hansen ES, Hasle H, Lander F. A cohort study on cancer incidence among Danish gardeners. *Am J Ind Med* 1992;21:651–660.
13. Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG, Jr., Bueno-de-Mesquita HB. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am J Epidemiol* 1998;147:891–901.
14. Kross B , Burmeister L , Ogilvie L , Fuortes L , Fu C. Proportionate mortality study of golf course superintendents. *Am J Ind Med* 1996;29:501-506
15. Lynge E. Cancer incidence in Danish phenoxy herbicide workers, 1947–1993. *Environ Health Perspec* 1998;106:Suppl-8.

16. MacLennan PA, Delzell E, Sathiakumar N, Myers SL. Mortality among triazine herbicide manufacturing workers. *Journal of Toxicology and Environmental Health, Part A* 2003;66:501–517.

17. 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;20:42–47.

18. Sathiakumar N, Delzell E, Cole P. Mortality among workers at two triazine herbicide manufacturing plants. *Am J Ind Med* 1996;29:143–151.

19. Sperati A, Rapiti E, Settimi L, Quercia A, Terenzoni B, Forastiere F. Mortality among male licensed pesticide users and their wives. *Am J Ind Med* 1999;36:142–146.

20. 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;57:718–720.

21. Zahm SH. Mortality study of pesticide applicators and other employees of a lawn care service company. *J Occup Environ Med* 1997;39:1055–1067.

Case-Control Studies:

22. Blair A, Cantor KP, Zahm SH. Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. *Am J Ind Med* 1998;33:82–87.

23. Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer* 2000;89:2315–2321.

24. Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM., Schuman L, Dick FR. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota [comment]. *Cancer Res* 1992;52:2447–2455.

25. 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;22:285–293.

26. Costantini AS, Miligi L, Kriebel D, Ramazzotti V, Rodella S, Scarpi E, Stagnaro E, Tumino R, Fontana A, Masala G, Vigano C, Vindigni C, Crosignani P, Benvenuti A, Vineis P. A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. *Epidemiology* 2001;12:78–87.

27. Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides [comment]. *Cancer* 1999;85:1353–1360.

28. 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;43:1043–1049.

29. 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;19:108–114.

30. Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno-de-Mesquita HB, Coggon D, Green L, Johnson E, Littorin M. 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.

31. McDuffie HH, Pahwa P, Spinelli JJ, McLaughlin JR, Fincham S, Robson D, Dosman JA, Hu J. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). *Am J Ind Med* 2002. Suppl:2–61.
32. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001;10:1155–1163.
33. Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. *Cancer* 1993;72:1773–1778.
34. Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, Cantor KP, Blair A. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes Control* 2001;12:509–517
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;43:641–649.

Ecological Studies:

36. 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;53:384–387.
37. Schreinemachers DM, Creason JP, Garry VF. Cancer mortality in agricultural regions of Minnesota. *Environ Health Perspec* 1999;107:205–211.

Excluded Studies:

38. 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 [comment]. *Journal of Occupational Medicine* 1993;35:1208–1212.
39. 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.
40. Burns CJ, Beard KK, & Cartmill JB. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945–1994: an update [comment]. *Occup Environ Med* 2001;58:24–30.
41. Viel, J.F. & Richardson, S.T. Lymphoma, multiple myeloma and leukemia among French farmers in relation to pesticide exposure. *Soc Sci Med* 1993;37:771–777.
42. 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;48:353–358.

Chapter 4 — Non-Hodgkin's Lymphoma

Table

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Asp 1994	Cohort study; employers from 4 chemical brushwood control companies in Finland; selected by convenience sampling; n=1909	Chlorophenoxy herbicides; exposure measured by self-report /questionnaire	Smoking habits	SMR, SIR, Poisson; follow-up complete	The overall cancer mortality was slightly less than the general population (SMR 0.83, 95% CI 0.75–0.94); no deaths due to NHL, although one case of NHL found.	4,4
Becher 1996	Cohort study; 2479 workers at one of four herbicide factories in Germany; selected by convenience sampling.	Phenoxy herbicides; exposure measured by records (a registry of workers exposed to phenoxy herbicides).	Smoking history (for some cohorts)	SMR, Cox regression; follow-up was not complete	There was an increase in risk of NHL associated with exposure to phenoxy herbicides (SMR 326, 95% CI 119–710) overall, SMR 0 for 0–10 yrs after exposure, SMR 364 (CI 44–1314) for 10–20 years after exposure, SMR 425 (CI 115–1088) or exposure over 20 years prior.	5,5
Hansen 1992	Cohort study; members of a trade union of gardeners in Denmark; selected by convenience sampling; n=4015 followed from 1975–1984 with regards to cancer incidence.	Combination; exposure measured by records.	None	SMR, Poisson; follow-up was complete	There was a small increase in NHL in gardeners (SMR 200, 95% CI 86–393); for male gardeners the SMR was 173 (CI 63–376 and females 364 (CI 44–1314).	4,4
Hooiveld 1998	Retrospective cohort, all people employed in a chemical factory in the Netherlands b/t 1955–1985 (many were exposed to an accident there in 1963); followed them to look for causes of death; 562 exposed, 567 non-exposed, 27 unknown.	Phenoxy herbicides; occupational exposure assessed by questionnaire (unclear if subject completed or company).	Age, calendar period, time since first employment (exposure)	SMR, Poisson	Increased risk of NHL (RR 1.7, CI 0.2–16.5); SMR 3.8 (CI 0.8–11.0); SMR for those exposed as a result of the accident 3.9 (CI 0.1–21.8)	4,4
Kross 1996	Retrospective cohort of white male golf course superintendents, members of a professional association, died between 1970 and	No exposure histories, no comment on specific pesticides, but high use of insecticides, fungicides and	No covariates	PMR, compared to white males in the U.S. population, CI	PMR 237 (CI 137–410)	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	1992, total of 203 cancer deaths.	herbicides with large differences in volume depending on region		calculated by method of Jensen et al (1991)		
Lynge 1998	Retrospective cohort; workers from 2 factories in Denmark; followed 2119 individuals.	Phenoxy herbicides; exposure measurements based on pesticide production; workers assessed according to their work area noted in personnel files.	None mentioned	SIR, Poisson	No risk indicated of NHL (SIR 1.1, CI 0.4–2.6).	4,4
MacLennan 2003	Retrospective cohort, followed workers from a pesticide plant (worked there for at least 6 most); 2213 followed for cause of mortality.	Triazine herbicides; proxy exposure according to area of the plant employed and work history, job description.	Age	SMR, Poisson	There were elevated levels of NHL (SMR 372, CI 101–952); for white men the SMR was 257 (CI 31–927) and non-white men 832 (CI 101–3007).	4,4
Morrison 1994	Retrospective cohort of male farm operators in Saskatchewan, Alberta, Manitoba in 1971; 155,547 farmers followed for cause of death.	Herbicides; exposure assessed by number of acres sprayed with herb from Census of Agriculture; farmers for farms of less than 1000 acres included.	Age, calendar yr period, number of acres sprayed	RR, Poisson	Increased risk of NHL with increased spraying (RR 2.11, CI 1.1–3.91); OR's ranged between 0.9–2.96 according to level of spraying for different western provinces.	4,5
Sathiakumar 1996	Retrospective cohort of workers from herbicide manufacturing plants in Alabama, followed 4917 men – worked at least 1 month b/t 1951–1986 in jobs related to chemical production and formulation.	Triazine herbicides; proxy exposure from work records – are worked, job description, classified as definite, probable, or possible contact with triazines; person-yrs accumulation.	None really – race?	SMR, Poisson	Exposed group had increased deaths from definite or probable NHL (SMR 385, CI 79–1124); for possible NHL SMR 1.0, total NHL SMR 279 (CI 91–652).	4,4
Sperati 1999	Retrospective cohort of male farmers and their wives in Italy; these farmers were licensed for buying and handling pesticides b/t	Mixed pesticides; exposure assessment method unclear; appears to be from some record of pesticide	Age, gender, calendar period	SMR, Poisson	NHL increased among women (SMR 2.29, CI 0.62–5.86), but not male farmers (SMR 0.90, CI 0.24–2.30).	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	1971–1973; followed for causes of mortality; 2978 men and 2586 wives.	license only – traced from this point until death.				
Thorn 2000	Retrospective cohort of Swedish lumberjacks; employees of forestry company b/t 1954–1967; excluded if exposed to pest other than phenoxy acids and DDT; 261 exposed and 250 unexposed.	Phenoxy acids; considered exposed if worked for 5 or more days (payslips, work records); notes about work types – 'pocketing' vs. 'spraying'; workers.	Age, calendar time, sex, county	SMR, SIR, Poisson	Three cases of NHL found – 2 were among the exposed workers (SIR 235, CI 29–850); SIR for male lumberjacks 192 (CI 3–1070), female lumberjacks 303 (CI 4–1686), and unexposed lumberjacks 81 (CI 1–452).	4,4
Zahm 1997	Retrospective cohort of employees of a lawn care company (n=32, 600); looked at mortality cause.	Herbicide, 2,4-D; exposure determined from work records; number of year worked and type of work done.	Gender, age, race, calendar time	SMR, Liddell method	There were four deaths due to NHL (SMR 1.14, CI 0.31–2.91) for all employees; SMR for men only 1.46, CI 0.29–4.27).	5,5
Case-Control Studies						
Blair 1998	Case-control; men in Iowa, Kansas, Nebraska, and Minnesota; selected by convenience sampling; 986 cases and 2895 population controls.	Lindane (insecticide); exposure measured by self-reports and questionnaires.	Age, marital status, smoking history, state of residence, use of private wells, hair dye use	Logistic regression, OR	The use of lindane is associated with an increase in NHL (OR 1.5, 95% CI 1.1–2.0) overall; OR's for lindane use ranged between 1.2–2.4 when controlled for different pesticides (Table ii); OR's ranged between 1–6.1 for a variety of other factors (Table i).	5,5
Buckley 2000	Case-control; children under 20 yrs of age with NHL newly dx b/t 1986–1990; 268 cases, 254 controls.	Mixed exposure; questionnaires re: occ and home exposures around time of index pregnancy and exposure of the child; ad hoc score of exposure created from this info.	Maternal ed, maternal race	OR, conditional logistic regression	Signif assoc with pest use in home (OR 7.3, extermination within home OR 3, postnatal ex OR 2.4); OR's ranged between 0.98–7.33 for different exposures and different family members exposed (Table 3).	4,5
Cantor 1992	Case-control study; men in Iowa and Minnesota; selected by convenience sampling; 622 cases and 1245	Combination; exposure measured by self-reports and questionnaires	Age, hair dye use, family history, smoking	Logistic regression, OR	There was a small increase in NHL in farmers (OR 1.2, 95% CI 1.0–1.5); OR's ranged between 0.9–1.4	6,5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
	population based controls.		history, method of application, use of protective equipment		according to ever having been a farmer, timing of farming occupation, and average size of farm (Table 2); OR's ranged between 0.6–3.1 for different pesticide groups (Table 3).	
Costantini 2001	Case-control; all incident cases b/t 20–74 yrs age from 12 areas in Italy b/t 1991–1993; 2737 cases and 1779 controls.	All pesticides and solvents; occ exposure assessed by questionnaire; ever/never exposed; exposure also determined by job type.	Smoking habits, age, hair dye use, x-rays, meds, education, occ history	OR, Mantel-hanzel	The only positive finding was an increase in small cell lymphoma in male agricultural workers OR 1.4 (CI 1.0–1.9).	5,5
Hardell 1999	Case-control study; all cases reported to the regional cancer registry in northern and middle Sweden greater than 25 yrs of age; all men; 442 cases and 741 controls.	Mainly phenoxyacetic acids, but also other pesticides; exposure determined through questionnaire about all exposure (home, occupational); cumulative exposure was assessed in yrs and days.	Smoking habits, diet, previous diseases, other exposures	OR, logistic regression	There was increased NHL with exposure to fungicides (OR 3.7, CI 1.1–13) and herbicides (OR 1.6, CI 1.0–2.5); OR's ranged between 1.1–3.7 for different pesticides; dose-response OR's for herbicides ranged between 1.0–6.8 (Table 2).	5,5
Hardell 2002	Case-control; cases age 25 and over, male, and living, with NHL and hairy cell leukemia; 515 cases and 1141 controls (also includes people dx with NHL); Sweden	Questionnaire; all pesticides – names of different ones collected in interview; exposure calculated as years exposed and number of days of exposure.	Area of residence	OR; conditional logistic regression	Increased risk for NHL found for herbicides (OR 1.75, CI 1.26–2.42), insecticides (OR 1.43, CI 1.08–1.87), fungicide (OR 3.11, CI 1.56–6.27) and impregnating agents (OR 1.48, CI 1.11–1.96); dose-response effect present for herbicides in general, and each of phenoxy acids, MCPA and "other."	4,5
Hoar 1993	Case-control study; pooled data from smaller studies; all newly dx white men with NHL, over the age of 20 yrs; 993 cases and 2918 controls.	Atrazine; also adjusted for 2,4-D use; exposure assessed by questionnaire; years of use, way handled, use of protective equip, used to determine	Age; use of 2,4-D	OR, maximum likelihoods	Unlikely that exposure to atrazine causes increased risk of NHL; slight increase which was eliminated after adjusting for 2,4-D use; OR's ranged between 0.9–3.2 according to atrazine use (Table 2)	5,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
		exposure.			when not adjusted for atrazine.	
Kogevinas 1995	Case-control study; cases from international agency for research in cancer, cancer registries, and death cert; 11 sarcoma, 55 controls; 32 NHL and 158 controls, 2 nested case-control studies.	Occ exposure assessed by industrial hygienists from job/company records – categorized into low, medium, high.	Year of first exposure, year from first exposure to disease	OR, logistic regression	Generally weak associations b/t NHL and pesticides except to 1,4,5-T (OR 1.9, CI 0.7–4.8); OR's ranged between 0.62–4.19 for varying chemicals at varying levels of exposure (Table 3).	4,5
McDuffie 2002	Case-control study of farmers in 6 Canadian provinces; all men (aged 19 and over) with NHL who lived or worked on a farm were cases; 235 cases and 673 controls.	Mixed exposure; assessed through mail-out questionnaire; questions about exposure, handling of pesticides, use of protective equip, accidents, animal handling; % who replied yes to these questions.	Age, province of residence, measles, personal history of cancer, length of farm residence	OR, conditional logistic regression	Cases and controls not that different with regards to pesticide exposure, but there was increased OR's for other variables (exposure to diesel fuel and exhaust, certain animals, previous history of measles); OR's ranged between 0.76–1.45 for pesticide safety handling practices (Table 1), none with statistical significance; in multivariate analysis for fungicide, carbamate insecticides, organophosphate insecticides and dicamba herbicides exposures, OR's were 1.04–1.86, none with statistical significance.	4,4
McDuffie 2001	Case-control; men in six Canadian provinces; cases dx with STS, HD, NHL, or MM b/t 1991–1994, and over the age of 19 yrs; from a variety of occupations; 517 cases and 1506 controls.	Mail-out questionnaire followed by telephone interview for those with pesticide exposure of 10h/yr or more; mixed pesticide exposure (included herbicides, insect, fungi, and fumigants); exposure classified by the number of pesticides reported by cases and controls as well as the number of days/yr of	Age, province of residence, history of measles, positive history of cancer in first degree relatives, other medical history	OR, conditional logistic regression	Risk of NHL increased by exposure to phenoxyherbicides, organophosph insecticides, dicamba (OR's 1.38–1.92, with stat. signif.) after adjustments for some covariates, still OR's 1.32–2.33 with stat. signif., for 2,4-D, mecoprop, dicamba, some insecticides; when adjusted for more covariates, OR's of 1.96–3.42, with stat. signif. for dicamba, mecoprop and aldrin.	5,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
		exposure to individual compounds.				
Persson 1993	Case-control study; cases dx with NHL, HD b/t 1975–1984 in Sweden (at least 20 yrs old, and living in catchment area); 31 HD, 93 NHL, 204 controls.	Phenoxy herb and 'other pesticides;' mail-out questionnaire; to be included had to have min exposure of 1 yr; questions about occ exposure to herb.	Smoking habits, x-ray, age, time at dx, some meds	OR, logistic regression	Increased risk of NHL with increased exposure to phenoxy herb (OR 2.3, CI 0.7–7.2).	4,4
Waddell 2001	Pooled case-control studies; random sample of NHL cases in Kansas, Nebraska, Iowa, and Minnesota, all men, farmers; 748 cases and 2236 controls.	Organophosphate pesticides; questionnaire with detailed questions on agricultural practices, types of pesticides, adys per/yr, type of crops.	Age, state, respondent type, smoking history, diet, alcohol	OR, logistic regression	Increased risk in farmers with organophosph use (50%); OR's ranged between 0.9–3.2 by type and class of OPP used (Table 4).	5,5
Zheng 2001	Case-control pooled analysis (seems to be the same group as the other studies from these researchers); Iowa, Minnesota, Nebraska, Kansas; male farmers over the age of 21 yrs; 985 cases, 2895 controls.	Carbamate insecticides; questionnaire regarding pest use, personal handling, year of first and last use, crop, animals.	Age at dx, type of respondent, state of res, first degree family history of cancer, use of hair dye, use of private wells, smoking history	OR, unconditional logistic regression	Farmers who had ever used carbamate insect had a 30% to 50% increased risk of NHL; ORs' ranged between 1.0–1.6 for carbamate use; 0.6–3.7 for carbaryl use, 1.0–3.7 for carbofuran use.	5,4
Ecological Studies						
Fontana 1998	Ecological study; to see if increased NHL in polluted areas of Italy; whole pop (900,000) b/t 1985–1988 and 1991–1993 – all cases of NHL and HD b/t people ages b/t 20–74.	2,4-D and 2,4,5-trichlorophenoxyacetic acid; exposure assessed through soil and water samples in area to determine level of pollution.	Age	OR, direct standardization	Areas with more phenoxy pollution had signif more NHL (60–100%); OR's in areas ranged between 0.8–1.9; women in rice growing job (from case-control study) increased NHL (OR 1.9, CI 0.6–6.0).	4,4
Schreinermachers 1999	Ecological study; compared cancer mortality in 4 agricultural regions of Minnesota.	Mixed pesticides; survey and questionnaires about most frequently used pest,	Gender, race, age	SRR, Poisson	Excess NHL for women in agricultural regions (SRR 1.35, CI 1.09–1.66).	5,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
		crop type, to get a proxy level of exposure.				

Chapter 5 — Leukemia

Leukemia is the ninth most prevalent cancer among new cases. Moreover, it is also the ninth most common cause of cancer-related death in Canada, accounting for 2.3% of new cancer cases in women and 2.9% of new cases in men. Nationally, it is the sixth ranked cancer in terms of potential years of life lost (33).

This review assessed a total of 23 studies on leukemia and pesticide exposure, categorized as follows:

- Cohort studies: 6 (5 positive, 4 with statistical significance, 1 negative)
- Case-control studies: 8 (8 positive, 8 with statistical significance)
- Ecological studies: 1 (0 positive)
- Lab study: 1 (1 positive)
- Excluded: 7 (5 positive, 4 with statistical significance, 2 negative)

Nearly all the acceptable studies were rated 4 or 5 out of 7 by both readers; Heacock et al. (11), a negative study, received one 6, and Ma et al. (18), a positive study, received a 6 and 7 from the assessors.

Cohort Studies

Of the 6 cohort studies, 5 showed positive associations (4 with statistical significance) and 1 showed a negative association. None had direct exposure histories due to the large number of subjects. Two of the studies (13, 12) showed increased rates of leukemia in workers with exposure to livestock. The first (13) showed an increase of acute leukemia (subtype undefined) in men engaged in dairy farming (RR 1.76, CI 1.02–3.05). The second (12) showed an increase in leukemia in children of farming parents engaged in pig farming (RR 2.26). This association between animal husbandry and cancers has often been found, and is thought to be due either to insecticide exposure or animal viruses. The study by Beard et al. (10) showed an increase in leukemia in a cohort of outdoor workers in Australia with an SIR of 20.90 (CI 1.54–284.41) for the most highly exposed group. The one negative study, Heacock et al. (11), the study given 6 by one of the readers, did not find a relationship between childhood leukemia and paternal exposure to chlorophenate fungicides among sawmill workers, though the total number of all cancers found was only 40. Waterhouse et al. (23) found an elevated SIR (1.4, CI 1.03–1.86) for chronic lymphocytic leukemia (CLL) and lymphomas (classed together) in a cohort study, and a nested case-control study showed an elevated though not significant OR. Kross et al. (14) was the only study looking at the mortality rates of golf course superintendents. These people encounter many occupational hazards such as sunlight and exposure to pesticides, fertilizers, and diesel exhaust. The PMR for leukemia was 162 (CI 83–316).

Case-Control Studies

All 8 case-control studies were positive. The study by Ciccone et al. (15) was one of the few studies looking at women. It showed an OR of 4.4 (CI 1.7–11.5) for acute and chronic myelocytic leukemia (AML and CML) in women exposed to pesticides; however specific pesticides were not named or quantified.

The study by Infante-Rivard et al. (16) showed increased rates of acute lymphocytic leukemia (ALL) in children whose parents used insecticides in the garden and on interior plants, especially when the mother was exposed while pregnant. The cases were derived from an urban area of Montreal, which would have excluded farm children who may have had higher pesticide exposures than the urban children, and whose data may have shown an even stronger association. In addition, a case-only cytogenetic study was done which found that an increased number of the children with ALL had specific metabolic mutations that were involved in carcinogen metabolism. This supports other studies that show that people with alterations in the cytochrome P-450 metabolic pathway ("slow metabolizers") are susceptible to certain illnesses with exposure to chemicals such as pesticides (discussed in Chapter 6, Genetic Polymorphisms).

Leiss et al. (17) found a strong association (OR 1.7–3.0) between use of pest strips containing dichlorvos (an insecticide) and ALL in children. Ma et al. (18), the study given 6 and 7 by the readers, showed increased rates of childhood leukemia with exposure to insecticides, with certain time periods of exposure being critical (pre-pregnancy, and both pre- and post-natal). Interestingly, the most crucial exposure period for later development of leukemia was found to be during pregnancy. Meinert conducted two studies, in 1996 (19) and in 2000 (20). Both showed increased rates of childhood leukemia with pesticide use on farms and in gardens. A study by Nanni et al. (21) showed an increase in CLL and low-grade non-Hodgkins lymphoma in farm animal breeders in Italy. Rates were increased with exposure to insecticides in general (OR 2.46, CI 1.07–5.63), to carbamates (OR 3.08, CI 1.05–9.00), and to organophosphates (OR 2.97, CI 1.28–6.91), with the latter showing a dose–response relationship. Richardson et al. (22) found increased rates of leukemia with exposure to weed killers (OR 3.5, CI 1.1–10.8) and insecticides (OR 1.7, CI 1.0–3.1), though specific types of pesticides were not identified.

Laboratory Study

The laboratory study of Cuneo et al. (24) examined a group of patients with AML and used questionnaires to obtain information about pesticide use. They divided the patients into two groups: those exposed and those not exposed to pesticides or organic solvents (although covariates were not measured). Chromosomal aberrations, cytologic features, peripheral blood and bone marrow indices, and the clinical picture of the illness were examined for both groups. The patients exposed to pesticides had the same recurring chromosomal aberrations and cytological features, which were different from those found in the unexposed group. In addition, the clinical picture differed considerably between the two groups. The exposed group had lower leukocyte counts and lower blast cell percentages in the bone marrow. The exposed group was refractory to treatment, with few attaining remission. This is in contrast to the unexposed group that attained almost 50% remission. The mean survival of the exposed group was 2 months and of the non-exposed group 9 months. What is most interesting is that the features found in the exposed group (cytologic and chromosomal changes, and a distinct clinical picture with poor prognosis) resemble those found in patients with secondary leukemia (leukemia caused by an insult such as radiation, chemotherapy, or some chemical exposures). This may implicate pesticides as an etiologic factor in the development of leukemia.

Ecological Study

The selected ecological study was by Reynolds et al. (25), who examined cancer cases in children and pesticide use from 1988 to 1994 in each of several thousand geographic areas into which California was divided for the study. No preponderance of childhood cancer was found in areas of heavy pesticide use; however, pesticide use was gauged by indirect database measures,

such as quantity applied, number of acres treated, and type of crop treated. Also, the study measured only agricultural and not home use of pesticides.

Excluded Studies

Seven studies were excluded, 5 of which were positive (4 with statistical significance) and 2 of which were negative. Scheele et al. (31) found similar concentrations of PCB and DDT in the bone marrow of children both with and without leukemia, though this could be confounded by the presence of less fat in the marrow of people with leukemia. That study was eliminated because these chemicals were not included in our list of pesticides. Smith et al. (32) studied cases of soft tissue sarcoma and lymphoma and found increased relative risks up to 2.7 with exposure to chlorphenoxy herbicides but without statistical significance. This study was excluded because it did not deal with leukemia. Deschamps et al. (26) did a case-control study on a cluster of childhood leukemia cases in a city in British Columbia; the study did not show a relationship between leukemia and pesticide exposure. It was, however, excluded because the exposure history was very poor, the number of cases was small, the results could have arisen from cluster analysis, and no adjustment was made for any of the covariates mentioned. Mulder et al. (29) looked at a cluster of hematopoietic malignancies that occurred in a horticultural community in the Netherlands, but the sample size was too small to allow any conclusions to be drawn (8 leukemia and 7 lymphoma cases). El-Sadek et al. (27) found that a group of farm workers had significantly higher lymphocyte, white blood cell, and platelet counts than a group of workers that were not exposed to pesticides. The study was eliminated because there were no details of exposure history and the methodology was poor, though the findings are interesting. Safi et al. (30) found increasing rates of cancer in the 1990–1999 period, corresponding to increasing use of pesticides in the Gaza Governorates; however, the study was excluded because the methodology was so poor and the cancer rate measurements were not reliable. Fagioli et al. (28) was excluded because it reported on the same data as Cuneo et al. (24), included in the Lab Studies section above.

Conclusions

In conclusion, it is clear from the findings of these studies that a positive association exists between pesticide exposure and leukemia. Of 16 studies included in this review, 14 show associations between pesticide exposure and leukemia, all but one with statistical significance — despite the limitations of cohort, case-control, and ecological studies. This is consistent with many previous studies that showed similar relationships. The dose–response effect found by some of the studies also corroborates this conclusion. In addition, Infante-Rivard explored the issue of gene polymorphisms which may predispose “slow metabolizers” to chemical-related illness; this issue was found in other studies, for example with respect to Parkinson’s disease (see Chapter 8, Neurological and Mental Health). The laboratory study (24) is particularly compelling, even though its study design is not the best. This implication of pesticides in the development of leukemia warrants further investigation and also political action to address this public health issue. In addition, the public should try to minimize occupational and environmental exposure to pesticides. Ways to do this would include: avoiding use at home, on pets, and in the garden; avoiding — if possible — exposure via purchased food; and wearing protective gear if pesticide use is deemed necessary.

Chapter 5 — Leukemia

References

Review Studies:

1. Acquavella J, Olsen G , Cole P, Ireland B, Kaneene J, Schuman S, Holden L. Cancer among farmers: a meta-analysis. *Ann Epidemiol* 1998;8:64–74.
2. Baldi I, Mohammed-Brahim B, Brochard P, Dartigues JF, Salamon R. Delayed health effects of pesticides: review of current epidemiological knowledge. *Rev Epidemiol Sante Publique* 1998;46:134–142.
3. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. *Environ Health Perspect* 1997;105:1068–1077.
4. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer. *Cancer Causes Control* 1997;8:420–443.
5. Keller-Byrne JE, Khuder SA, Schaub EA. Meta-analysis of leukemia and farming. *Environ Res* 1995;71:1–10.
6. Maroni M, Fait A. Health effects in man from long-term exposure to pesticides. A review of the 1975–1991 literature. *Toxicology* 1993;78:1–180.
7. Sathiakumar N, Delzell E. A review of epidemiologic studies of triazine herbicides and cancer. *Crit Rev Toxicol* 1997;27:599–612.
8. Zahm SH, Blair A. Cancer among migrant and seasonal farmworkers: an epidemiologic review and research agenda. *Am J Ind Med* 1993;24(6):753–66.
9. Zahm SH, Ward MH. Pesticides and childhood cancer. *Environ Health Perspec* 1998;106 Suppl 3:893–908.

Cohort Studies:

10. 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 Perspec* 2003;111(5):724–730 .
11. Heacock H, Hertzman C, Demers PA, Gallagher R, Hogg RS, Teschke K, Hershler R, Bajdik CD, Dimich-Ward H, Marion SA, Ostry A, Kelly S. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. *Environ Health Perspec* 2000;108:499–503
12. 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.
13. 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.
14. Kross B, Burmeister L, Ogilvie L, Fuortes L, Fu C. Proportionate mortality study of golf course superintendents. *Am J Ind Med* 1996;29:501–506.

Case-Control Studies:

15. Ciccone G, Mirabelli D, Levis A, Gavarotti P, Rege-Cambrin G, Davico L, Vineis P. Myeloid leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case-control study. *Cancer Genet Cytogenet* 1993;68:35–139.
16. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms [comment]. *Epidemiology* 1999;10:481–487.
17. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study [comment]. *Am J Public Health* 1995;85:249–252.
18. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, Reynolds P. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspec* 2002;110:955–960.
19. 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:1943–1948.
20. 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;151:639–646.
21. Nanni O, Amadori D, Lugaresi C, Falcini F, Scarpi E, Saragoni A, Buiatti E. 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;53:652–657.
22. Richardson S, Zittoun R, Bastuji-Garin S, Lasserre V, Guihenneuc C, Cadiou M, Viguie F, Laffont-Faust I. Occupational risk factors for acute leukaemia: a case-control study. *Int J Epidemiol* 1992;21:1063–1073.
23. 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;77:763–770.

Lab Study:

24. Cuneo A, Fagioli F, Pazzi I, Tallarico A, Previati R, Piva N, Carli MG, Balboni M, Castoldi G. Morphologic, immunologic and cytogenetic studies in acute myeloid leukemia following occupational exposure to pesticides and organic solvents. *Leuk Res* 1992;16:789–796.

Ecological Study:

25. 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 Perspec* 2002;110:319–324.

Excluded Studies:

26. Deschamps M, Band P. Study of a cluster of childhood leukemia. *Health Rep* 1993;5:81–85.

27. El Sadek WY, Hassan MH. Chronic lymphocytic leukaemia in Egyptian farm workers exposed to pesticides. *East Mediterr Health J* 1999;5:960–966.

28. Fagioli F, Cuneo A, Piva N, Carli MG, Previati R, Balboni M, Tomasi P, Cariani D, Scapoli G, Castoldi G. Distinct cytogenetic and clinicopathologic features in acute myeloid leukemia after occupational exposure to pesticides and organic solvents. *Cancer* 1992;70:77–85.

29. 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 Community Health* 1994;48:161–165.

30. 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.

31. Scheele J, Teufel M, Niessen KH. Chlorinated hydrocarbons in the bone marrow of children: studies on their association with leukaemia. *Eur J Pediatr* 1992;151:802–805.

32. Smith JG, Christophers AJ. Phenoxy herbicides and chlorophenols: a case control study on soft tissue sarcoma and malignant lymphoma [comment]. *Br J Cancer* 1992;65:442–448.

Chapter reference not listed above:

33. McLaughlin JR, Dryer D, Mao Y, Morrison H, Schacter B, Villeneuve G, Whylie B, editors. Canadian Cancer Statistics [downloadable report]. Toronto: Canadian Cancer Society; 2003 [cited 2004 March 29]. Available from: http://www.cancer.ca/ccs/internet/standard/0,3182,3172_14291__langId-en,00.html

Chapter 5 — Leukemia

Table

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Beard 2003	Retrospective cohort; looked at about 20 different health conditions (leukemia was one of these); Males having worked as field officers or lab staff for the Board of Tick Control between 1935–1996; 1999 exposed, 1984 not exposed.	Exposure categorized into 'modern chemical use,' but specifics not given; period of employment was used to estimate exposure and dose (in 3 or 5 yr periods); employment records used.	Age, smoking history, alcohol consumption neuropsych score.	OR, SMR, SIR; Poisson regression	There are a number of values given on p. 726 and 727; nonsignif increases in SMR for leukemias as a group in modern era period; when exposure lag removed increase of borderline signif (SMR 3.62, CI 0.99–9.26); highest doses of pest resulted in higher SIRs (SIR 20.90, CI 1.54–284.41).	4,5
Heacock 2000	Retrospective cohort; children born in BC b/t 1952–1988, younger than 20 yrs at dx and dx b/t 1969–1993 who were offspring off fathers who worked in BC sawmills between 1950-1985; fathers 23, 829, children 19,674	Chlorophenates; exposure based on records from sawmills and interviews to determine pesticide use in mill; created 3 categories of exposure (low, medium, high) and an index of cumulative duration of exposure based on job history at the mill.	Age, gender	SIR, OR; regression analysis	No clear relationship b/t paternal occ exposure to chlorophenate fungicide and risk of childhood cancer; SIR 1.0 CI 0.5–1.8; risks for developing childhood cancer (all types) ranged from OR 0.8–1.7 for varying windows of parental exposure; For leukemia, the OR's ranged between 0.8–1.8 for different ages of dx.	5,6
Kristensen 1996	Retrospective cohort; all offspring born 1952–1991 to farm holders in agricultural censuses in Norway in 1969–1989; 323, 292 children and 1275 children had cancer.	Exposure taken from agricultural censuses done every 3 yrs; exposure presented as dichotomy (present/absent); from variables including location of farm, area, $$	Age, gender	SIR, RR Poisson regression	Rates were not elevated for pesticide exposure but were elevated for cattle, dairy, chicken and pig farming with statistical significance for pig farming only (RR 2.26, 1.07–4.12).	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
		spent on pesticides, spraying equip on farm, type of crop.				
Kristensen 1996	Retrospective cohort; all people who were farm holders and born later than 1924; 136,463 men and 109,641 women, total 3333 men and 2145 women with cancer.	Agricultural census data used to gather exposure info; exposure presented as dichotomy (present/absent) from variables including location of farm, area, $ spent on pesticides, spraying equipment on farm, type of crop.	Age, gender	OR, Poisson regression	There was a relationship b/t increased rates of leukemia and men and dairy cattle; RR 1.76 (CI 1.02–3.05); the tables only included values for positive associations – this was the only one for leukemia, therefore we cannot provide other RR values or ranges.	4,4
Kross 1996	Retrospective cohort of white male golf course superintendents, members of a professional association, died between 1970 and 1992, total of 203 cancer deaths.	No exposure histories, no comment on specific pesticides, but high use of insecticides, fungicides and herbicides with large differences in volume depending on region.	No covariates	PMR, compared to white males in the U.S. population, CI calculated by method of Jensen et al (1991)	PMR 162 (CI 83–316)	4,4
Waterhouse 1996	Cohort study; individuals over the age of 16 yrs in Tecumseh, Michigan; 6702 residents.	All acres within the county were assigned an exposure level according to annual number of acres and % treated with chemicals.	Smoking history, alcohol, exposure to radiation, occupational & household exposure, history of similar neoplasms in relatives	SIR, OR, Poisson	Census block groups with high use of propargite did have signif elevated levels of childhood leukemia, but no dose-response trend (RR 1.48, CI 1.03–2.13); otherwise, no assocations; RR's ranged between 0.68–1.48 for propargite, methyl bromide, metam sodium, trifluralin, simazine, dicofol, and chlorothalonil; when they examine leukemias by block group for organochlorines, organophosphates,	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
					carbamates, and dithiocarbamates the RR's ranged between 0.70–1.07.	
Case-Control Studies						
Ciccone 1993	Case-control; newly dx cases of acute or myeloid leukemia treated in the main hospital in Torino, Italy b/t 1989–1990, b/t ages of 15–74 yrs; 50 with AML, 17 CML, 19 MDS; 246 controls.	Exposure categorized as 'pesticides' but no further info provided; collected with questionnaires; occ hygienist then divided exposure as exposed to some, not exposed, possibly exposed, probably exposed.	Smoking habits, age, area of residence	OR, logistic regression	OR for AML and CML in women 4.4. 95% CI (1.7-11.5); no value given for men.	4,4
Clavel 1996	Case-control; all cases dx b/t 1980–1990 from 18 French hospitals; controls selected from people hospitalized at the same time; 226 cases (farmers) and 425 controls.	Questionnaire; all pesticides, divided into chemical categories; designated definite or possible exposures and low, medium or high exposure depending on number of days per yr, spray height, equipment, exposure route.	Smoking habits, education, ses, dx before or after 1984 (b/c mortality lower after 1984)	OR, conditional logistic regression	Increased risk of HCL with farmers compared to non-farmers; only positive association was for organophosphorous insecticides (OR 7.5, 95% CI 0.9–61.5); overall OR's for insecticide, fungicide, and herbicide ranged from 1.5 to 2.4.	5,4
Infante-Rivard 1999	Case-control; cases dx b/t 1980–1993 in Quebec and b/t ages 0–9 yrs from tertiary care centres; 491 cases and 491 controls; also looked at gene polymorphisms in cases and controls.	Questionnaire (only mothers had questions about pesticides); number of exposure events divided into categories – 1 month before pregnancy to birth and birth to dx.	Maternal age, age, sex	OR, conditional logistic regression	Indoor use of some insecticides by the owners and pesticide use in the garden and on interior plants associated with increased risk of leukemia; OR herbicide 3.72 (CI 0.72–19.06); plant insect OR 4.01 (CI 1.12–14.32); several pages of tables in the text with many OR ranges; "slow metabolizers" (with gene polymorphisms) had higher rates of AML.	5,5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Leiss 1995	Case-control; all cases of childhood cancers (age 0–14) dx among residents of the Denver 1970 standard metro area b/t 1976–1983; 252 cases and 222 controls.	Questionnaire to determine home exposure; Dichotomized 'use' vs 'no use;' 3 exposure periods: 3 months prior to birth, birth thru 2 yrs prior to dx, 2 yrs prior to dx thru dx.	Age at dx, fathers ed, mothers age, ses, residential stability, maternal smoking, race, magnetic exposure	OR, Mantel-Hanzel	Relationship b/t increased rate of leukemia and use of pest strips; OR 3.0 (first exposure category), OR 1.7 (second exposure cat), OR 2.6 (third exposure cat); OR's ranged from 0.3–3.0 for pesticide exposure from home extermination, yard treatment, and pest strips.	5,5
Ma 2002	Case-control; all newly dx with leukemia ages 0–14 yrs residing in the area, no hist of cancer; California; 162 cases and 162 controls.	Home exposure thru questionnaire; 3 time windows (did not use, used less than 5 times, 5 or more times); all pesticides – recorded name of product.	Age, gender, race, income, maternal education, maternal age	OR, conditional logistic regression	E xposure to household pesticides is assoc with increased risk of leukemia; esp use of professional pest. services (OR 2.8); OR's ranged between 1.0–3.6 for different types of pesticide exposure (please refer to table on page 958).	6,7
Meinert 1996	Case-control; born after 1975, age at dx less than 15 yrs, dx b/t 1988–1993, residing in state at dx; Germany; 173 cases – 2 groups of controls; also 175 children with other solid tumours.	Questionnaire for home exposure; all pesticides; Parents had to specify if hazard present yr before pregnancy, during pregnancy, and/or after child's birth.	Age, gender, ses, degree of urbanization	OR, conditional logistic regression	Only stat. signif finding was a more frequent use of pesticides in garden when leukemia cases compared with local controls (OR 2.52); several tables and large range of OR's; for exposure from 2 yrs before birth to date of dx OR's ranged between 0.83–2.55.	4,4
Meinert 2000	Case-control; included all children younger than 15 yrs who have lived in community for at least 6 months; in Germany; 234 cases with NHL, 940 with solid tumours, 1184 with leukemia.	Home exposure assessed by interview of parents; parents had to specify if hazard present yr before pregnancy, during pregnancy, and/or after child's birth.	Age, gender, ses, degree of urbanization	OR, conditional logistic regression	U se of pesticides on farms was weakly related to childhood leukemia (OR 1.5, CI 1.0–2.2); occ exp to herbicides, insecticides, and fungicides showed signif higher OR's that ranged between 1.3–3.6; use of pesticides in gardens, farms, and homes had OR's between 1.0–1.8.	5, 5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Nanni 1996	Case-control; all incident cases of NHL and CLLs in a province of Italy b/t 1987–1990; 187 cases and 977 controls.	Occupational exposure assessed by questionnaires; estimates of pesticide use based on criteria: usual dose, number of trtmts, surface area cultivated, period in yrs cultivation; all pesticides.	Age, sex, altitude of municipality, first degree family cancer history, work hist, use of drugs, exposure to radiation	OR, unconditional logistic regression	When the analysis was limited to CLLs and low grade NHLs a positive signif assoc emerged for insecticides in general, carbamates, and phosphates; OR's varied between 1.17–3.18 for different types of pesticides (i.e. herbicides, fumigates, fungicides, carbamates, phosphates).	5,4
Richardson 1992	Case-control; cases admitted to hospitals in France, over 30 yrs of age; 185 cases and 513 controls.	Occ exposure assessed by questionnaire; occ hygienist then coded exposure as low, medium, high based on time exposed; all pesticides included.	Age, sex, place of residence; occ and health probs of family, med hist, drug use	OR, conditional logistic regression	Signif positive relationship b/t leukemia and exposure to weedkillers (OR 3.5, CI 1.1–10.8) and insecticides (OR 2.1, CI 0.8–5.4); OR for acute lymphoblastic leukemia was 2.82 and for acute myelogenous leukemia was 1.38.	4,4
Ecological Studies						
Reynolds 2002	Cross-sectional ecological study; all cases of invasive cancer dx in children under 15 yrs b/t 1988–1994 in California; 7143 cancer cases.	Home exposure determined by database info – PUR (pesticide reporting database); combined with GIS info and divided into blocks; estimated average annual pesticide use for each block by summing the average pounds applied and then divide by block area; they selected the 7 most widely used pesticides for evaluation.	Ses, degree of urbanisation, race, sex, age	RR, Poisson regression	Census block groups with high use of propargite did have signif elevated levels of childhood leukemia, but no dose-response trend (RR 1.48, CI 1.03–2.13); otherwise, no assocations; RR's ranged between 0.68–1.48 for propargite, methyl bromide, metam sodium, trifluralin, simazine, dicofol, and chlorothalonil; when they examine leukemias by block group for organochlorines, organophosphates, carbamates, and dithiocarbamates the RR's ranged between 0.70–1.07.	4,4
Lab Studies						

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cuneo 1992	Type of case report or case series; 70 people with AML divided into exposed and unexposed to pesticides and chromosomes analyzed; consecutive pts admitted to hospital b/t 1986–1991 in Italy.	Questionnaire; all pesticides; exposure index developed where hours per day X days per yr X years.	None mentioned	Number and type of chromosomal aberrations	Clonal chromosome aberrations were more frequently encountered among exposed pts than unexposed, blood and bone marrow counts differed and the exposed group had poorer clinical outcomes; exposed patients resembled what is seen in secondary leukemia.	4,4

Chapter 6 — Genotoxicity, Immunotoxicity, and Genetic Susceptibility to Pesticide Health Effects Mediated by Genetic Polymorphisms

Genotoxicity is of interest as a pesticide health effect because most human carcinogens are genotoxic, and genotoxicity may be a useful biomarker as an intermediate endpoint in carcinogenesis (32, 34). Immunotoxicity refers to the effect of pesticides on immune system components such as cytokines. Genetic polymorphisms are metabolizing systems such as cytochromes that may be favourable (fast) or unfavourable (slow) in their capacity to detoxify pesticides.

Three distinct types of studies were assessed by reviewers in this area:

① Genotoxicity studies testing for clastogenic or mutagenic effects of pesticides on genetic material in cells taken from pesticide-exposed subjects and controls (22 papers)

② Immunotoxicity studies examining immune system parameters or clinical immune function as the health effects of concern (2 papers)

③ Genetic polymorphism studies examine the mediating effects of "poor metabolizer" genetic polymorphisms on health effects of pesticides (3 papers)

Details on the findings of these studies appear in the tables for this chapter.

① Genotoxicity

In the Group 1 studies of genotoxic effects of pesticides, the most frequently used test for genetic damage is classical chromosome aberration (CA) analysis of peripheral blood lymphocytes (PBLs). The lymphocytes are collected from single or multiple timed blood samples and prepared by a standard technique to undergo mitosis. Usually 100 or 200 metaphases per exposed and control subject are examined and the results are reported in terms of the percentage of cells affected. An inexpensive and simpler test looks for micronuclei (MN), whole or fragmented extra chromosomes resulting from abnormal mitosis. Some studies use newer tests to assess DNA damage (1, 34); these tests include sister chromatid exchange (SCE), Comet assay, FISH assay, and challenge dicentrics. However, the mechanisms that produce these forms of genetic damage are not as well understood as those revealed by the classical chromosome aberration test, and their clinical significance is not established. While the newer tests may be more sensitive and better suited to field testing, there is currently no longitudinal validation study to show that they predict increased cancer risk. Of all the tests for genetic damage used in the Group 1 studies, only CA frequency has been shown by a long-term prospective study to be predictive of an increased cancer rate in a pooled Nordic and Italian prospective cohort (n = 5271, follow-up 13–23 years) (35). Further longitudinal studies are required to assess the clinical predictive validity of other types of pesticide-induced genetic damage.

Methodological Issues

Important confounders for the genotoxic effect of pesticides are gender, smoking, diet, caffeine, and alcohol consumption. Alcohol induction of liver enzymes may alter pesticide metabolism, and smoking induces chromosome damage as well as increasing oral exposure if

workers smoke while handling the pesticides (1). Results are mixed as to whether the number of chromosomal aberrations increases with age. Women consistently experience greater genetic damage, with a higher percentage of chromosomal aberrations, than men on a population basis. Few studies analyzed the effects of all five potential confounders.

Other causes of chromosomal aberrations in populations include diagnostic and therapeutic radiation, and the use of mutagenic drugs such as chemotherapy agents. The latter has become a more important confounder in more recent studies since more chemotherapy drugs are now used for common non-malignant medical conditions including rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Many studies excluded subjects who had x-rays or took mutagenic drugs in the year prior to cytogenetic testing.

The control groups used in some of the genotoxic studies involved participants living in the same geographic area as the exposed subjects. This may confound results, as background pesticide exposure from an area's diet, drinking water, air, and soil may cause an elevated baseline rate of cytogenetic damage among control subjects. The problem of contaminated controls could occur both in agricultural areas and highly industrialized sites. Examples of three studies in which this may be a problem are Hoyos (13) and Bolognesi (6) (agricultural), and Kaioumova (15) (industrial). This may result in a bias toward not finding genotoxic pesticide health effects.

The timing of blood sampling in relation to the spraying season is not considered important by some authors who believe that the genotoxic effects are long lasting. The three reviewed studies that found no association between pesticide exposure and chromosome aberrations (11, 13, 25) share the potential problem that blood sampling was not timed to occur during the season of peak exposure. Some studies found significant differences in the percentage of chromosomal aberrations pre- and post-spraying season, suggesting that pesticide-induced abnormalities can normalize rapidly after cessation of exposure (14, 20). A similar pre–post season trend was also found for micronuclei frequency (6). Using Comet tail assay, Lebailly (19) found increases in DNA damage after only one day of pesticide spraying, and concluded that this test was very sensitive for measuring current rather than cumulative exposure effects. An excellent discussion of the time-dependence of cytogenetic damage is found in a new review (1). Future studies of genotoxic pesticide effects will be more useful if the biomarker chosen is appropriate to the exposure condition, especially the timing of exposure with respect to the blood sampling.

An interesting problem raised by Scarpato (25) is that highly damaged cells may fail to undergo mitosis, the first step in growing cells to metaphase for laboratory analysis of cytogenetic damage. In other words, cytogenetic damage severe enough to be fatal to cells cannot be assessed by any of these methods. For example, Pastor (21), in a study of pesticide-exposed men, found a large increase in miscarriage among their partners, but no cytogenetic effects. A possible explanation would be that the pesticides killed cells (which were then unable to undergo mitosis), and caused significant reproductive effects. A study of exposed female banana farm workers and non-exposed local controls (24) found no significant differences in MN frequency between groups, but exposed women who had stillbirths or spontaneous abortions were 1.45 times more likely to have increased MN frequency than co-workers who did not experience these adverse reproductive outcomes. Beyond these two examples, few studies combine a search for cytogenetic abnormalities with measurement of relevant clinical endpoints such as reproductive outcomes. In the future, studies that combine cytogenetic and physiologic assessments with discussion of clinically relevant short-term and long-term health effects will be extremely useful.

Conclusions—Genotoxicity Studies

As in Bolognesi's (1) review, positive associations between pesticide exposure and chromosome aberrations were found in the majority of studies. Of the 22 Group 1 studies (4–26) assessed acceptable by reviewers (see Chapter 2—Methods for a description of the assessment tool), 11 find a statistically significant increase in frequency of chromosome aberrations (CAs) in the pesticide-exposed group. One study finds a significant dose–response relationship between micronuclei (MN) frequency and years of exposure (6), and three other studies show significant pesticide effects on MN frequency (9, 14, 26). Two studies find no pesticide effects on MN frequency, but one of these is positive for effect of male pesticide exposure on miscarriage (21) and the other is positive for increased rate of female miscarriage in the exposed group (23). Five studies show statistically significant associations between pesticide exposure and abnormal Comet tail assay; one is positive for DNA damage in exposed subjects (24) and one is positive for pesticide effects for both DNA repair response of cells, and challenge dicentrics (5). Two studies showing no pesticide effects on CAs and one showing no effect on micronuclei share the problem of blood sampling not being timed to pesticide exposure (11, 13, 25).

The use of a reproducible laboratory measurement (chromosomal aberrations per 100 metaphases) to assess a pesticide health effect allows for aggregation of results across studies. For percent chromosome aberrations, the *n*-weighted average across 15 positive and negative studies is 2.36% for controls (n = 500) and 5.25% for pesticide-exposed subjects (n = 529) (Figure 1). It has been proposed that the "normal" rate of CAs in the population is 1%. The aggregated results thus suggest substantial exposure effects in the aggregated control group, and a significant pesticide-related increase in CAs in the exposed group. Chromosome aberrations have been proven to be a biomarker for cancer risk by a large, long-term prospective study (35), so it can be clearly stated that at least some pesticides are carcinogens.

② Immunotoxicity

An excellent literature review (3) on immunotoxicity summarized the research to date on pesticide effects on the immune systems of laboratory animals, wildlife, and humans. Three important concepts were highlighted by the review:

(i) The three components of the immune system—humoral, cell-mediated and non-specific immunity—work in an interregulating way, so that an alteration in one part of the system may cause a compensatory change in another. Thus pesticide-induced, immune-mediated disease may result from either direct immunotoxicity or a compensatory response.

(ii) The immune system can be stimulated or suppressed by pesticides; the same pesticide (e.g., malathion) can have either of these effects depending on the dose.

(iii) Acute toxicity is not directly related to the immunomodulating properties of pesticides. For example, the carbamate aldicarb is the most acutely toxic in its group, but is the least potent inhibitor of T-cell proliferation through the mechanism of reduced production of interleukin-1 (IL-1).

Two studies published since Voccia's 1999 review (3) were found. Both studied organochlorines, but were included because the pesticides studied have been in wide use, are in the process of being phased out, and are very persistent.

The results of both Group 2 studies are positive for measurable effects of pesticides on immune system function. Daniel (27) studied 190 patients with high pentachlorophenol (PCP) exposure and found that increased blood levels of this commonly used wood preservative were significantly associated with impaired responses to humoral and cellular immune stimulation tests. Phillips (28) found that children exposed to chlordane and/or heptachlor had more cytokine panel abnormalities than matched controls.

Summary—Genotoxicity and Immunotoxicity

The Group 1 and 2 studies do not answer the question as to which pesticides are most likely to cause chromosome aberrations. One study found a strong effect for synthetic pyrethrins on CAs (20), and one study where 88% of exposed subjects had depressed RBC cholinesterase levels and very high CA frequencies (20.6%) suggests an important organophosphate effect (22). Garry (10) found significant increases in the frequency of CAs in fumigant and insecticide applicators compared with controls. The fumigant and herbicide applier groups also showed increased frequency of the most common chromosome rearrangements observed in non-Hodgkin's lymphoma patients (10).

Subjects in the majority of studies assessed were repeatedly exposed to several classes and types of pesticides including fungicides, phenoxy herbicides, and the insecticide classes pyrethroids, carbamates, and organophosphates. Further in vitro studies, such as Whalen (40), which showed cytotoxic effects of triazine herbicides and carbamates on human natural killer cells, are needed to determine whether some classes of pesticides are more genotoxic and immunotoxic in humans, and to which cells and components of the human immune system. There is also important information in animal studies about the relative immunotoxicity of specific pesticides; this is reviewed by Voccia (3) but was beyond the scope of this review.

③ Genetic Susceptiblity to Pesticide Health Effects Mediated by Genetic Polymorphisms

The Human Genome Project has created a new and potentially powerful method for studying the mechanisms of individual susceptibility to pesticide health effects. Gene mapping has allowed the identification of genetic polymorphisms in individuals that are associated with impaired metabolization of xenobiotics, including drugs and pesticides. Although all the pathways for pesticide detoxification are not fully understood, the process involves three main systems: the cytochrome P450 enzymes, glutathione S-transferases, and the paraoxanase system that metabolizes organophosphate insecticides. Inheritance of the unfavourable "poor metabolizer" versions of these genes has been shown to cause increased activation or reduced detoxification and elimination of environmental mutagens such as pesticides (5). It is hypothesized that, subject to comparable pesticide exposures, poor metabolizers would develop higher rates of cancer and other health effects than would normal metabolizers. Bolognesi's recent study (1) contains an excellent review and discussion of genetic polymorphism studies. Three examples of papers investigating the relationship of genetic polymorphisms and pesticide susceptibility follow:

1. Infante-Rivard (29) studied children with acute lymphocytic leukemia (ALL) who had been genotyped at birth. Children with poor metabolizer polypmorphisms, representing just over 40% of the Montreal study group, had overall interaction odds ratios (ORs) of 1.05 to 5.55 for ALL if exposed to pesticides during pregnancy or childhood. The highest

ORs (4.33–5.55) were for exposure to repellants and sprays for outdoor insects during pregnancy, and exposure to mite and spider killers during pregnancy or between birth and leukemia diagnosis. Herbicide use (mainly 2,4-D) both during pregnancy and childhood, showed a consistent interaction with poor metabolizer genes and was associated with a 2-fold increase in leukemia incidence.

2. Hubble et al. (30) compared patients who had the dementia subtype of Parkinson's disease with a control group of Parkinson's disease patients without dementia. Genetic markers for poor metabolism were measured in both groups and found to occur in equal frequency. However, occurrence of the poor metabolizer gene combined with pesticide exposure was more common in the dementia group (12%) than in the Parkinson's patients without dementia (2%). This study suggests a possible mechanism for the consistent findings of epidemiological studies that pesticide exposure is a risk factor for the development of Parkinson's disease (35).

3. Au (5) studied Costa Rican banana farmers who had been previously exposed to dibromochloropropane (DBCP), a now-banned pesticide known to cause reduced sperm counts, and who were currently heavily exposed to agricultural pesticides in their work. The workers with poor metabolizer polymorphisms had an impaired DNA repair response, compared with co-workers who were normal metabolizers. The study also found that poor metabolizers were significantly underrepresented in the farmers' group compared with controls. The author speculated that poor metabolizers might have selected themselves out of farming because of their increased susceptibility to adverse health effects from high pesticide exposure.

Summary—Genetic Polymorphisms

Genetic susceptibility to the adverse effects of pesticide exposure is an important new concept for further study and application, and may represent the cutting edge of pesticide health effects research. It may be a mediating factor to explain mechanisms for "healthy worker" effects, variations in results between racial groups, and mixed results in epidemiological studies. In other areas of environmental health risk assessment, genetic polymorphisms have been investigated as a predictor of lung cancer risk in smokers (33), and lead poisoning severity in children (36). Screening for poor metabolizer genetic susceptibility certainly offers hope of preventing cancer in the future by educating those who are most susceptible to pesticide health effects to limit their pesticide exposures. However, until such techniques become clinically available, the presence of increased susceptibility to pesticide health effects in about 40% of Canadians, as suggested by the Montreal leukemia study (29), makes a strong argument for a general reduction of pesticide use and human exposure.

References

Review Studies:

1. Bolognesi C. Genotoxicity of pesticides: a review of human biomonitoring studies. *Mutat Res* 2003;543:251–272
2. Holsapple MP. 2002. Autoimmunity by pesticides: a critical review of the state of the science. *Toxicol Lett* **127**, 101–109.
3. Voccia I, Blakley B, Brousseau P, Fournier M. Immunotoxicity of pesticides: a review. *Tox Ind Health* 1999;**15:**119–132.

Primary Studies:

① Genotoxicity

4. Antonucci GA , de Syllos Colus IM. Chromosomal aberrations analysis in a Brazilian population exposed to pesticides. *Teratogenesis, Carcinogenesis, & Mutagenesis* 2000;20:265–272.
5. Au WW, Sierra-Torres CH, Cajas-Salazar N, Shipp BK, Legator MS. Cytogenetic effects from exposure to mixed pesticides and the influence from genetic susceptibility. *Environ Health Perspec* 1999;107:501–505. (also in genetic polymorphisms list)
6. Bolognesi C, Parrini M, Reggiardo F, Bonassi S. Biomonitoring of workers exposed to pesticides. *Int Arch Occup Env Health* 1993;65(S):185–187.
7. Carbonell E, Xamena N, Creus A, Marcos R. Cytogenetic biomonitoring in a Spanish group of agricultural workers exposed to pesticides. *Mutagenesis* 1993;8:511–517.
8. Carbonell E, Valbuena A, Xamena N, Creus A , Marcos R. Temporary variations in chromosomal aberrations in a group of agricultural workers exposed to pesticides. *Mutat Res* 1995;344:127–134.
9. Garaj-Vrhovac V, Zeljezic D. Assessment of genome damage in a population of Croatian workers employed in pesticide production by chromosomal aberration analysis, micronucleus assay and Comet assay. *J Appl Toxicol* 2002;22:249–255.
10. Garry VF Tarone RE Long L Griffith J Kelly JT Burroughs B. 1996. Pesticide appliers with mixed pesticide exposure: G-banded analysis and possible relationship to non-Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers Prev* 5:11–16.
11. Gregio D'ArceLP, Colus IM. Cytogenetic and molecular biomonitoring of agricultural workers exposed to pesticides in Brazil. *Teratogenesis, Carcinogenesis, & Mutagenesis.* 2000;20:161–170.
12. Grover P, Danadevi K, Mahboob M, Rozati R, Banu BS, Rahman MF. 2003. Evaluation of genetic damage in workers employed in pesticide production utilizing the Comet assay. *Mutagenesis* 2003;18(2):201–205.
13. Hoyos LS, Carvajal S, Solano L, Rodriguez J, Orozco L, Lopez Y, Au WW. Cytogenetic Monitoring of farmers exposed to pesticides in Colombia. *Environ Health Perspec* 1996;104 Suppl 8:535–538.

14. Joksic G, Vidakovic A , Spasojevic-Tisma V. Cytogenetic monitoring of pesticide sprayers. *Environ Res* 1997;75:113–118.

15. Kaioumova DF, Khabutdinova LK. Cytogenetic characteristics of herbicide production workers in Ufa. *Chemosphere* 1998;37:1755–1759.

16. Kourakis A, Mouratidou M, Barbouti A, Dimikiotou M 1996. Cytogenetic effects of occupational exposure in the peripheral blood lymphocytes of pesticide sprayers. *Carcinogenesis* 1996;17:99–101.

17. Lander BF, Knudsen LE, Gamborg MO, Jarventaus H, Norppa H. Chromosome aberrations in pesticide-exposed greenhouse workers. *Scand J Work Environ Health* 2000;26:436–442.

18. Lebailly P, Vigreux C, Lechevrel C, Ledemeny D, Godard T,Sichel F, LeTalaer M, Henry-Amar M, Gauduchon P. DNA damage in mononuclear leukocytes of farmers measured using the alkaline comet tail assay: Discussion of critical parameters and evaluation of seasonal variations in relation to pesticide exposure. *Cancer Epidemiol Biomarkers Prev* 1998a;7:917–927.

19. Lebailly,P,Vigreux C, Lechevrel C,Ledemeny D, Godard T,Sichel F, LeTalaer M, Henry-Amar M , Gauduchon P. DNA damage in mononuclear leukocytes of farmers measured using the alkaline comet tail assay: Modifications of DNA damage levels after a one-day field spraying period with selected pesticides. *Cancer Epidemiol Biomarkers Prev* 1998b;7:929–940.

20. Mohammad O, Walid AA, Ghada K. Chromosomal aberrations in human lymphocytes from two groups of workers occupationally exposed to pesticides in Syria. *Environ Res* 1995;70:24–29.

21. Pastor S, Gutierrez S, Creus A, Cebulska-Wasilewska A, Marcos R . Micronuclei in peripheral blood lymphocytes and buccal epithelial cells of Polish farmers exposed to pesticides. *Mutat Res* 2001;495:147–156.

22. Paz-y-Mino,C, Bustamante G, Sanchez ME, Leone PE. Cytogenetic monitoring in a population occupationally exposed to pesticides in Ecuador. *Environ Health Perspect* 2002;110:1077–1080.

23. Ramirez V, Cuenca P [Micronuclei frequency in lymphocytes of individuals exposed to pesticides] [Spanish] *Rev Biol Trop* 2001;49;(1):1–8.

24. Ramirez V, Cuenca P. [DNA damage in female workers exposed to pesticides in banana plantations at Limon, Costa Rica]. [Spanish]. *Rev Biol Trop* 2002;50:507–518.

25. Scarpato R, Migliore L, Angotzi G, Fedi A, Miligi L, Loprieno N. Cytogenetic monitoring of a group of Italian floriculturists: no evidence of DNA damage related to pesticide exposure. *Mutat Res* 1996;367:73–82.

26. Varona M, Cardenas O Crane C, Rocha S, Cuervo G, Vargas J. [Alteraciones citogeneticas en trabajadoras con riesgo ocupational de exposition a plaguacidas en cultivos de flores en Bogota.] [Spanish] *Biomedica* 2003;23:141–152.

② Immunotoxicity

27. Daniel V, Huber W, Bauer K, Suesal C, Mytilineos J Melk A, Conradt C, Opelz G. Association of elevated blood levels of pentachlorophenol (PCP) with cellular and humoral immunodeficiencies. *Arch Environ Health* 2001;5:77–83.

28. Phillips TM. Assessing environmental exposure in children: immunotoxicology screening. *J Expo Anal Environ Epidemiol* 2000;10:769–775.

③ Genetic Polymorphisms

29. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pestcides and with gene polymorphisms. *Epidemiology* 1999;10(5):481–487.

30. Hubble JP, Kurth JH, Glatt SL, Kurth MC, Schelleneberg GD, Hassanein R, Lieberman A, Koller WC. Gene-toxin interaction as a putative risk factor for Parkinson's disease with dementia. *Neuroepidemiology* 1998;17:96–104.

31. Au WW, Sierra-Torres CH, Cajas-Salazar N, Shipp BK, Legator MS. Cytogenetic effects from exposure to mixed pesticides and the influence from genetic susceptibility. *Environ Health Perspec* 1999;107:501–505.

** Reference 31 also appears in Genotoxicity list. **

Chapter references not listed above:

32. Albertini RJ, Anderson D, Douglas GR, Hagmar L, Hemminki K, Merlo F et al. IPCS guidelines for the monitoring of genotoxic efects of carcinogens in humans. International Programme on Chemical Safety. *Mutat Res* 2000;463(2):111–172.

33. Cajas-Salazar N,Au WW, Sierra-Torres CH, Slama SA, Alpard SK, Tyring SK. Effects of epoxide hydrolase polymorhisms on chromosome aberrations and risk for lung cancer. *Cancer Genet Cytogenet* 2003;145(2):97–102.

34. Hagmar L, Stromberg U, Tinnerberg H, Mikoczy Z. The usefulness of cytogenetic biomarkers as intermediate endpoints in carcinogenesis. *Int J Hyg Environ Health* 2001;204(1):43–47.

35. Hagmar L, Bonassi S, Stromberg U, Brogger A, Knudsen LE, Norppa H, Reuterwell C. Chromosomal aberrations in lymphocytes predict human cancer: a report from the European study group on cytogenetic biomarkers and health (ESCH). *Cancer Res* 1998;58:4117–4121.

36. Long J, Covington F, Delaney-Black V, Nordstrom B. Allelic variation and environmental lead exposure in urban children. *AACN Clinical Issues* 2002;13(4):550–556.

37. Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. 2000. A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* 21 (4), 435–440

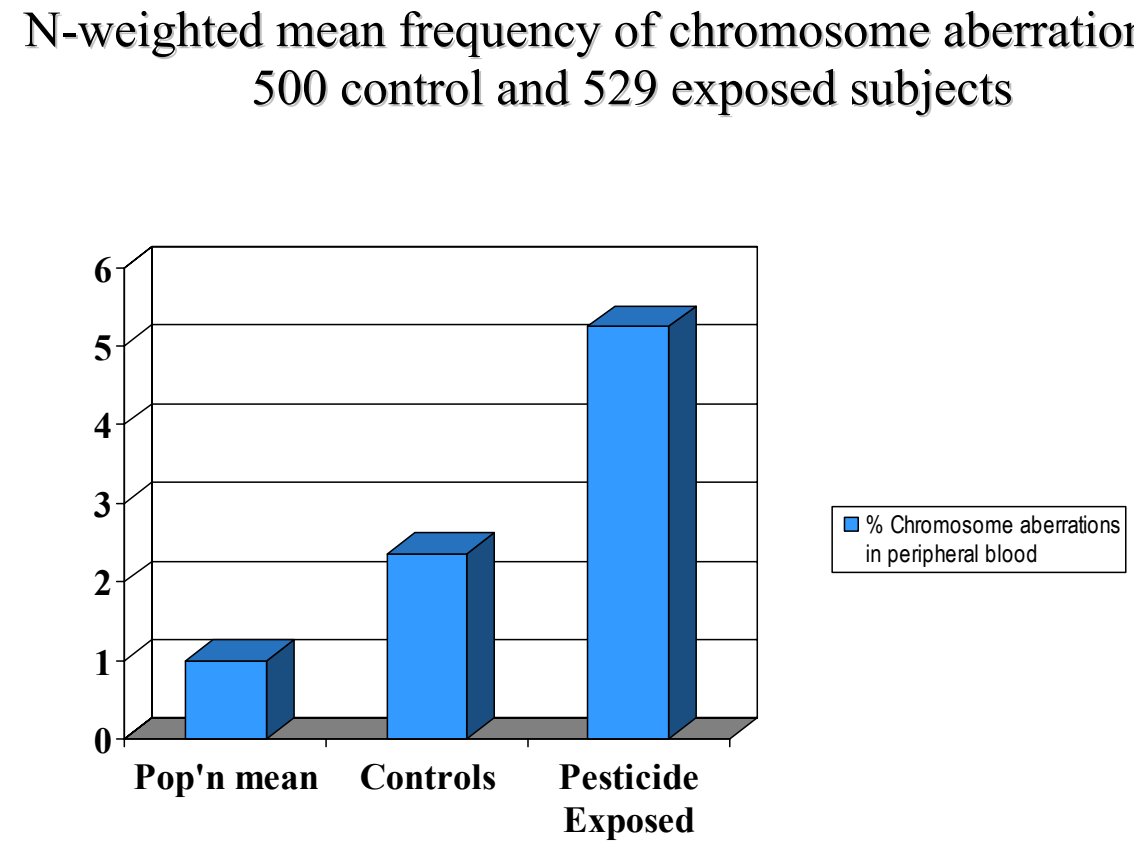
Excluded Studies:

38. Ford JH, Behrens D, McCarthy C, Mills K, Thomas P, Wilkin, HB. Sporadic chromosome abnormalities in human lymphocytes and previous exposure to chemicals. *Cytobios* 1998;96:179–192. (Poor exposure assessment)

39. Vine MF, Stein L, Weigle K, Schroeder J, Degnan D, Tse C-K J. Effects on the immune system associated with living near a pesticide dump site. *Environ Health Perspect* 2000;108(12):1113–1124. (Organochlorine)

40. Whalen M, Loganathan BG, Yamashita N, Saito T. Immunomodulation of human natural killer cell cytotoxic function by triazine and carbamate pesticides. *Chem Biol Interact* 2003;145:311–319. (In vitro study)

Figure 1: N-weighed frequency of chromosome aberrations in exposed and non-exposed subjects



Chapter 6—Systematic Review of Pesticide Health Effects

Tables

Table 1 Genotoxicity

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
Antonucci 2000	23 E sprayers 23 NE controls-Brazil	carbamates, organophosphates +others mean= 11 yr. employed Used protective equip.	age, smoking, exposure time all non-smokers	CA's lymphocytes	r McNemar Test-matched pairs	Exposed vs controls 13% vs 4% (p<.05)	5,5
Au 1999	20 Costa Rican banana farmers, 20 controls	ALL PREV DBCP EXP – 6 currently used-named	all non-smokers, genotype for detoxifying polymorphisms	CA's,DNA repair response,FISH assay	1-way ANOVA, indep t + fischer's exact for genotype	CA's NSE1.6%, NE 1.3%- Repair rsponse Poor detox>normal>control for challenge dicentrics Poor detoxifiers under-rep. in farmers	6,6
Carbonell 1995	29n Spanish flower/friut farmers taking pesticide applicator course; 2 control groups 29 + 24	17 pest used by 10% or more; # hrs, spray setting(indoor/outdoor), pers. protection	age,smoking, alcohol NS l	CA's, LFT's, hematologic	Mann-Whitney U	E vs NE 6.93 vs 4.52 (p<.05)	5,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
Carbonell 1993	70 Spanish E farmers and 69 C ofice workers	# hrs/yr spraying,type, work activity, protective gear #hrs/yr spraying,type, work activity, protective gear	age,smokng NS Signif. more alcohol in E group-not analyzed	CA's, SCE's	CA's-Mann-Whitney U SCE's-t-test	CA's:E 5.93% vs C 4.2%(p<.001) SCE's higher smokers	5,5
Garaj-Vrhovac 2002	10 pesticide workers Croatia,20 contols	x 22.25 yr. producing pesticides--2.,4D,atrazine, alachlor,cyanazine, malathion	Smoking-asked not analyzed Smoking higher in E	CA's in PBL,MNA, Comet tail assay	Chi sq. t-test.Comet	CA 1.02% C 7.8% E MNA 3.85 C 30.5 E Comet More DNA migration E (p<.001)	4,5
Garry 1996	61 male pesticide applicators 33 occupationally unexposed male controls Minnesota	herbicides n=20 insecticides n=18 fumigants n=23	controls matched for age and smoking status Current health status,medication use	Chromosome rearrangement (translocation or inversion).	wicoxon rank sum, 2-sided P values	1.Chromosome rearrangements significantly increased in fumigant and insecticide appliers, both 1.4% (p<.05) 2.Band 14q32 excess and band 18q21 excess in fumigant and herbicide appliers respectively-the 2 most common rearrangements observed in non-Hodgkin's lymphoma	6, Good exposure assessment. Pesticide-specific results. Suggests possible mechanism for excess NHL in pesticide appliers.

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
						patients	
Gregio D'Arce 2000	36 Brazilians 20 E, 16 C	19 listed pest's used,2-5 app's/wk., blood sampling NOT timed to high exposure	age,smoking, GSTM1	CA's,mitotic index	t-test, ANOVA	No diff CA's E vs C (1%, .9%) Higher MI controls	4,4
Grover 2003	54 Indian pest workers, 53 controls	carbamates, organophosphates, pyrethroids	Age,sex NS Smoking p<.02 ,yrs exp. p<.003	Comet tail assay	t-test,Chi sq., ANCOVA	Non-smokers C 7.03, 18.26 Smokers C 10.34,E19.75	6,5
Hoyos 1996	Colombia-30 E potato farmers, 30 C living in same area	Carbamates, organophosphates, dithiocarbamate fungicides, >5 yr, mean=16.5 yr.	smoking,alcohol, age all NS diet not assessed -? control group exp. by potato-eating	CA's,SCE's	CA- Chi sq SCE's-t-test	CA's: 1.7% E 2.1% NE SCE's 5% E 4.8%NE Both NS	5,5 no info re:timing bloodwork vs spraying
Joksic 1997	27 Yugoslav vineyard workers, 15 controls - local, 20 controls city	9 pesticides,active sustances listed 3 herb's,1 organophos.,5 fungicides,hr' sprayed, pre+post, airpack measures	age,sex,smoking matched	CA's, SCE's, MN measured pre,post, end of spray season	Wilcoxon rank sum, ANOVA	CA's ^ .79% E, .067% and .055% C; MN^ pre-post 5.41vs 39.92, control 0;SCE NS	5,5
Kaioumova 1998	19 Russian pest workers, 36 NE controls, 21 local controls	workers prev. made 2,4,5-T switched to 2,4-D 1987	none	CA's in PBL	t-test	CA's 4.47% workers, 2.18% and 2.29% controls	4,3 all groups CA's higher than

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
							normal (1%)-?diet
Kourakis 1996	Exposed 56 Controls 30	Organophos Carbamates Dithiocarbamates Organochlorine No protective gear Indoor + outdoor used same pest's	Age, sex Smoking – NS	CA's in PBL	Chi Sq.	E xp. 2.66% Cont .53% (.001 Indoor/outdoor 3.37% 1.88% indoor-industrial 3.37 non-industrial 2.14%	4,4 Lack of exposure measurement
Lander 2000	116E greenhouse floriculturists 29 NE non-smokers	# sprays/mo., what pesticide, use of protective gear 50 pest's – 10 insect., 6 fungicide, 3 growth reg (most used)	Age, smoking, caffeine use, use of gloves for re-entry work after spraying	CA's	Log-linear regression	CA's pre/post 1.87% vs. 2.34% and 1.62% for controls .02,.05 RR=2.88 – not wearing gloves during re-entry	6,6
Lebailly 1998a	French farmers with pesticide exposures; control slides for assessment of Comet tail assay reliability	Timing and cumulative area sprayed;no info on type	Age, smoking,alcohol, medications,passive smoking	Hematologic parameters; comet tail assay for DNA damage	Anove, t-test	DNA damage –ve correlated with number of days since spraying; DNA damage higher in mid and end-spray season. Interaction for DNA damage between smoking and exposure (p<.0001)	4,5 Lab methods and controls good; exposure assessment weak.
Lebailly 1998b	55 enrolled 41 blood	1 day of spraying-4 groups each using a different pesticide	Use of protective equipment	comet tail assay, cell vaiblity, hematologic	Paired sample t-test pre-post 1 day exposure:	Increases in DNA damage with fungicide-insecticide	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
	sampled Volunteer French farmers	combination		parameters	Student's t and Wilcoxon	mixtures but not with triazine herbicide. Signif. trend (p<.01) between area sprayed and increased DNA damage.	
Mohammad 1995	22 Syrians: 9 sprayers(acute) 7dealers(chronic) 6 controls	-deltamethrin cepermethrin 3 hr./day sprayers -mixed yr.-round exp. dealers	controls non-smokers Acute vs chronic	CA's in PBL -spray group tested 3 X	Chi sq.	contols 4.9% dealers 15.28% Sprayers B 7.5% M 11.9% E 15.3%	5,4
Pastor 2001	49 Polish men occup exp 50 controls NE	% using each of 30 pest's deltamethrin 38% Duration, use of protective gear	age,smoking,diet , coffee alcohol	MN in PBL and buccal cells Miscarriage rate	t-test confounders linear regression	E = NE for MN in PBL and buccal cells Miscarriage C 2/49 E 11/50	4,4
Paz-Y-Mino 2002	41E men and women Ecuador 41 age+sex-matched NE living in same area	Type, duration , type of work activity	age and sex-matched; smoking not asked -duration of work -place of work	CA's in PBL, RBC cholinesterase	Chi sq for E vs NE; r for RBC chol./ CA's	88% E had reduced RBC chol. CA's 20.6% E and 2.7% NE (p<.001) r= -0.416 RBC chol vs CA's	6,5
Ramírez 2001	Exposed; 32 Women working in banana farms . Unexposed: 37	Mainly exposed to Imalzalile and Thiabendazole and chloropyriphol	Personal habits, exposure to chemical substances,	Genotoxic effect measure through the frequency of micronuclei in	Man-Whitney Wilcoxon test. Logistic regression.	There was no differences in micronuclei frequency between both groups.	4, 4 Low power but it is a interesting and useful study.

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
	women from the same region without occupational exposure to pesticides.	(Organophosphorus insecticide and fungicides). Questionnaire and Records (work process). Grouping by months of exposition.	medication, radiation and others.	cultured peripheral lymphocyts. _ Dichotomous: Present or absent.	Stratified analysis by months of exposure.	However, women who worked at the packagin plant and had still birth or spontaneus abortions were 1.45 times more likely to have an increased micronuclei frequency that their coworkers who lacked those disorders. Genetic susceptibility?	Mixed methods.
Ramírez 2002	58. 30 banana workers and 28 unexposed select "voluntarily"	Fungicide Imazalil and Thiabendazole and Insecticide OP Chlorpirifos. Questionnaire and data related with job.	Age, smoking, infectious diseases and X-Ray exposure.	DNA ruptures measure through comet assay. Double blind and laboratory quality control.	Only crude analyses. T-student, ANOVA and linear regression (simple)	Damage to single stranded DNA after working 5-15 years (R^2=0.12), it means lineal relation between exposure time and AND damage, but is crude.	4,4 Low power, mixed methods and crude analyses but is useful as a pilot study.
Varona 2003	31 exposed 30 unexposed (administrative) Women worker in flowers industry	Mixed. Insecticides 70.6%, fungicides 17.6% and herbicides 5.9%. Questionnaire and information related with work.	Demographic, clinics, socioeconomic, but they only used them for description, not for adjustment.	Cytogenetic Alterations (micronuclei and chromosome aberrations), DNA repair deficiencies.	Only crude analysis. Proportions and differences of proportions.	Exposed group had a significantly higher frequency of cells with chromosome aberrations and micronuclei ($p<0.05$). AC among normal	4,4 Low power and poor statistical analyses, but good design and quality control in

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
		Acetyl cholinesterase (AC).		Laboratory. Quality control		values and no differences between both groups.	the laboratory analyses. Useful for demonstrate that AC doesn't discriminate sub chronic exposure.

Table 2 Immunotoxic

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
Daniels 2001	190 PCP-exposed Germans,95 men,95 women - study done over 3-9 yr period after PCP banned in Germany	At least 6 mo. exp. to PCP-containing pesticide	None	28 measures of immune response-counts+stimulation assays	Spearman's rank,Wilcoxon's, Fischer's exact	More abnormalities if PCP blood > 10ug/l Blood PCP-ve assoc. with counts and +ve assoc. with # impaired stimulation tests	5,5
Phillips 2000	25 exp.children aged 4-7;25 age-matched controls	12-14 mo exp. to chlordane and /or heptachlor	sick vs. "well" exposed children Age-matched	8 cytokine profiles corresponding to 8 immune parameters tested 1 mo. post-exp.	t-test	Exp- cytokine abn vs controls signif .05 on 3/8 panels. Doctor visits over 1 yr. NS	6,5

Table 3 Genetic Polymorphisms

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
Au 1999	20 Costa Rican banana plantation workers,20 controls	6 currently used + all prev exposed to DBCP	genotype for detoxifying polymorphisms	CA's, DNA repair response,FISH assay	1-way ANOVA,t-test;Fischer's exact for genotype	CA's NS: E 1.6%,NE 1.3%. Slower repair response assoc. with poor detoxifying polymorphisms.	6,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
						Poor detoxifiers underepresented in farmers	
Hubble,1998	246 patients with Parkinson's screened; 43 met dx. criteria for Parkinson's disease with dementia (PD+D)	Unspecified-questionnaire+ structured interview	Age,gender, education,pesticide exposure, family Hx PD, poor metabolizer genetic polymorhism	Parkinson's disease with Dementia	Chi Square, t-test, multiple regression	Pesticide exp. in combination with poor metabolizer genetic polymorhism signif. asosoc. with PD+D (p<.032)	5,5
Infante-Rivard 1999	491 leukemia(ALL) cases and 491 controls ages 0-9 yr.-Quebec. Case-only genotyping study N=123	Mothers filled out questionnaire on pesticide exposures from 1 month preconception to birth, and birth to dx. Includes home and garden use, use on pets.	Maternal age, age,sex	OR,regression analysis	OR for ALL increases with # of pesticides used, and maternal frequency of use(OR's 3.0-4.2 for >5 times used) Case-only:Increases in interaction OR's with poor metabolizer genes and increased pesticide exposure		5,5

Chapter 7 — Dermatologic Health Effects of Pesticides

Skin is the primary route of exposure to pesticides, particularly while spraying, but also while handling pesticides in other ways. Excluding acute pesticide intoxications, the most common adverse effect of pesticides is said to be contact dermatitis (1).

Contact dermatitis caused by pesticide exposure can be of either irritant or allergic type, and as well as exposure to pesticides, other coexisting or predisposing factors are important. These include individual susceptibility, other work-associated exposures such as to plant materials, solvents, fuels, rubber, cleansers, creams, moisture, and cold temperatures, physical abrasion of skin, as well as pre-existing skin disorders. Plant-related dermatitis is likely more common than pesticide dermatitis. Skin effects can be acute or sub-acute on top of chronic for any of the above factors.

Nature of dermatology literature

We did not locate any systematic reviews of pesticides and skin effects nor any summaries of the actual prevalence of dermatitis. Eleven of the twelve primary studies found were of adequate quality; one was excluded because of a low methodological quality score. All were cross-sectional, and examined the prevalence of dermatoses attributable to pesticide exposure. Three studies examined referral-based populations and considered only the positivity of patch tests for pesticides. The others were population based but frequently lacked specific exposure data and adequate descriptions of the populations and selection methods. The agricultural groups were heterogenous including those working in general farming, floriculture, and fruit growing (including monocultures of products such as potatoes or bananas).

The most commonly described outcome was contact dermatitis but one study was of actinic keratoses. There were no Canadian studies, and the two US studies did not concern agriculture, but rather paraquat production and pet grooming applications (3, 7). The studies involved many types of exposures to various mixtures of organophosphates, carbamates and fungicides on most continents. Pesticides exposures varied depending on crop, climate, location, and regulatory requirements.

Methodological Issues

The most important difficulty with this area of study, with only cross-sectional data available, is the attribution of a “pesticide induced case” as distinct from the other coexisting, irritant and sensitizing exposures, especially to plants.

Contact allergic reactions are known for all pesticides tested except paraquat (9). Patch-tested subjects were also found to be allergic to various plant and other agricultural-based materials they had contact with, and studies which did not patch test for plants and other materials are difficult to interpret. Patch testing methods varied and standardized patch tests for many pesticides were not available. Patch tests can cause false positives due to irritation of the skin — the “excited skin syndrome.”

Exposure assessments in these studies were mainly based on self-reporting, questionnaires, job title, or area usage records. Only one of the studies (6) used a biomarker of exposure dose, RBC cholinesterase, and a graded system of exposure classification.

Prospective cohort studies would be most helpful in sorting out exposure relationships and also in avoiding underestimation of the true effect. Such underestimation is a problem in cross-sectional studies due to the "healthy worker effect," the variable nature of the dermatitis, and the possibility that farmers may not seek medical care for skin complaints.

Skin outcomes found

Prevalence of dermatitis in agricultural settings ranged from 12% to 68%, but this represents dermatitis from all coexisting exposures, and does not clearly attribute pesticide effects. Irritant plant effects appeared to be common in two studies of floriculture (9) and bulbs (2), with both studies showing some cases of sensitization to both plant materials and pesticides. The strongest association was identified by Cole et al. (6), who showed a dose–response relationship between dermatitis and years of fungicide exposure, or poor application practices in potato farmers.

Patch testing was carried out in several studies and showed variable rates of allergic sensitization to pesticides, particularly fungicides. Results of patch testing indicated pesticide sensitivity among workers ranging from 2% in floriculture (9) to 28% in banana cultivation (10), and probably varied with the type of pesticides in use.

Paraquat is known to be a highly irritant pesticide, and one study (4) reported skin rash or burn in 53% of applicators using backpack sprayers under conditions lacking in use of personal protective gear.

Relevance to Canadians

Studies in agricultural settings in other countries and climates, especially where protective gear is little used, are largely not generalizable to Canadian "environmental" exposures, but may apply in some agricultural settings. Many of the pesticides examined, for instance, the insecticides carbofuran and methamidophos, are restricted or little used in Canada. Unfortunately, we found little specific data found in our review on pyrethroids, which are commonly used in Canada. In an American study rashes were reported in pet groomers who did more than 75 pyrethroid applications per month (3).

As dermal exposure and absorption of pesticides can occur, practices such as use of protective gear and/or washing well soon after intentional exposure are essential. A rash from an acute exposure to a pesticide may possibly be the only clinical indicator that a person has been exposed.

Irritant and/or allergic skin effects of pesticides are potential problems, depending on the type of pesticide and individual susceptibility, both constitutional and due to coexisting environmental circumstances. The prevalence of this problem in Canada, even among the occupationally exposed, has not been studied. It can be assumed that sub-populations such as allergic individuals may develop irritant dermatitis from applications or residues of pesticides, most likely in an occupational setting, however the extent of the problem is unknown.

Chapter 7 — Dermatologic Health Effects of Pesticides

References

Review Study: not systematic

1. *Spiewak R. Pesticides as a Cause of Occupational Skin Diseases in Farmers.* Ann Agric Environ Med *2001;8:1–5.*

Primary Studies

2. Bruynzeel DP, de Boer EM, Brouwer EJ, de Wolff FA, de Haan P. Dermatitis in bulb growers. *Contact Dermatitis* 1993;29:11–15.
3. Bukowski J, Brown C, Korn LR, Meyer LW. Prevalence of and potential risk factors for symptoms associated with insecticide use among animal groomers. *J Occup Environ Med* 1996;38:528–534.
4. Castro-Gutierrez N, McConnell R, Andersson K, Pacheco-Anton F, Hogstedt,C. Respiratory symptoms, spirometry and chronic occupational paraquat exposure. *Scand J Work Environ Health* 1997;23:421–427.
5. Cellini A , Offidani A. An epidemiological study on cutaneous diseases of agricultural workers authorized to use pesticides. *Dermatology* 1994;189:129–132.
6. Cole DC, Carpio F, Math JJ, Leon N. Dermatitis in Ecuadorean farm workers. *Contact Dermatitis* 1997;37:1–8.
7. Cooper SP, Downs T, Burau K, Buffler PA, Tucker S, Whitehead L, Wood S, Delclos G, Huang B, Davidson T. A survey of actinic keratoses among paraquat production workers and a nonexposed friend reference group. *Am J Ind Med* 1994;25:335–347.
8. Guo YL, Wang BJ, Lee CC, Wang JD. Prevalence of dermatoses and skin sensitisation associated with use of pesticides in fruit farmers of southern Taiwan. *Occup Environ Med* 1996;53:427–431.
9. Paulsen E. Occupational dermatitis in Danish gardeners and greenhouse workers (II). Etiological factors. *Contact Dermatitis* 1998;38:14–19.
10. Penagos HG. Contact dermatitis caused by pesticides among banana plantation workers in Panama. *Int J Occup Environ Health* 2002;8:14–18.
11. Rademaker M. Occupational contact dermatitis among New Zealand farmers. *Australas J Dermatol* 1998;39:164–167.

Excluded Study

12. Bener A, Lestringant GG, Beshwari MM, Pasha MAH. 1999. Respiratory Symptoms, Skin Disorders and Serum IgE Levels in Farm Workers. *Allerg Immunol (Paris)* XXXI(2):52–56.

Chapter 7 — Dermatologic Health Effects of Pesticides

Table

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes & Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
Bruynzeel (1993)	The Netherlands. 103 bulb growers and employees exposed to pesticides for more than 10 years . 49 controls were not employed in the bulb growing industry. Age matched, all male.	Self-report/ questionnaire, records 50 different pesticides, mostly soil disinfection		HX & PHYS EXAM: major dermatitis (eczema: erythema, papules, vesicles fissures) or minor dermatitis (ery-thema, slight chapping, scaling). PATCH TESTS for pesticides & bulb extracts.	Chi square	Hx of pesticide related skin complaints in 13 of 103 growers. Minor dermatitis in 30% of the bulb growers and 8% of controls, P < 0.01, most likely attributed to narcissus sap.	2.4 CHANGED to 4,4 (only useful data is prevalence of approx. 9% by history alone of pesticide related symptoms)
Bukowski J et al (1996). "Prevalence of and potential risk factors for symptoms associated with insecticide use among animal growers" in *Journal of Occupational & Environmental Medicine*, 38, 528–534	New Jersey, USA; 278 veterinary and licensed pet pesticide applicators, 75 % female, age 35 (17–70) Population was 28% of those who received anonymous, volunteer, mail in survey.	OP/Carbamate and pyrethrins Self-report /questionnaire	Age, sex, types of pesticides, types of, and numbers of applications, protective usage, applicator status	Surveyed for 17 symptoms potentially ass'd with pesticide exposure.	Univariate analysis & chi square for symptoms. Logistic regression for ORs of risks of sx.	Prevalence of rash 15.7%. For skin symptoms >75 Pyrethroid treatments the OR was 2.04 (1.02–4.09). For eye symptoms, highest quartile total treatments per season, the OR was 4.75 (1.14–18.23)	4,4 (CHANGED was 5, 2/3) (several confounders were uncontrolled, view cautiously)
Castro-Gutierrez N et al (1997).	Nicaragua	Paraquat	Hx of skin rash/burn,	Proportion of exposed workers reporting		53% of exposed workers reported rash/burn from	5,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes & Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
"Respiratory symptoms, spirometry and chronic occupational paraquat exposure" in *Scandinavian Journal of Work, Environment, & Health*, 23, 421–427	134 paraquat knapsack sprayers on banana plantation and 152 unexposed workers, M and F	Self-report /questionnaire based on 24 cumulative months. Rash or burn used as surrogate for exp. Intensity.	unexposed, low exposed, high exposed, age, sex	having experienced a skin rash or burn from paraquat exp proportion of exposed workers reporting having experienced a skin rash or burn from paraquat exp		paraquat exposure. Epistaxis 25%, nail damage 58%, eyes splashed 42%.	
Cellini A and Offidani A. "An Epidemiological Study on the Cutaneous Diseases of Agricultural Workers Authorized to use Pesticides" in *Dermatology* 1994;189:129–132	Italy 426 agricultural workers authorized to use pesticides & 100 matched controls subjects described as "the entire rural population"	No data other than "agricultural workers authorized to use pesticides," and "many" reported systemic sx due to preparation, application & after use of pesticides	——	History of dermatoses & link to biological, plant or pesticide causes & exam by 2 dermatologists for prevalence of skin disorders. Patch tests but no specific data.	——	Sx reported from use of pesticides, eyelids: 2.5%, conjunctiva: 6.5%, tearing: 2%, irritative dermatitis hands: 1%, red face: 1%, itching lips: 0.4%, Contact dermatitis of mixed causes was seen in 12% cases vs 6% control.	4,4 Only value is prevalence data on agricultural contact dermatitis
Cole DC et al (1997). "Dermatitis in Ecuadorean farm workers" in Contact Dermatitis, 37, 1–8	Ecuador From a farm population census, potato farm workers: 123 applicators, 28 exposed field workers, 23 consumers. 72 urban age, sex, education	Fungicides: 80% maneb. Insecticides: (both restricted in Canada) 47% carbofuran, 43% methamidophos 66 different pesticides in use. Self-report/ questionnaire, records, lab AChE	age, sex, education, other skin hx, solvent exp, # pesticide poisonings, AChE, exposure amount & type	clinical skin exam, hx of med dx'd skin/ allergic disorders dermatitis. If reported maneb aggravation-patch tests (n=17)	Chi square for difference in proportions of skin findings with exposures. Logistic regression	Dermatitis 68% of exposed, 55% applicators, 31% controls $p<0.001$. 5% positive to maneb patch testing. ORs for dermatitis per year using fungicides 1.12, indicating a dose response relationship from chronic fungicide exposure.	6,6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes & Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
	matched controls	levels, other tests.			for predictors and ORs.		
Cooper SP et al (1994). "A survey of actinic keratoses among paraquat production workers and a nonexposed friend reference group" in *American Journal of Industrial Medicine*, 25, 335–347	Texas All 112 paraquat production plant workers and 232 matched friend controls 80% male	Intermediates in paraquat production, in closed automated plant with prob low exposure. Technicians rotated through stages. Exp classification system graded 1–6 used as well as duration.	workers, friends, high & low exposure age, skin type (Fitzpatrick), freckling before age 16, tanning past yr, sunscreen, residential sun exp as adult, PAH occupational exposure	Blinded, full body derm exam for presence of 1 or more actinic keratoses on sun-exposed body areas excluding the trunk, (endpoint 1) and 2 or more (endpoint 2)	prevalence proportions and likelihood ratio. chi -square and logistic regression	Prevalence proportion endpoint 1, friends 0.28, workers 0.30; for endpoint 2, friends 0.2, workers 0.20. On regression, endpoint 1, OR for high exposed was 1.9 (CI 0.9–4.2), and for endpoint 2, OR was 2.2(CI 0.9–5.3).	5, 5/6 well done study but non sig effect of exposure on health outcome. Exp may have been low. Not generalizable in comm. exposure sense.
G uo YL et al (1996). "Prevalence of dermatoses and skin sensitisation associated with use of pesticides in fruit farmers of southern Taiwan" in *Occupational and Environmental Medicine*, 53, 427–431	Taiwan 122 fruit farmers from Fruit Farmers Production Assoc'n and 63 printer controls. Included all member farmers from 3 of 6 villages, randomly selected.	Ops, carbamates, glyphosate, paraquat, others. Some use still of banned toxic Captofol, Folpet and Captan Self-report/questionnaire	Sensitized farmers, sensitized controls, patch test agents, farmers, controls, allergic reaction	skin diseases & sxrandomly selected from all members of the Fruit Farmers Production A by hx, derm exam, photographs of hands (for blinded confirmation) & patch tests	chi square	Farmers dermatitis 30.3%; farmers sensitized to agri chemicals 40%, controls 19%, p=0.004, but most frequently to the 3 banned fungicides. No dermatitis prevalence for controls provided.	5,3 CHANGED to 4,4
Paulsen E (1998).	Denmark	Self-report /questionnaire	——	Clinical exam for eczema and patch	——	13 of the 250 with skin symptoms had positive	4,2/3

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes & Measurement (for non-cancer papers)	Statistical Analysis	Measures of Association and Values	Global Rating
"Occupational dermatitis in Danish gardeners and greenhouse workers (II). Etiological factors" in *Contact Dermatitis*, 38, 14–19	252 gardeners and greenhouse workers with occupational skin sx & 52 without invited from postal questionnaire from part I of study. Random selection of controls.	Only info is pesticide types based on recorded freq exposures #1, Bemonyl, #2 captan and #8 maneb		tests for chemicals and 9 plant families		reactions to fungicides, 10 to captan, 3 to maneb. Reactions to plants were far more common. Prev. reported prevalence of occup'nl dermatitis was 19.6%	CHANGED to 4,4 Need prior Paulsen paper, (really part I to this one) to obtain prevalence. This paper shows low sensitization from pesticides thus attributing derm effects to plants or other irritant effects.
Penagos H (2002) "Contact Dermatitis Caused by Pesticides among Banana Plantation Workers in Panama" in *Int J Occup Environ Health*, 8(1), 14–18	Panama 281: all the workers (field or packing station) with skin injuries who consulted the departments of occupational medicine of the 2 hospitals in the 2 districts.	Questionnaire aerial aerosols: propiconazole, maneb, chlorothalonil, dithane, and backback: dalaphon, ametrine, gramoxone. Packing station: imazilal, thiabendazole, $Al(OH)_3$, formaldehyde	——	Questionnaire, exam and patch tests for plant (banana leaf), standard series, and pesticide series customized for freq use in area.	——	Contact dermatitis was allergic with pos patch tests in 27.8%, mainly due to fungicides esp chlorothalonil. The remainder were irritant type dermatitis which can be due to irritant effects of pesticides. Pesticide patch trays are incomplete.	4,4 Useful to show proportion of contact dermatitis that is allergic, but patch testing may underestimate due to incompleteness or overestimate due to irritant effects of the patch.
Rademaker M (1998). "Occupational contact dermatitis among New Zealand farmers" in *Australasian Journal of Dermatology*, 39, 164–167	New Zealand 46 farmers referred for patch testing from a hosp based derm clinic	Records, none revealed except occupation as farmers	——	Patch tests for sensitivities to standard series, agricultural series and others	——	28 farmers (61%) had one or more positive patch test, 8 to fungicides inc $CuSO_4$, captofol, maneb, and mancozeb	4,2 CHANGED to 4.4 shows proportion of referred cases who have allergic component inc to pesticides

Chapter 8 — Neurological and Mental Health Impacts of Pesticides

Neurotoxic symptoms and signs have long been known to be important in acute poisonings with several chemical classes of pesticides, starting from the initial development of organophosphorus compounds as "nerve gases" for military use. Chronic effects have been less accepted, although over the past decade a number of studies have investigated them.

Study Types

We uncovered four relevant reviews: two included considerable animal and pathological data (2, 3), one gave a very useful overview of human case reports and epidemiological studies (1), and one was a systematic review on Parkinson's disease (PD) and pesticide exposure, which included a meta-analysis (4). We built on the meta-analysis by searching for omitted and more recent studies, and used the first three reviews as background.

We found 61 relevant reports of primary studies in the peer-reviewed literature in the four languages, from all continents of the world. Among these we judged 42 to be of sufficient quality to meet our review objectives (see Reference & Study column in the Tables 1–3, on health impacts; the table are organized by design, date of publication, and alphabetical order). In terms of epidemiological design and health impacts, one was an *ecological* study looking at rates of PD across counties in California. As found in the review of Colosio et al. (1), the majority, 28, were *cross-sectional* studies looking at function via symptoms including mental health, sensory capacities, neurobehavioural tests, and/or nerve conduction measures. However, eight were *case-control* studies, two focusing on mental health-related mortality and six on neurodegenerative disorders. Four *cohort* studies came from wealthier countries with adequate information systems for the long-term tracking of neurodegenerative disorders. Unfortunately, no intervention evaluations involving reduction of pesticide use and potential reversibility or improvement of neurotoxic effects were found. This is consistent with Keifer's (65) systematic review which primarily uncovered studies on exposure reduction with only a few of adequate quality documenting impacts on acute poisonings, and none on reductions in pesticide-related sub-acute or chronic effects.

Exposures Included

The majority of studies documented mixed human exposure to pesticides, both by use (insecticide, fungicide, herbicide, etc.) and chemical type (organophosphorus, carbamate, pyrethroids, dithiocarbamate-metal, etc.) (see Pesticides Type column in tables). Organophosphorus and carbamate compounds were most commonly studied in cross-sectional studies in keeping with their known neurotoxic effects. Cross-sectional studies were often able to include biological markers either of absorbed dose, such as herbicide or alkyl-phosphates in urine, or acute and sub-acute pathophysiological effects, such as acetylcholinesterase levels in blood (see Exposure Assessment notations in same column). Some studies did an exceptionally good job of documenting exposures to specific substances, e.g., exposure to fumigants by Calvert et al. (17). Surprisingly few studies of pyrethroids were found, consistent with Colosio et al. (1) who found only case series for their review.

Health Impacts

Mental & emotional impacts – Table 1

The four cross-sectional studies primarily focused on the mental and emotional impacts of pesticides are presented in Table 1a. One followed up on the subsequent effects of an acute spill in the community (5) which may have involved some generalized stress effects as well as chemical specific effects. Two found associations between an earlier pesticide poisoning and current minor psychiatric morbidity (6) or depression (9), in keeping with earlier case series involving follow-up of those experiencing a pesticide poisoning (67). Unsettlingly, Keifer et al. (7) found that substantially higher proportions of residents — including adolescents — who were often subject to drift from aerial spraying, had mental and emotional symptoms compared with those who were not subject to such drift, consistent with other studies of broader nervous system function listed in Table 2. Further, the two case-control studies (Table 1b.) found some evidence of an association between pesticide use and suicide among Canadian farmers (8) and death from mental disorders (particularly neurotic disorders of women) among the US population with occupations involving pesticide exposure (10).

Functional nervous system impacts – Table 2

Very wide ranges of remarkably sophisticated physiological, sensory, motor, cognitive, and emotional tests have been applied in cross-sectional studies (Table 2) to determine associations between pesticide exposures and functional impacts in a wide range of populations globally. Analytically, most of the acceptable studies measured and controlled for covariates that might also affect nervous system function.

Associations between previous pesticide poisonings, particularly from organophosphates and carbamates, and decrements in current function are most consistently positive. A number of newer studies tried to separate effects associated with past pesticide-related illness from current exposure, often successfully (e.g., Wesseling et al., 46). Yet distinctions between the effects of chronic or cumulative exposure and current intensity of exposure were harder to make, except when organophosphorus compounds were of primary interest and cholinesterase levels could be used as a surrogate for current and sub-acute exposures. Associations between exposure and both cholinesterase levels and neurological decrements, see e.g., Ernest et al. (23), are indicative of current exposure effects; however, depressed cholinesterase levels, accompanied by significant deficits among the exposed, is indicative of chronic effects, see e.g., Srivastava et al. (40). Unfortunately for many exposed populations, such as Ecuadorian farm families (18, 19), mixed past poisoning, cumulative exposure, and current work and home exposures are overlaid. Further, maternal, in-utero, and early childhood exposures are likely all involved in producing neuro-developmental effects in pre-schoool children in such pervasive exposure situations as Mexican valley agriculture (28).

Those with greater exposures, including the occupationally exposed such as termiticide applicators (20) or farmers who frequently handle concentrates (36), also more consistently show decrements in function. Neurobehavioural and neuropsychological testing that is more integrative more consistently detects differences between pesticide exposed and non-exposed groups. Together, these studies provide important evidence of subclinical effects of pesticides on the nervous system that may become manifest in a smaller proportion of clinical cases.

Neuro-degenerative impacts - Table 3

The studies on neurodegenerative outcomes included one ecological study (Table 3.a), two case-control studies (Table 3.b), and four cohort studies (Table 3.c) where Parkinson's disease (PD) was the outcome. In terms of exposure, some studies focused on herbicides but most examined mixtures of occupational exposures. Health outcomes ranged from PD on clinical examination, through adjusted PD hospitalization incidence, to deaths from PD. Nevertheless, all found positive associations between exposure and PD measures. Combined with the earlier review (4), overall 8 + 7 = 15 of the published 19 + 7 = 26 studies of pesticide–PD associations have been significantly positive. Given that some of the newer studies reported here had measures of effect that were higher, e.g. RR 5.6 in Baldi et al. (14), and some lower, e.g. SHR for PD = 130 in Tuchsen et al. (45), than the combined odds ratios in Priyadarshi et al. (4), the range of 1.8 to 2.5 in different parts of the world would likely be little changed. These data provide remarkably consistent evidence for a relationship between PD and past occupational pesticide exposure.

One case-control study among PD patients found that a genetic marker–pesticide interaction was positively associated with the dementia subtype of PD (29). One case-control (26) and one cohort study (14) focused on Alzheimer's disease (AD). Although the former did not find associations with any pesticide exposure measures, the latter did among men. The one case-control study on amyotrophic lateral sclerosis (ALS) (33) found consistently elevated adjusted odds ratios for pesticide exposure among both genders. Hence, evidence of other neurodegenerative effects of pesticides is also accumulating.

Relevance and Implications

We uncovered a remarkable consistency of findings of nervous system effects of pesticide exposures from pathophysiological and functional tests, through clinical examinations, to health care use and mortality data. Further, the time course varied from current exposures through past poisonings to lifetime occupational exposure. Strikingly, only two studies including effects on children were found (7, 28), despite the considerable concern about pesticide effects on sensitive populations such as inner-city children (66). Nevertheless, the findings in children were consistent with those found in working age adults and seniors.

Taken together, the research provides sufficient evidence supporting the reduction of exposure by known methods in occupational settings (65). It also supports reductions in use in other settings, though fewer studies exist of non-occupational exposure. The extent to which particular pesticides should be prioritized for reduction in use is difficult to ascertain, given that mixed exposures were by far and away the most common types found in epidemiological studies. Linkage with animal studies, clinical case literature, and other sources of information on particular pesticide use and toxicity would be required to initiate such work.

Chapter 8 — Neurological and Mental Health

References

Review Studies:

1. Colosio C, Tiramani M, Maroni M. 2003. Neurobehavioral effects of pesticides: state of the art. *Neurotoxicology* 2003;24:577–591.
2. Eriksson P, Talts U. Neonatal exposure to neurotoxic pesticides increases adult susceptibility: a review of current findings. *Neurotoxicology* 2000;21(2):37–48.
3. Eyer P. Neurospychopathological changes by organophosphorus compounds – a review. *Hum Exp Toxicol* 1995;14:857–864.
4. Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of Parkinson's Disease and exposure to pesticides. *Neurotoxicology* 2000;21:(4):435–440.

Primary Studies:

I. Mental Disorders

Note: Some of the following may appear in the Nervous System Disorders list.

5. Bowler RM, Mergler D, Huel G, Cone JE. Psychological, psychosocial, and psychophysiological sequelae in a community affected by a railroad chemical disaster. *J Trauma Stress* 1994;7:601–624.
6. Faria-Neice M, Facchini LA, Fassa AG, Tomasi E. [A cross-sectional study about mental health of farm-workers from Serra Gaucha (Brazil)]. [Portuguese]. *Rev Saude Publica* 1999;33:391–400.
7. Keifer M, Rivas F, Moon JD, Checkoway H. Symptoms and cholinesterase activity among rural residents living near cotton fields in Nicaragua. *Occup Environ Med* 1996;53:726–729.
8. Pickett W, King WD, Lees RE, Bienefeld M, Morrison HI, Brison RJ. Suicide mortality and pesticide use among Canadian farmers. *Am J Ind Med* 1998;34:364–372.
9. Stallones L, Beseler C. Pesticide poisoning and depressive symptoms among farm residents. *Ann Epidemiol* 2002;12:389–394.
10. van Wijngaarden E. Mortality of mental disorders in relation to potential pesticide exposure. *J Occup Environ Med* 2003;45(5):564–568.

II. Nervous System Disorders

Note: Some of the following may appear in the Mental Disorders list.

11. Amado F, Carvallo B, Silva JI, Londono JL and Restrepo H. Prevalencia de discromatopsia adquirida y exposicion a plaguicidas y a radiacion ultravioleta solar. *Rev Fac Nac Salud Publica* 1997;15(1):69–93.
12. Ames RG, Steenland K, Jenkins B, Chrislip D, Russo J. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. *Arch Environ Health* 1995;50:440–444.

13. Baldi I, Filleul L, Mohammed-Brahim B, Fabrigoule C, Dartigues JF, Schwall S, Drevet JP, Salamon R, Brochard P. Neuropsychologic effects of long-term exposure to pesticides: results from the French Phytoner study. *Environ Health Perspec* 2001;109:839–844.

14. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly. *Am J Epidemiol* 2003;157:409–414.

15. Bazylewicz-Walczak B, Majczakowa W, Szymczak M. Behavioral effects of occupational exposure to organophosphorous pesticides in female greenhouse planting workers. *Neurotoxicology* 1999;20:819–826.

16. Beach JR, Spurgeon A, Stephens R, Heafield T, Calvert IA, Levy LS, Harrington JM. Abnormalities on neurological examination among sheep farmers exposed to organophosphorous pesticides. *Occup Environ Med* 1996;53:520–525.

17. Calvert GM, Mueller CA, Fajen JM, Chrislip DW, Russo J, Briggle T, Fleming LE, Suruda AJ, Steenland K. Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. *Am J Public Health* 1998;88:1774–1780.

18. Cole DC, Carpio F, Julian J, Leon N. Assessment of peripheral nerve function in an Ecuadorian rural population exposed to pesticides. *Journal of Toxicology and Environmental Health, Part A* 1998;55:77–91.

19. Cole DC, Carpio F, Julian J, Leon N, Carbotte R, De Almeida H. Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians. *Neurotoxicol Teratol* 1997;19:277–286.

20. Dick RB, Steenland K, Krieg EF, Hines CJ. Evaluation of acute sensory-motor effects and test sensitivity using termiticide workers exposed to chlorpyrifos. *Neurotoxicol Teratol* 2001;23:381–393.

21. Engel LS, Keifer MC, Checkoway H, Robinson LR, Vaughan TL. Neurophysiological function in farm workers exposed to organophosphate pesticides. *Arch Environ Health* 1998;53:7–14.

22. Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT Jr., Scott KC, Hudnel K, Anger WK, Camicioli R. Parkinsonism and occupational exposure to pesticides. *Occup Environ Med* 2001;58:582–589.

23. Ernest K, Thomas M, Paulose M, Rupa V, Gnanamuthu C. Delayed effects of exposure to organophosphorus compounds. *Indian J Med Res* 1995;101:81–84.

24. Farahat TM, Abdelrasoul GM, Amr MM, Shebl MM, Farahat FM, Anger WK. Neurobehavioural effects among workers occupationally exposed to organophosphorous pesticides. *Occup Environ Med* 2003;60:279–286.

25. Fiedler N, Kipen H, Kelly-McNeil K, Fenske R. Long-term use of organophosphates and neuropsychological performance. *Am J Ind Med* 1997;32:487–496.

26. Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. *Environ Res* 2001;86:37–45.

27. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. *Neurology* 1998;50:1346–1350.

28. Guillette EA, Meza MM, Aquilar MG, Soto AD, Garcia IE. 1998. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. *Environ Health Perspec* 1998;106(6):347–353.

29. Hubble JP, Kurth JH, Glatt SL, Kurth MC, Schellenberg GD, Hassanein RE, Lieberman A, Koller WC. Gene-toxin interaction as a putative risk factor for Parkinson's disease with dementia. *Neuroepidemiology* 1998;17:96–104.

30. Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. *Neurology* 1997;48:1583–1588.

31. London L, Nell V, Thompson ML, Myers JE. Effects of long-term organophosphate exposures on neurological symptoms, vibration sense and tremor among South African farm workers. *Scand J Work Environ Health* 1998;24:18–29.

32. McConnell R, Keifer M, Rosenstock L. Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. *Am J Ind Med.* 1994;25:325–334.

33. McGuire V, Longstreth WT Jr., Nelson LM, Koepsell TD, Checkoway H, Morgan MS, van Belle G. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. *Am J Epidemiol* 1997;145:1076–1088.

34. Misra UK, Prasad M, Pandey CM. A study of cognitive functions and event related potentials following organophosphate exposure. *Electromyogr Clin Neurophysiol* 1994;34:197–203.

35. Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, Masaki KH, Blanchette PL, Popper JS, Foley D, Launer L, White LR. Plantation work and risk of Parkinson disease in a population-based longitudinal study. *Arch Neurol* 2002;59:1787–1792.

36. Pilkington A, Buchanan D, Jamal GA, Gillham R, Hansen S, Kidd M, Hurley JF, Soutar CA. An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers [comment]. *Occup Environ Med* 2001;58:702–710.

37. Ritz B,Yu F. Parkinson's disease mortality and pesticide exposure in California 1984–1994. *Int J Epidemiol* 2000;29:323–329.

38. Ruijten MW, Salle HJ, Verberk MM, Smink M. Effect of chronic mixed pesticide exposure on peripheral and autonomic nerve function. *Arch Environ Health* 1994;49:188–195.

39. Sack D, Linz D, Shukla R, Rice C, Bhattacharya A, Suskind R. Health status of pesticide applicators: postural stability assessments. *Journal of Occupational Medicine* 19993;35:1196–1202.

40. Srivastava AK, Gupta BN, Bihari V, Mathur N, Srivastava LP, Pangtey BS, Bharti RS, Kumar P. Clinical, biochemical and neurobehavioural studies of workers engaged in the manufacture of quinalphos. *Food Chem Toxicol* 2000;38:65–69.

41. Stallones L, Beseler C. Pesticide illness, farm practices, and neurological symptoms among farm residents in Colorado. *Environ Res* 2002;90:89–97.

42. Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. *Am J Public Health* 1994;84:731–736.

43. Steenland K, Dick RB, Howell RJ, Chrislip DW, Hines CJ, Reid TM, Lehman E, Laber P, Krieg EF Jr., Knott C. Neurologic function among termiticide applicators exposed to chlorpyrifos. *Environ Health Perspec* 2000;108:293–300.

44. Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H, Harrington JM. Neuropsychological effects of long-term exposure to organophosphates in sheep dip [comment]. *Lancet* 1995;345:1135–1139.

45. Tuchsen F, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981–1993. *Scand J Work Environ Health* 2000;26:359–362.

46. Wesseling C, Keifer M, Ahlbom A, McConnell R, Moon JD, Rosenstock L, Hogstedt C. Long-term neurobehavioral effects of mild poisonings with organophosphate and n-methyl carbamate pesticides among banana workers. *Int J Occup Environ Health* 2002;8:27–34.

Excluded Studies:

Studies noted with an asterisk were assessed as adequate quality but were included in the meta-analysis by Priyadarshi (4).

47. Amr MM, Halim ZS, Moussa SS. Psychiatric disorders among Egyptian pesticide applicators and formulators. *Environ Res* 1997;73:193–199.

48. Baer RD, Penzell D. Research report: susto and pesticide poisoning among Florida farmworkers. *Cult Med Psychiatry* 1993;17:321–327.

49. Bukowski J, Brown C, Korn LR, Meyer LW. Prevalence of and potential risk factors for symptoms associated with insecticide use among animal groomers. *J Occup Environ Med* 1996;38:528–534.

*50. Hertzman C, Wiens M, Snow B, Kelly S, Calne D. A case-control study of Parkinson's disease in a horticultural region of British Columbia. *Mov Disord* 1994;9:69–75.

51. Horowitz SH, Stark A, Marshall E, Mauer MP. A multi-modality assessment of peripheral nerve function in organophosphate-pesticide applicators. *J Occup Environ Med* 1999;41:405–408.

52. Jamal GA, Hansen S, Pilkington A, Buchanan D, Gillham RA, Abdel-Azis M, Julu PO, Al Rawas SF, Hurley F, Ballantyne JP. A clinical neurological, neurophysiological, and neuropsychological study of sheep farmers and dippers exposed to organophosphate pesticides [comment]. *Occup Environ Med* 2002;59:434–441.

*53. Jimenez-Jimenez FJ, MateoD, Gimenez-Roldan S. Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. *Mov Disord* 1992;7:149–152.

54. 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;65:163–169.

*55. Morano A, Jimenez-Jimenez FJ, Molina JA, Antolin MA. Risk-factors for Parkinson's disease: case-control study in the province of Caceres, Spain. [Review] [92 refs]. *Acta Neurol Scand* 1994;89:164–170.

56. Neuberger M, Rappe C, Bergek S, Cai H, Hansson M, Jager R, Kundi M, Lim CK, Wingfors H, Smith AG. Persistent health effects of dioxin contamination in herbicide production. *Environ Res* 1999;81:206–214.

57. Ngowi AV, Maeda DN, Partanen TJ, Sanga MP, Mbise G. Acute health effects of organophosphorus pesticides on Tanzanian small-scale coffee growers. *J Expo Anal Environ Epidemiol* 2001;11:335–339.

58. Richter ED, Chuwers P, Levy Y, Gordon M, Grauer F, Marzouk J, Levy S, Barron S, Gruener N. Health effects from exposure to organophosphate pesticides in workers and residents in Israel. *Israel Journal of Medical Sciences* 1992;28:584–598.

59. Salvi RM, Lara DR, Ghisolfi ES, Portela LV, Dias RD, Souza DO. Neuropsychiatric evaluation in subjects chronically exposed to organophosphate pesticides. *Toxicol Sci* 2003;72(2):267–271.

*60. Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology* 1996;46:1275–1284.

*61. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology* 1992;42:1328–1335.

62. Smith-Rooker JL, Garrett A, Hodges LC, Shue V. Prevalence of glioblastoma multiforme subjects with prior herbicide exposure. *J Neurosci Nurs* 1992;24:260–264.

63. Stokes L, Stark A, Marshall E, Narang A. Neurotoxicity among pesticide applicators exposed to organophosphates. *Occup Environ Med* 1995;52:648–653.

64. Vanacore N, Nappo A, Gentile M, Brustolin A, Palange S, Liberati A, Di Rezze S, Caldora G, Gasparini M, Benedetti F, Bonifati V, Forastiere F, Quercia A, Meco G. Evaluation of risk of Parkinson's disease in a cohort of licensed pesticide users. *Neurol Sci* 2002;23 Suppl 2:S119–S120.

Chapter references not listed above:

65. Keifer MC. Effectiveness of interventions in reducing pesticide overexposure and poisonings. *Am J Prev Med* 2000;18 Suppl 4:80–89.

65. Landrigan PJ, Claudio L, Markowitz SB, Brenner BL, Romero H, Wetmur JG, Matte TD, Gore AC, Godbold JH, Wolff MS. 1999. Pesticides and inner-city children: exposures, risks and prevention. *Environ Health Perspec* 1999;107 Suppl 3:431–437.

67. Savage EP, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar BJ. Chronic neurological sequelae of acute pesticide poisoning. *Arch Environ Health* 1988;43:38–45.

68. *Lawn and Garden Pesticides: A review of human exposure and health effects research*. Toronto: Toronto Public Health; April 2002.

Chapter 8 — Neurological and Mental Health

Tables

Table 1 Adequate Quality Studies of Mental & Emotional Health Impacts

1. a. Cross-sectional Studies (n=4)

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Bowler R et al (1994)	Residents of a community exposed to chemical spill in Northern California; controls from nearby community upstream from spill; N=334	Metam sodium; self-reported exposure	Cases and controls matched by age, education, gender, race, number of children; odour perception, litigation status	Structured clinical interview, self-administered questionnaire, impact of event scale, mood scale, env worry scale, perceived social support scale, perceived control scale, Minnesota Multiphasic Personality Inventory 2, profile of mood states-revised. Salivary cortisol, BP, pulse 30 min after initial clinical interview (high stress) and then after final exit interview, 2-3 hr later (low stress)	paired t-test, McNemar chi square	Greater levels of depression, anxiety, somatic symptoms in spill residents, greater environmental worry and lower perceived social support. Also higher systolic BP. Cortisol levels unchanged between high and low stress measurements in spill residents. Significant differences for those who perceived the odour on a number of scores and scales. Litigants differed from non-litigants on mood scale, IES scale, intrusion subscale of IES, social support (higher for all).	5.5
Keifer M et al., (1996)	100 residents 10 yrs and over, majority female each from an exposed rural community and a control urban community	Organo-phosphorus and pyrethroid compounds, Aerial spraying in last 15 days via questionnaire: sighting spray planes, 24% daily and 85% 3 or more in exposed community vs. 0 drifted upon by a spray plane 44% in exposed vs. 0% , crossed recently sprayed fields 57% vs 2%,	Age, sex, current smoking & drinking	Acute symptoms, modified Q-16 neurotoxic symptom questionnaire includes considerable mental & emotional symptoms, red blood cell cholinesterase level	ANOVA for differences in mean cholinesterase, chi-square for univariate proportions, Polychotomous logistic regression for symptom category	prevalence odds ratios significantly elevated for myriad of nervous system, mental and emotional symptoms. Adjusted prevalence odds ratios for residence in exposed community, by symptom categories: non-specific 1.6 (0.8-3.2), possible 4.1 (1.7-10.2), probable 9.9 (2.9-34.4)symptoms	4
Faria-Neice et	1282 farm workers from	Questionnaire identifying:	Sex, age, municipality,	Medicine use and psychiatric hospitalization record.	Kappa for concordance	Prevalence of MPM: 38% of the farm workers (34.9 – 40.2)	5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
al., (1999)	446 farms	– Hectares cultivated – Level of industrialization. – Equipment use.	marital status, ethnic group, years schooling	– Alcoholic (CAGE). – Work injuries. – and Minor psychiatric mordibity (MPM) based on SRQ-20 (self-report questionnaire of 20 items), cutoffs for women 8/20 abnormal, men 6/20	among interviewers. Adjusted rates. Conditional logistic regression for crude and adjusted OR.	"Pesticide poisoning (previous)" was strongly associated with MPM: OR 2.65 (1.83-3.86). For MPM in > 25 Ha, OR = 1.46 ($CI_{95\%}$1.07 – 8.98)	
Stal-Iones et al (2002)	Farm residents from 8 counties in Colorado; N=761	Organo-phosphates, other pesticides; self-reported illness from pesticide exposure in past 12 months	Gender, age, race, education, marital status, social support, negative life events, involvement in farm work, self-reported health status, ETOH use	Symptoms of pesticide poisoning; depression as assessed using Center for Epidemiologic Studes-Depression (CES-D) scale (16+ = clinical depression)	OR, conditional logistic regression	Depression associated with pesticide-related illness OR=5.87 (CI 2.56–13.44)	4

1.b. Case-control studies (n=2)

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Pickett W et al., (1998)	Canadian Farm Operators Cohort. N=13089 Cases committed suicide between 1971-87; controls matched for age and province.	Insecticides and herbicides; responses to 1971 Census of Agriculture; main variables were: 1) # of acres sprayed for control of insects; 2) # of acres sprayed for control of weeds; 3) $ spent on agricultural chemicals	21 variables from 1971 Census of Agriculture, including size of farm, type of agricultural practices carried out, financial characteristics of farm operation, also socioeconomic status, ratio of income to expenditures, single marital status, no reported agricultural sales, weeks of paid labour	Suicides reported in Canadian Mortality Database of individuals in the CFOC	OR, stepwise logistic regression	OR 1.71 CI (1.08-2.71) for 1-48 vs 0 acres sprayed of herbicides amongst those who had no hired help. No association for main analyses.	4.5
van Wijn-gaarden et al., (2003)	U.S. mortality detail files 1988-92; N=338,208	Usual occupation and industry as listed on death certificate; classified as exposed/unexposed based on occupational code (listed in paper).	Marital status, race, age, gender, geographic location	Death from mental disorder - cause of death from death certificate	OR, logistic regression	OR=1.46 (CI 1.33-1.60) for employment in jobs potentially involving pesticide exposure. Stronger among women, OR=2.65 (CI 1.89-3.71), especially for deaths from neurotic disorders, OR=4.3 (CI 2.4-7.6)	4.5

Table 2. Adequate Quality Studies of Functional Nervous System Impacts (all cross-sectional studies, n=24)

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Sack et al., (1993)	37 male volunteers from 102 pesticide applicators with 9 or more years of work in lawn care company, 35 volunteers nonexposed from U of Cincinnati community	Organo-phosphates, carbamates, organochlorine insecticides Chlorphenoxy herbicides	age, ethanol cigarette consumption, height, weight	– Detailed physical exam including neurological – postural sway testing with fixed, strain-gauge platform	bivariate correlation, multiple regression, stepwise regression analysis	– Sway length values significantly higher among exposed (p=.0001) – Exposure to pesticides (p=.0215) and recent Organophosphates exposure (p=.0391) associated with higher sway.	4
Ruijten et al., 1994	Exposed were flower bulb farmers in the Netherlands, controls were from general population; N=198	Zineb and maneb fungicides; exposure assessed by self-report, generating a personal exposure index	Age, alcohol consumption, education, physical work activity, socioeconomic status, growing flowers (in addition to bulbs)	Health symptoms questionnaire, autonomic nerve function (cardiotachogram - resting arrhythmia, forced respiratory sinus arrhythmia, muscle-heart reflex), peripheral nerve function (motor nerve conduction velocity, motor response amplitudes, distal latency of median and ulnar nerves, antidromic sensory nerve conduction velocity)	Z-scores, t-tests, ANCOVA, multiple linear regression	Decreased conduction velocities in motor fibers of median (-1.1m/s) and peroneal (fast fibers: -1.2m/s, slow fibers: -1.3m/s) nerves and in sensory fibers of median (-1.4m/s) and sural (-0.9m/s) nerves. Refractory period increased in sural and peroneal nerves. Decrease found in resting sinus arrhythmia (-10%)	5
Ames et al., 1995	Agricultural pesticide applicators in California with prior hx. of documented cholinesterase inhibition; controls were friends who did not work with pesticides brought by case subjects; N=135	Organophosphates and carbamates; used medical-supervision records to determine exposure	Age, ethnicity, BMI, education, test language	Nerve-conduction amplitude & velocity, vibrotactile thresholds, 8 tests from neurobehavioural evaluation system, Santa Ana dexterity test, pursuit aiming test, postural sway test	Multiple linear regression	No association found between exposure and impaired performance on tests	4
Mc-Connell et al (1994)	36 previously poisoned cases and	Poisoning by methamidophos and other	age, height, history of	Vibrotactile thresholds measured using Vibratron	Univariate & multi-variate	Vibration thresholds significantly increased in all tested areas, and	5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	36 age, sex & SE background matched controls	organo-phosphates via questionnaire	working with pesticides, recent alcohol consumption, history of solvent exposure, history of working with vibrating machinery, extent of callus formation	2	analysis Jonck-heere test for ordered categories comparing metha-midophos cases vs other OP cases vs controls	markedly more increased between methamidophos poisoned and other OP poisoning. (p<0.007)	
Misra et al., (1994)	32 pesticide workers engaged in spraying fenthion, 25 hospital employees matched for age, sex, education and SE status	fenthion, questionnaire on practices, AChE levels	age, sex, education, socio- economic status, nutritional deficiencies, drugs, alcohol, other previously diagnosed neurological disorders	– Med history and exam, – Neuropsychological tests, Benton Visual Retention Test, Weschler memory scale, Alexander Passalong test and the finger dexterity test	Student's T, linear correlation coefficient for relationship between AChe and others	Significantly poorer performance among exposed for: – Benton Visual Retention test (p<0.01), Weschler memory scale (p<0.05) and Alexzander Passalong test(p<0.01). – Serum AChE significantly reduced in exposed (p<0.01) – ERP: P3 latency of only 1 exposed was prolonged, however the group difference was significant (p<0.01)	4.5
Steen-land et al., (1994)	128 poisoned men and 90 non poisoned, non exposed, volunteers and their friends as controls	California surveillance data on pesticide poisoning, various organo-phosphates,	age, race, BMI, education, preferred language, hours of sleep, alcohol consumption the evening prior to the test, smoking habits, use of prescription RX, medical history, current exposure to	– Nerve conduction studies – Vibrotactile thresholds – 8 computerized neurobehavioral tests from the Neurobehavioral Evaluation System, version 4.22, – 2 non-computerized neurobehavioral tests of psychomotor function – computerized measurement of postural sway	Multi-variate linear regression	For all poisoned subjects: only significant for test of sustained visual attention (p=0.05). – For those with definite poisoning, vibrotactile sensitivity was ALSO significantly worse(p<0.05) – For those hospitalized, the symbol digit test (p=0.04) was ALSO significantly altered – Chlorpyridos and phosalone poisoned subjects showed some decrement in peripheral nerve function.(p<.05) – Signif. worse performance on 6	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			solvents or peseticides, coffee consumption the morning of the test.	– Standard neurological examination		tests by those who took > 1 day off from work (p<.05)	
Ernest et al., (1995)	34 all possible males in the subject group working in insecticide manufacturing plant, and 34 in the control	Organo-phosphorus compounds, questionnaire, length of exposure to pesticides, pseudo-cholinesterase activity,	age, noise levels in plant, past exposure in controls	Assessment of hearing impairment and pseudo-cholinesterase levels, liver functions, brain stem pathology and peripheral neuropathy, questionnaire and liver function tests, audiometry, EMG, brain stem auditory evoked responses and full neurological exam.	Student's T Test , Chi square analysis with Yates correction and Fisher's exact probility test	Correlations between exposure and: pseudo-cholinesterase (p<0.001), peripheral neuropathy (p<0.001) – No statistically significant difference by exposure group for EMG recordings & evoked brain stem auditory potentials	4
Ste-phens et al., (1995)	Exposed - 146 sheep farmers, every 10th farmer on the wool marketing board list Controls – 143 quarry workers	Organo-phosphates, questionnaire and urine test to rule out recent pesticide exposure	age, educactional level, laterality, lifetime ROH consumption, smoking habits, other substance abuse, recent viral infection, caffeine consumption, computer familiarity, first language, time of day of testing	neuropsychological functions- digit span for short term memory, Simple reaction time for sustained attention, symbol-digit substitution test for information processing speed, and category search for long term memory function.	ANCOVA	After adjusting for covariates, farmers significantly slower in performance of 3 tests: simple reaction time(p<0.0001), symbol digit substitution(p=0.04) and syntactic reasoning(p=0.04) – Significant effect of dose-response for syntactic reasoning test (p<0.0001)	6
Beach et al., (1996)	146 exposed sheep farmers and 143 unexposed quarry workers, selection based on symtomatology after	Organo-phosphates, questionnaire to calculate: avearage number of sheep in flock x number of dips a year x number of years using organo-	current or previous illnesses, medcns, family history of neuro disease,	acute toxicity symptoms, neurological symtoms, assessment by self report/ questionnaire and clincal neuro exam	Chi Square for categorical data or Kruskal Wallis test	Significant difference in 2 point discrimination of dorsum of hand(p=.011) and foot(p<.001) between symptomatic sheep farmers, asymptomatic sheep farmers and controls	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	dipping(10 most sx, 10 least and 10 controls	phosphates	alcohol, exposure to other neurotoxins..		for non-parametric data		
Amado et al., (1997)	154 flower + 139 textile = 293 workers	Questionnaire. Pesticide exposure (re-entry times, hygiene practices, safety practices. – sun exposure). Industry type, job type and job duration in flower production. Categories of exposure (only flowers vs. combined)	Age, Sex, Ultraviolet radiation.	Chromatic confusion index (CIC) for each eye. Obteined as average of the measurements of both eyes, resulting from the addition of the values from the corresponding table of Lonthony method.	Differences of prevalence (X2); OR crude and adjusted. Stratified analysis, OR_{MH}, weighted by age and sex.	Prevalence of dichromatopsy exposed: 59.1 Controls 50.4 p=0.07 (marginal) High exposure: 60.3% low exposure or no exposure : 50.0 p= 0.04 OR: Crude = 1.5 ORadj: 1.7 (1.04 –2.7)	4
Fiedler et al., (1997)	Exposed: tree fruit farmers; controls: blueberry/cranberry growers and hardware store owners; New Jersey; N=99	Organophosphates; exposure determined by occupation and self-report to generate exposure metric	Age, education, intellectual ability (as measured by Wide Range Achievement Test-Reading), years of farming	Neuropsych: Tests of concentration (simple reaction time for dominant and non-dominant hand, continuous performance, Stroop colour-word task), visuomotor coordination (hand-eye coordination - grooved pegboard, Trails A & B, digit symbol), verbal memory (California verbal learning test - List A total, digit span), visual memory (visual reproduction I & II, continuous visual memory), verbal ability (information), expressive and receptive language (animal naming, revised token test). Psych: MMPI-2	Student's t-test, covariate analyses, stepwise regression	Exposed TFF vs controls: increased simple reaction time, dominant hand F=6.83, p=0.01; non-dominant hand F=6.41, p=0.01. High exposed vs low exposed: increased simple reaction time, dominant hand F=5.61, p=0.02.	4.5
Cole et al.,	Pesticide applicators	Organophosphate &	Concomitant	Neurobehavioural Core	Univariate	Farm group performed worse on	5.5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
(1997)	in Ecuador, other farm workers, consumers, non-farm workers as controls; N=246	carbamate insecticides, dithiocarbamate fungicides; exposure determined by self-report and by farm records of pesticide usage	medical problems, EtOH, age, education, solvent exposure	Test Battery (Digit span, Benton visual retention, digit symbol, simple reaction time, Santa Ana, pursuit aiming test, profile of mood states), digit vigilance, Trails A & B, block design, Weschler Adult Intelligence Scale (information, similarities, vocabulary); grouped into attention, visuo-spatial, psychomotor, motor, affective	regression, linear regression	most tests	
Guillette, et al., (1998)	4 & 5 year old Yaqui children in two communities of Sonora, Mexico. Foothill (n=17) and valley (n=33)	Interviews with residents and farmers. Foothill annual DDT spraying, valley mixed organochlorine, organophosphorus, & pyrethroid compounds, 2 crops/year up to 45 applications/crop, daily household bug sprays	Diet, education, socioeconomic status broadly described for two communities. Maternal reproductive history individually	Rapid assessment tool for pre-school children included anthropometry, stamina and Developmental Scales (Bayley & McCarthy)	ANOVA valley vs. foothill, Scheffe's F tests	Among valley children, significantly lower stamina, ability to catching balls, fine eye-hand coordination, 30 minute recall, and ability to draw a person	4
Calvert et al., (1998)	123 exposed recruited from 40 fumigation companies (volunteer), 120 controls were recruited by fumigation workers: friends within 5 years of age and never exposed to pesticides	Fumigants, Sulfuryl Fluoride and Methyl Bromide principally	age, race, BMI, limb surface temperature, education , language in which test is taken, alcohol consumption, smoking	Questionnaire – Nerve conduction test – Vibration testing – 7 computer administered neurobehaviora tests from NES(Hand-eye coordination, Simple Reaction time, continuous performance test, Symbol digit test, Pattern Memory, Serial Digit Learning, Mood Scales) – NES vocabulary test	Student's t for continuous demo-graphic character-istics , Chi square to compare categorical demo-graphic charac-teristics and	No diff between groups for chronic bronchitis, urinary protein concentrations, color vision test or postural sway test – Significant deficits on smell test particluarly among those exposed to sulfuryl fluoride (p=0.03) – Significantly lower performance of exposed in Santa Ana test of perferred hand (p=0.03) – Significantly reduced nerve conduction velocity of the median motor nerve in the forearm (p=0.02)	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
				– Santa Ana Dexterity – Postural sway testing, – Contrast sensitvity via Pelli-Robson chart, – Color visitin with Farnsworth D-15 panel, - Olfactory function with U of Pennsylvania Smell Identification Test. – Spot unine – Chronic bronchitis evaluation with questions by ATS – Neuro exam by MD for gross neuro abnormalities not related.	outcomes, Fisher exact when expected table frequencies <5, multiple linear regression.	– Pattern Memory the only computer neurobehavioral test which exposed did significantly worse that control (p=0.05)	
Cole et al., (1998)	Pesticide applicators in Ecuador, other farm workers, consumers, non-farm workers as controls; N=246	Organophosphate and carbamate insecticides, dithiocarbamate fungicides; exposure determined by self-report and by farm records of pesticide usage	Age, concomitant medical conditions, past pesticide poisonings, EtOH use, height, years using solvents, callus, air temperature, potato intake, BMI	Symptom questionnaire, neuro exam (standard protocol - finger-nose, heel-ankle, Romberg, Mingazini, gait, deep tendon reflexes, power, deep sensation, vibration sensation)	Polytomous logistic regression, multiple linear regression	Applicators had more current PNS symptoms (OR=3.1), signs of poor coordination (OR4.3), abnormal deep tendon reflexes (OR=2.9), reduced power (OR=2.1), higher toe vibration thresholds (beta=0.035)	5.5
Engel et al., (1998)	67 Hispanic farm workers and 68 age, gender, ethnicity and education matched controls, volunteer sample	Thinners were exposed primarily to azinphosmethyl and possibly to phosmet or methyl parathion, questionnaire and serum erythrocyte cholinesterase activity. Timing of thinning relative to testing, use of	age, gender, height, other (non-thinning)farm work performed in current season, history of farm work, history of	Mean cholinesterase activity: mean diff of -1.4(95%CI = -2.5, -0.3, p=.01) Sensory and motor nerve functions as well as neuromuscular junction testing, assessment via electrodes	Conti-nuous outcomes using Student's T test and multiple regression. Dicho-tomous	dose-response relationship between thinning hours and any neuro-physiological measure (p=.20)	6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		protective clothes and practices, number of days work clothes were worn between washing, and frequency of bathing.	working with pesticides, proximity of the home to nearby farms, use of pesticides in or around the home, alcohol and tobacco use.		outcomes – prevalence ratios via stratified analysis		
London et al., 1998	Fruit farms belonging to 3 large cooperatives; exposed were applicators, controls were other workers; South Africa; N=247	Job-exposure matrix to take into account lifetime direct and indirect exposures; plasma cholinesterase as biological marker of recent exposure; also considered potential exposure to pesticides at home	Age, height, education, numeracy, visual acuity, alcohol intake, past pesticide poisoning, recent OP exposure, nonoccupational residential exposure, long-term occupational OP exposure	14 symptoms, vibration sense (Vibatron II), static motor steadiness, dynamic steadiness, motor tremor, neurobehavioural test battery	Chi-square, OR; Linear and logistic regression	OR for high score for neurological symptoms: past pesticide poisoning 4.08 (1.48–11.22), current applicator 2.25 (1.15–4.39)	5.5
Bazylewicz-Walc-zak et al., (1999)	Garden enterprise employees in Poland; cases worked in greenhouse, controls worked in other jobs; N=51	Organophosphates (Dichlorvos, Methamidophos, Methidathion, Pirimiphos-Methyl), carbamates, synthetic pyrethroids, dithiocarbamates; pesticide exposure determined by air sampling, measuring pesticide concentrations on clothing, skin washes	Age, education, smoking, alcohol, drugs	Polish adaptation of The Neurobehavioral Core Test Battery: 6 tests of cognitive and psychomotor functions (Simple Reaction Time, Digit Symbol, Digit Span, Benton Visual Retention, Santa Ana, Aiming) and 2 symptom questionnaires (Profile of Mood States, Finnish Subjective Symptoms Questionnaire)	ANOVA	Fatigue: F=2.71, p=0.10 for increase in fatigue for exposed compared to controls, over time; GI Sx: F=5.63, p=0.02 for increase in GI Sx for exposed compared to controls, over time	4.5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Steen-land et al., (2000)	Current and former termiticide applicators in North Carolina; controls were friends and blue-collar state employees; N=380	Chlorpyrifos; exposure assessed by self-report, urine TCP	Age, race, education, smoking, BMI, prior night's hours of sleep, prior night's alcohol consumption, current exposure to solvents, coffee consumption day of tests, history of diabetes, carpal tunnel syndrome, nerve disorder, nerve injury, back disorder.	Neurobehavioural evaluation system, vibrotactile test, arm/hand tremor, postural sway, manual dexterity, eye-hand coordination (Trails A and B), vision (acuity, contrast sensitivity, colour vision), olfaction, nerve conduction velocity, clinical neurologic examination, 24-item questionnaire; also did subgroup analyses (workers currently applying, workers formerly applying, workers with self-reported poisonings)	Linear regression, logistic regression	Poisoned group significantly worse on sustained attention & mood. Hospitalized cases had significantly lower vibrotactile sensitivity.	5.5
Srivas-tava et al., (2000)	59 exposed workers in pesticide manufacturing plant, and 17 controls not engaged in production or handling.	Quinalphos and various other chemical compounds used in it's prodution, questionnaire and AChE levels	age, work history, physical activity at work, gender, social charac-teristics, use of cigarettes, alcohol	– Detailed clinical history – Detailed neurological examination – Lab work – Neurobehavioral tests: Digit span, Digit symbol test, Bourdon Weirsma vigilance test.	Student's t test, chi-square and Fisher's exact test	– AChE values in exposed (24.27 +/-11.21) vs non exposed (24.21=/-12.60) – Significantly ($p<0.05$) more complaints of weakness, abnormal plantar and Ankle reflexes, and poorer performance on memory, learning & vigilance testing.	4
Baldi I et al (2001)	Vineyard workers in Gironde, France; convenience sample; N=917	Mainly fungicides; exposure measurement by work records	Demographics, education, smoking, EtOH, environmental pesticide exposure (e.g. drinking well water), depression, use of psychotropic	Battery of 9 neuro-psychological tests	chi-square, multivariate logistic regressions	Adjusted risks of low performance for directly exposed vs. non-exposed: OR=3.5 for BVRT; OR=3.1 for TMT-B; other tests, OR=1.4-3.0	6

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			drugs, current exposure				
Dick et al., (2001)	Current termiticide workers who reported using chlorpyrifos-containing products within past 3 weeks; controls were same-gender friends of cases; North Carolina; N=158	Chlorpyrifos (OP) – e.g. Dursban TC, Equity, Cyren TC; exposure determined by urinary TCP concentration	Age, wt, ht, BMI, gender, ethnicity, education, tobacco use, EtOH, diabetes, high BP, depression, neck/back disorder, neurologic problems, serious injury to nervous system, carpal tunnel syndrome	Sensory tests: cross-cultural smell identification test, visual acuity and functional acuity contrast sensitivity test, Farnsworth D-15 and Lanthony D-15d color vision tests, vibrotactile threshold. Motor tests: arm-hand tremor test, grooved peg board (manual dexterity), trail-making test (eye-hand coordination), sway (postural stability)	Linear regression model with Bonferroni correction	Color vision (Lanthony) increased for L (p=0.001) and R (0.041) in relation to TCP; Postural sway increased for HEC-Length (p=0.000), SEO-Length (p=0.032), SEC-Length (p=0.000), SEC-Area (p=0.000) in relation to TCP	4.5
Pilking-ton et al., (2001)	Expose: English and Scottish sheep dippers; controls: non-sheep dipping farmers, ceramic workers; N=772	Organophosphates; exposure assessed by self-report of practices, including handling of concentrate	Age, sex, alcohol, country,	Symptom questionnaire (motor, sensory, autonomic), quantitative sensory tests (heat, cold, vibration)	OR, Linear logistic regression, multiple linear regression, generalized additive models	Elevated adjusted odds ratios for concentrate handling and symptoms (p=0.005), with majority of effect among small group of highly exposed concentrate handlers	4
Wesse-ling et al., (2002)	Poisoned identified by compulsory occupational accident reports to the Nat'l Insurance Institute.Of the 162, 94 were identified.-81 of 82 eligible participated (mean # months since poisoning =27, range 12-43)	Poisonings from organo-phosphates and carbamates. Controls via questionnaire ; some with varying exposures to pesticides, others without any exposure.	age, education, ROH, smoking, other solvents exposure, visual acuity, history of loss of consciousness, history of convulsions, other neuro or psychiatric	Neurobehavioral functionning among those with past mild poisoning vs non history of poisoning, via: Memory testing(Visual via Benton visual retention; Verbal via Rey verbasl learning), Attention(Visual via Digit Vigilance; Verbal via Dibit Span), Psychomotor	multiple linear regression analysis	-Poisoned group performed less well in 13 of 14 tests. -Significant difference for Digit symbol (p<0.05), Questionnaire 16 and Brief symptom inventory (P<0.01) -Significant differences in Questionnaire 16 and BSI among those poisonned with OP, but not with those poisoned with Carbamates	5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	Random selection of control subjects = 130 (10 refusals) from banana plantations		conditions, malaria, chronic metabolic or infectious diseases, current use of Rx, hours of sleep night before testing, sense of well-being and liquor, caffeine intake on the day of testing.	(Coordination via Santana dexterity; Steadiness via Pursuit aiming 2, Speed via Finger tapping, Reaction via Simple reaction time), Visuomotor (Coding via Digit-symbol, Planning via Trails-A, Problem solving via Block design), Language via Vocabulary and Neuropsych. symptoms via Questionnaire-16, affect via Brief symptom inventory (BSI)		-Worse performance among those exposed recently to pesticides, although not significant.	
Farahat et al., (2003)	52 exposed matched by age, SE class and years of education (>=12) to controls.	OP pesticides, questionnaire assessment	age, smoking, BMI, education, coffee consumption	Clinical examination incl. neurological testing of cranial nerves, motor system, reflexes sensory system. Neurobehavioral tests: Similarities, Digit Symbol and Trailmaking part A and B, Block Design, Paced Auditory Serial Addition Test, Letter Cancellation, Digit Span, Benton Visual RetentionTest, Story Recall parts A and B, Eysenck Personality Questionnaire – serum AChE	multiple regression analysis, Holm's modifi-cation of the Bonferroni correction for multiple compa-risons.	AChE significantly lower in the exposed (p=.0001), -Significantly lower performance among exposed on Similarities (P=0.003), Digit Symbol (p=0.001), Trailmaking A(p=.03) and B (p=.015), Letter Cancel (p=0.037), Digit Span Forward (p=0.037) and Backward (0.003), Benton (p=0.003) -Significant trend towards lower performance as duration of exposure rose for many tests -Neuro symptoms of dizziness and numbness were significantly higher in exposed (<0.008)	4
Sta-llones et al., (2002)	Farmers in 8 counties in NE Colorado; N=761	OP pesticides, herbicides; work activities (rel. to pesticide exp.), exposure was episode of pesticide poisoning	Neurological symptoms, types of pesticides, years of	24 neurological symptoms	OR, condi-tional logistic regression	OR of having had a pesticide-related illness: (female?) gender 0.27 (0.14-0.52), depressed 2.39 (1.36-4.20), sleep too much 3.09 (1.62-5.89), use OP 2.34 (1.17-	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			schooling, alcohol, farm income, age, sex			4.66)	

Table 3 Neurodegenerative Impacts

3.a. Ecological study

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Ritz et al., (2000)	Deaths in California counties from 1984-1993 or 4	Agricultural census data of %age of land treated with pesticides used to classify counties of residence as none, low, medium & high, exposure, with duration of living in county of residence prior to death.	age, race, gender, place of birth, education	Proportion of deaths by county comparing cause of death (underlying or associated) for PD vs IHD	Logistic regression	Proportional odds of PD significantly higher in pesticide use areas using continuous and ordinal exposure classification. OR from 1.44 to 1.52, all CI not including 1	6

3.b. Case-control studies (n= 5)

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
John-son et al., (1997)	144 PD patients and 464 control subjects matched for age, race and sex	various herbicides, insecticides and fungicides via questionnaire	age, sex, race, smoking	Clinically diagnosed Parkinson's disease	ANOVA	Farming significantly associated with PD (adjusted for age, sex, race p=0.043), also significant after adjusting for 3 pesticides) *herbicide (p=0.012) /insecticide (p=0.001) contact at work (association greater with those having >=10 years of exposure)	5
Liou et al., (1997)	120 patients with Parkinson's (PD) and 240 hospital control subjects matched on age and sex	paraquat, other pesticides and herbicides un specified, Open ended questionnaire	drugs, infection, tumor, previous stroke, know toxins, age, sex	Neurologist evaluation for dx of parkinson's (based on 2 or more cardinal signs of PD)	Matched analysis, Chi square calculatedusi ng the extended Mantel-Haenszel method	Significantly increased risk for PD with occupational or residential exposure to pesticides /herbicides OR= 2.9 (2.3, 3.7) -strong association between paraquat & PD OR 3.2 (2.4, 4.3).	5
Mc-Guire et al., (1997)	Cases: Dx of ALS in 4 yr period; matched controls randomly selected from population; Washington State; N=522	Job Hx from age 15 to date of Dx, exposure to chemicals, PPE, home activities /hobbies (unblinded); panel assessment of occupational exposures (blinded) for exposure index	Age, sex, respondent type (self or proxy), education, exposure to metals /solvents /agricul-tural chemicals	Dx of Amyotrophic Lateral Sclerosis	Condi-tional logistic regression	OR for exposure to agricultural chemicals: both sexes: self-report 1.6 (1.0-2.7), panel 2.0 (1.1-3.5); men: self-report 2.1 (1.1-3.8), panel 2.4 (1.2-4.8); insecticides, both sexes, panel 2.1 (1.1-4.1); self-report and panel 2.5 (1.1-5.7); dose-response for insecticides for men, panel: low exposure 2.0 (0.5-7.7), high exposure 2.8 (1.1-6.8); home and workplace exposure to pesticides, men, panel 2.8 (1.2-6.7)	6
Hubble et al., (1998)	246 screened, 43 met dx criteria for PD with Dementia and 51 met the criteria for PD without dementia	Interview re occupation, farm living, lifelong residence hx, water source, pesticide exposure	Age, head trauma, alcohol, family history of AD or PD, smoking,	Unified Parkinson's Disease Rating Scale, neuro examination, Neuropsy evaluation included Mattis Dementia Rating Scale(DRS).	Chi square, t-test, multiple logistic regression	pesticide exposure in combination with a genetic trait (CYP 2D6 29B+ allele) was significantly associated with PD+D (p=0.032) Pesticide alone was not significantly associated with PD+D	4.5

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
			Genetic Markers			(p=0.584).	
Gaut-hier et al., (2001)	68 cases of Altzheimer'sDisease and 68 age and sex matched controlsx	multiple types of exposure and types of pesticides used, questionnaire and regional pesticide data	age, occupational exposure, education level, presence of family cases, ApoE allele	3 steps to Dx of AD: 1. 3MS test-score of <=78 2. cognitive function via (CERAD battery, Benton's test of verbal fluency). Dx in accordance with DSM4 3. NINCDS-ADRDA criteria – Blood samples for genotyping of ApoE	Logistic regression	No significant relationship with exposure to neurotox substances and AD (p=1) – No signifcant relationship with long term expoure to pesticides (OR 1, CI 0.45-2.21)as well as herbicide (1.08, CI 0.49-2.37) and insecticide (1.73 CI 0.79-3.78) and AD even after adjusting for education, family history and ApoE presence.	5.5

3.c. Cohort studies (n=4)

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Tuch-sen et al., (2000)	2273872 participants, of which 90430 men 38505 women where expected to be occupationally exposed	Occupational codes of farming, horticulture and related groups	Age, gender	Hospitalization due to Parkinson's assessed via National Inpatient Register	Age standardized hospitalization ratio by gender	Among male self employed farmers SHR for PD= 130 (95%CI 103-163), consistent but not significant pattern of high risk in other likely exposed work groups	5
Engel et al, (2001)	Cohort of mostly orchardists who participated in earlier cohort study; controls from various occupations; Washington State; N=310	All types of pesticides; exposure determined by self-report questionnaire	Age, race, EtOH, smoking, use of well water, farm employment, size of farm, Hx of stroke, neck/back disorders, neurological disorders, arthritis	20-minute structured neurological exam administered by nurse - unified Parkinson's disease rating scale for presence & severity of motor signs; Parkinsonism if 2+ of: rest tremor, rigidity, brady-kinesia, impaired postural reflexes; or 1 sign plus on anti-parkinsonian meds	Prevalence ratio; Generalized linear model	PR=2.0 (1.0-4.2) for PD among subjects in highest tertile of years of exposure to pesticides; no increased risks associated with specific pesticides/classes	4

Reference	Population Description	Pesticides Type and Exposure Assessment	Co-variates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Petro-vitch et al., (2002)	Follow up of 7986 japanese american men born between 1900 and 1919 who were enrolled in the longitudinal Honolulu Heart Program	Work on pineapple or sugarcane plantations, pesticide exposure at home or work for at least one year	age, sex, cigarette smoking, coffee and caffeine intake	Developpment of PD, via questionnaire, clincal diagnosis and records (hospitalization records, death certificates, medical records from local neurologists).	Proportional hazards regression models , Relative risks estimated	After age adjustment, significant association with PD and length of time working on a plantation (p=0.01). Incidence of PD tended to increase with reported years of exposure to pesticides, but not significant (p=0.10) -After adjustment for age, cigarettes and caffeine, a significant association for work on a plantation vs none (p=.006 for those working >20 yrs))	6
Baldi et al., (2003)	Population of the PAQUID study 1507 French elderly living in Gironde, France in their home or institution	Assessed by self-report questionnaire, used to construct job-exposure matrix	history of smoking, age, sex, education level, rural living or living in proximity to vineyards.	Cognitive impairment, depression, Parkinson's and dementia, evaluated by questionnaire and clinical examination (Mini Mental State Exam – MMSE)	Prevalence odds ratios for cross-sectional comparison of baseline MMSE Age based Cox proportional hazards model for incident cases	OR = 1.45 (95% CI 1.04-2.02) for occupational exposure and reduced MMSE score In men, RR parkinsons for occupationally exposed= RR 5.6 (95% CI 1.5-21.6) & for Alzheimers RR= 2.9 (95CI% 1.0-5.6)	5

Chapter 9 — Reproductive Outcomes

Introduction

A review conducted by Sever et al. (1) focusing on pesticide exposure found three main outcomes related to embryonic damage caused by parental exposure to pesticides:

- Spontaneous abortion/fetal death
- Congenital malformations
- Altered growth (intrauterine growth retardation)

Our review included these effects and others related to fecundability (time to pregnancy—TTP) and fertility. In total, 62 papers were reviewed and the results are summarised in the following six tables:

- Congenital malformation (CM)
- Fecundability (TTP)
- Fertility problems, male and female
- Altered growth: low birth weight, intrauterine growth retardation (IUGR), small for gestational age (SGA), preterm delivery, and fetal length
- Fetal death: abortions, fetal death, stillbirth, and neonatal death
- Mixed outcomes: including sex ratio, placental damage, and hormone disturbances

Please note that some papers are represented in more than one table.

Adverse Reproductive Effects

Congenital Malformations – Table 1

Since 1992, there have been a number of studies examining the association between pesticides and congenital malformations (CM). These studies originated from the United States (2–6), Spain (7–9), Latin America (10, 11), Norway (12), Finland (13), Denmark (14), the Philippines (15), and Canada (16). A variety of study designs was employed including case-control, retrospective cohort, cross-sectional, and ecological. Pesticide exposures were measured indirectly through work records, questionnaires, census data, databases, and place of residence (e.g. industrial, agricultural, or urban). A few of the studies used an industrial hygienist's review (6, 13) or an expert estimation of exposure (16) in an attempt to represent the exposure more accurately. However, none of the studies used a direct biomarker measure of exposure.

In most of the studies the outcome was more accurately assessed than was the exposure. Often there was a medical record check or the study utilized a population-based registry. However, there are several methodological problems in studying congenital malformations. The prevalence of birth defects is usually derived from foetuses that survive until birth; however, such an approach ignores malformations associated with syndromes incompatible with fetal life, or those borne by foetuses electively aborted due to prenatal screening (17). It is estimated that between one fifth and three quarters of all concepti are naturally aborted, many of which possess chromosomal abnormalities (18). Also, where multiple CMs were being measured, their various causes could well have obscured specific associations.

In spite of these difficulties, there were some consistencies in study findings. Significant increases in risk were seen for a number of congenital anomalies including: any birth defect (8–10, 13, 15), limb reduction defects (2, 6, 12), urogenital defects (7, 12, 14), central nervous system defects (6, 12), orofacial clefts (13), heart defects (5, 6), and eye anomalies (16). It is often difficult to isolate the effects of specific products because in many cases there are multiple exposures and the types of pesticides used vary with season. Nevertheless, increases in risk were identified with parental exposure to the specific pesticide active ingredients glyphosate (3), and pyridil derivatives (8). Noteworthy, most of the authors were able to obtain valid data in relation to confounders, representing a methodological advance over studies included in a previous review (73).

These results add to the growing body of evidence of the harmful effects of pesticides during fetal development. However, given the limitations to both the exposure and outcome assessments of the vast majority of these studies, it is difficult to interpret these findings definitively. It is evident that there are gaps in the literature and there is a great need for a well-designed prospective study. A number of recent review articles have been written, in preparation for the US National Children's Study, that address methods for improving the assessment of early life exposures (19–22). Ideally, such a study would span the pre-conception and pregnancy period to allow for repeated biomarker measures in maternal serum during pregnancy, possibly amniotic fluid pre-birth and umbilical cord blood, meconium at birth. Such methods would increase the sensitivity, specificity and power of the study (23).

Fecundability or Time to Pregnancy (TTP) – Table 2

Eight papers from Denmark (24, 25), France and Denmark (26, 27), Finland (28), Italy (29), the Netherlands (30), and Canada (Ontario) (31) analyzed the association between pesticide exposure and fecundability, as measured by time to pregnancy (TTP).

Most authors relied on retrospective information for their studies. In terms of this outcome both designs are equally valid, because it has been recognised that valid data on TTP can be derived retrospectively, with a recall time of 14 years or more (72). All of the papers measured the outcome using a modified version of the key question developed by Baird et al. (68): "How many months were you having sexual intercourse before you got pregnant for the first time?" Five papers focused on the most recent pregnancy or live birth, two on the first pregnancy, and one on all pregnancies; this variation introduced different classes of bias into the analysis and obstructed comparison.

All of the studies used questionnaires to gather exposure information. This included questions on the respondent's job, type of crops cultivated/tended, tasks, the type of pesticide products used and their active ingredients, as well as the use of personal protective equipment. Uniquely, one paper used a field study to validate the questionnaire results, by also monitoring dermal and respiratory exposures (26). Another study gathered data from greenhouse employers (24), while the Ontario study (31) identified exposure to specific pesticide classes, families, and active ingredients for each month of trying to conceive.

The authors were adequately able to control for confounders, and most used Cox proportional models (modified) to obtain the "fecundability odds ratio" (F-OR). Five papers showed a positive association while three others showed no association. Interestingly, the papers showing no association collected exposure and outcome information from men, through questionnaires sent by mail. The differing validity of data on reproductive outcomes provided by men as

opposed to women has been documented (76). The Ontario paper (31) found a decrease in fecundability of 20% or more when women were engaged in pesticide activities, specifically with the pesticide active ingredients dicamba, glyphosate, and 2,4-D, or the pesticide classes phenoxy herbicides, organophosphates, and thiocarbamates. However, none of the estimates was statistically significant.

Although most of the studies relied on self-reported exposures, the results are consistent and suggest that occupational exposure to agricultural chemicals may cause impaired fecundability with increased time to pregnancy. Considering Ontario's extensive agricultural land base, it is important for physicians to bear this outcome in mind in order to properly monitor the underlying causes of reproductive problems in patients.

Fertility – Table 3

Fertility and fecundability are defined differently and are influenced by different factors; we therefore considered them to be independent health effects.

A variety of studies from the Netherlands (32, 33), the United States (34, 35), Denmark (36–38), Israel (39), Mexico (40), Argentina (41, 42), and China (43) examined the impact of pesticide exposure on fertility.

Cross-sectional, case-control, and cohort study designs were used to measure fertility factors including semen quality, sperm aneuploidy, erectile function, sex hormones, infertility, and fertility rates. Uniquely, one prospective study (33) followed patients in an IVF clinic to measure the implantation rate. Pesticide exposure was measured using both indirect (questionnaires, industrial hygienist reviews, and work records) and direct exposure measures (dermal, urine, and serum analysis).

Studies of semen quality produced inconsistent results. Abell et al. (36) found some evidence that pesticides affect semen quality, while Tielemans et al. (32) found no significant association between pesticide exposure and reduced semen parameters. Recio et al. (40) found some evidence of an association between organophopshate metabolites and sperm sex aneuploidies, especially for the metabolite DEP. However, a Danish study (37) showed no association between pesticide exposure, based on total hours sprayed and sperm aneuploidy.

Greenlee et al. (44) found a significant, though imprecise, increase in the risk of infertility among women who had mixed or applied herbicides in the two years prior to trying to conceive. Place of residence on a farm, ranch, or rural home was found to have a protective effect in the case of both women and men. Heacock et al. (45) found no association between chlorophenate exposure and fertility. A slight trend toward increasing fertility with cumulative exposure was seen, which may reflect a "healthy worker effect." Other studies found associations between pesticide exposure and erectile dysfunction (42), and differences in sex hormone levels (38, 39, 42).

It is difficult to compare the findings of these studies given the inconsistencies (of methodology, sample, focus, etc.) between the studies and the variety of measures chosen for the exposure and outcome assessments. Furthermore, many of the studies suffered from design limitations such as crude exposure assessments, small sample sizes, low participation rates, or limited control for confounders. Given this, further prospective studies using direct exposure measures are warranted.

Altered Growth – Table 4

Low birth weight, prematurity, and IUGR are known to be major determinants of health problems during the first year of life. Because birth weight is related to both the rate of fetal growth and length of gestation, the IUGR construct, usually defined as birth weight below the 10th percentile of a reference standard for a given gestational age, has emerged as a useful tool in epidemiological studies of reproductive health. IUGR is the second most common known cause of fetal death (77), and has been associated not only with poor neonatal health but with considerable chronic problems later on in adulthood (46). It marks an improvement over the findings of prior literature reviews to find that half of the papers that analyze growth effects consider this outcome.

Ten papers from Europe (47–50), the United States (51, 52), Canada (16), Mexico (53), and the Phillipines (15) examined the association between pesticide exposure and fetal growth through examining the following outcomes: birth weight, intrauterine growth retardation (IUGR), small for gestational age (SGA), and preterm delivery.

As in most of the studies on reproductive outcomes, the authors made great efforts to measure exposure in a range of ways, since there is no single biomarker for sub-chronic exposure for the full spectrum of frequently used pesticides. The Canadian study (16) presented an approach for constructing an index based on expert estimates of exposure time. A study from Mexico (53) used acetylcholine measurements combined with geographical and occupational information, while an ecological paper (52) assigned exposure according to the pesticides measured in water sources.

Information on confounders was available, but most papers did not seek information on the precise date of the last menstrual period (LMP), which is crucial for studying such outcomes (IUGR in particular). This imprecision can cause non-differential misclassification with a bias toward the null value. Statistical analysis was done using linear or logistic multiple regression.

Seven papers showed a positive association, one of them focusing on the association with pyrethroid exposure (48). As well, another study found an association between chloropyrifos and reduced birth weight and length (54). Importantly, decreased birth length is associated with morbidity and mortality, especially in the first year of life (74, 75). Nevertheless, other papers produced mixed results (50) or no association between pesticide exposure and growth disturbances (16, 50). In conclusion, the results of this review suggest that there may be a possible association between occupational exposure to agricultural chemicals and intrauterine growth retardation, but there is a need for more advanced study designs that include precise measurements of the date of LMP.

Fetal Death – Table 5

We found seven papers that focused exclusively on the association between pesticide exposure and spontaneous abortion (4, 15, 55–59); four focused on the association with fetal death, stillbirth, or neonatal death (16, 57, 60, 61).

Retrospective cohort was the preferred research design, being used in six studies; cross-sectional design was used in three papers, and case-control in two. Exposures were measured by means of questionnaires that included questions on job type, type of crops cultivated/tended, tasks, commercial products used and their active ingredients, and the use of personal protective

equipment. The Ontario study (55, 56, 59) constructed monthly pesticide-use histories for individual farms for 17 pesticide categories, using information obtained from farm operators.

Outcome definition varied among the studies. For example, in Gerhard (62) the outcome was not miscarriage but levels of various hormones according to miscarriage status. Spontaneous abortions, especially early in pregnancy, were based on clinical records or maternal report. Other papers used stillbirths (> 20 weeks of gestation) and neonatal death (within 24 hours of birth) as the outcome studied. An exceptional outcome measure was used by Pastore et al. (61) who restricted the case population to 2 causes of fetal or neonatal death: 1) death due to congenital anomalies, and 2) death due to complications of the placenta, umbilical cord, or fetal membranes.

Nine of the 11 studies found a positive association, while only one study from Canada (British Columbia) found no association between stillbirth or neonatal death and any category of exposure. The British Columbia (16) study mentioned non-differential misclassification, and other sawmill exposures to substances such as diesel exhaust, asbestos, and sawdust as possible explanations of the findings.

A very strong association was observed between spontaneous abortions or birth defects and farming households that used conventional pesticides in the period from three months before conception to the first three months of pregnancy, compared to those that used integrated pest management (15). Arbuckle et al. (55, 56) revealed an association between phenoxy herbicides and spontaneous abortion, while Jarrell et al. (57) observed a positive association between spontaneous abortion and maternal exposure to hexachlorobenzene contaminated seeds in childhood. As well, the Ontario Farm Study suggested that there may be critical exposures windows when chemical insults may be more harmful (55, 56, 59).

For all of the studies information on confounders was available. The majority of the studies used multiple logistic regression in statistical analysis, one study used multivariate proportional hazard models, and one study presented crude associations. However, confounding factors related to agricultural work (biological exposures such as animal viruses, heavy metals, etc.) were not controlled for in any of the studies.

Also there are a number of methodological problems that arise when studying spontaneous abortions. It is difficult to obtain population data on spontaneous abortion rates because there are no administrative databases and hospital records are based on admissions, which are only a subset of the actual number of spontaneous abortions that occur. Therefore, the true incidence is not known. A relatively high percentage of pregnancies end in undetected spontaneous abortions unless the pregnancy is diagnosed using close hormonal surveillance (17). As well, the accuracy of self-reports by women depends on their self-awareness of menstrual cycle, how regular their cycle is, their use of home fertility and pregnancy kits, and their desirability of a pregnancy.

In conclusion, the results suggest that exposure to pesticides may be associated with fetal death; however many of the studies were plagued by poor exposure or outcome assessments. Nevertheless, the papers do possibly point to critical exposure windows when the fetus may be more vulnerable to toxic exposures (55, 56, 61).

Mixed outcomes (sex ratio, placental damage, and hormone disturbances) – Table 6

A number of studies from Canada, the USA, Turkey, Mexico, and Germany examined the association between pesticide exposure and a range of adverse reproductive outcomes, including:

- Gynaecological and endocrine dysfunction in women with recurrent pregnancy loss and altered placental characteristics (63)
- Blood cholinesterase activity and placental characteristics (64)
- Pregnancy outcomes: miscarriage, preterm birth, SGA, stillbirth, neonatal death, low birth weight and length, fetal distress, and sex ratio (4, 15, 16, 51, 54, 57, 59, 65, 66)
- Child development after in utero exposures (developmental delay, death, retarded growth parameters including reduced weight, height, and head and arm circumference) (66)
- Chromosomal aberrations, DNA damage (67)

The extent to which pesticide exposure affected these outcomes was measured using several different methods. Many of the exposure assessments were self-reported or used proxy measures such as geographic area. However, a few used biomarkers (54, 63) or examined critical exposure windows (16, 59). Furthermore, exposure assessments often took note of the particular pesticide class, family, or active ingredient.

Given the diversity of outcomes, a variety of methods were used to capture them. Maternal factors were measured by lab diagnosis, while pregnancy and child development outcomes were obtained either from clinical records or self-reporting. Notably, one study used a population-based surveillance registry to obtain information on pregnancy outcomes.

Studies dealing with pregnancy outcomes suggest that there may be critical windows when pesticide exposures are more harmful to the developing foetus. In the pre-conception period, presumably during spermatogenesis for the father, both Savitz et al. (59) and Hourani (51) found an association between paternal pesticide exposure and miscarriage, while Dimich-Ward (16) observed an increase in eye anomalies. However, mothers who applied DEET daily to their bodies from the third to seventh month of pregnancy experienced no increase in adverse pregnancy or child development outcomes (66).

Uniquely, one study found a significant reduction in blood cholinesterase activity in women exposed to the organophosphate pesticide parathion compared to unexposed women. There was suggestive evidence of morphological changes in the placenta in the exposed women (64).

The results of these studies should be interpreted cautiously given the often imprecise nature of the exposure and outcome assessments. Nevertheless, given the widespread use of pesticides in Ontario, future well-designed prospective studies are needed to confirm or refute these findings.

Conclusions

All papers share similar problems in relation to exposure measurement, and these are considered in each of the summary tables. The most important problem is the lack of biomarkers for measuring exposure to pesticides. Also, there is an increasing body of scientific evidence suggesting there are critical windows when chemical insults may be more harmful to the development of the fetus. Only a minority of studies examined the effect of a specific pesticide exposure during a defined exposure window. Efforts to construct exposure indices and matrices,

based on data gathered via questionnaires, vary among the studies, and this influenced the quality score assigned to each one (see Chapter 2, Methods). Validating the data by means of field studies or the use of business data (e.g., tax receipts for farm pesticide purchases) helped enhance the quality of selected studies.

More recently the Children's Environmental Health Study in the United States has conducted studies to measure more directly organophosphate exposure in pregnant women (69, 70, 71). Pesticide metabolites were measured in the serum and urine of pregnant women and subsequently in their umbilical cord blood at birth. In addition, levels of maternal and infant serum paraoxonase (PON1, an enzyme that can detoxify the chlorpyrifos oxon before it can inhibit acetylcholinesterase in the peripheral nervous system), were measured and analyzed for effects on infant growth and development. Not only did this study collect biomarkers of exposure; it also addressed the important issue of gene–environment interactions.

In spite of the methodological problems encountered in the assessed studies, we are able to make some general recommendations based on the suggestive findings:

- The results of this review suggest that occupational exposure to agricultural chemicals may be associated with adverse reproductive effects including: birth defects, fecundability, fetal death, and intrauterine growth retardation.
- Because of the limitations of the exposure and outcome assessments for the majority of studies examining pesticide exposures and reproductive outcomes, there is a strong need for a well-designed longitudinal study to validate the results of this review. In terms of methodology, it is important to take into account both paternal and maternal exposures and critical exposure periods, avoid dichotomous classification, and use biomarkers when possible.
- It may also be advisable to recommend the implementation of protective norms for couples thinking of having a child, considering that adverse reproductive outcomes have been seen for both maternal and paternal exposures.

Chapter 9 — Reproductive outcomes

References

Review Studies:

1. Sever LE, Arbuckle TE, Sweeney A. Reproductive and developmental effects of occupational pesticide exposure: the epidemiologic evidence. *Occup Med* 1997;12:305–325.

Primary Studies:

I. Congenital Anomalies

2. Engel LS, O'Meara ES, Schwartz SM. Maternal occupation in agriculture and risk of limb defects in Washington State, 1980–1993. *Scandinavian J Work Environ Health* 2000;26:193–198.
3. Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. Birth Defects, Season of Conception, and Sex of Children Born to Pesticide Applicators Living in the Red River Valley of Minnesota, USA. *Environ Health Perspec* 2002;110:441–449.
4. Garry VF, Harkins ME, Lyubimov A, Erickson LL, Long L. Reproductive Outcomes in the Women of the Red River Valley of the North. I. The spouses of Pesticide Applicators: Pregnancy loss, age at menarche, and exposure to pesticides. *Journal of Toxicology and Environmental Health, Part A* 2002;65:769–786.
5. Loffredo CA, Silbergeld EK, Ferencz C, Zhang J. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. *Am J Epidemiol* 2001;153:529–536.
6. Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 1999;10:60–66.
7. Garcia-Rodríguez J, Garcia-Martin M, Nogueras-Ocana M, de Dios Luna-del-Castillo J, Espigares-Garcia M, Olea N et al. Exposure to pesticides and cryptorchidism: geographical evidence of a possible association. *Environ Health Perspec* 1996;104:1090–1095.
8. Garcia AM, Benavides FG, Fletcher T, Orts E. Paternal exposure to pesticides and congenital malformations. *Scand J Work Environ Health* 1998;24:473–480.
9. Garcia AM, Fletcher T, Benavides F, Orts E. Parental Agricultural Work and Selected Congenital Malformations. *Am J Epidemiol* 1999;149:64–74.
10. Rojas A, Ojeda ME, Barraza X. [Congenital malformations and pesticide exposure]. [Spanish]. *Rev Med Chil* 2000;128:399–404.
11. Medina-Carrilo L, Rivas-Solis F, Fernandez-Arguelles R. [Risk for congenital malformations in pregnant women exposed to pesticides in the state od Nayarit, Mexico]. [Spanish] *Ginecol Obstet Mex* 2002;70:538–544.
12. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Birth Defects among offspring of Norwegian farmers, 1967–1991. *Epidemiology* 1997;8:537–544.
13. Nurminen T, Rantala K, Kurppa K, Holnberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. *Epidemiology* 1995;6:23–30.

14. Weidner IS, Moller H, Jensen TK, Skakkebaek N. Cryptorchidism and hypospadias in hons of gardeners and farmers. *Environ Health Perspec* 1998;106:793–796.

15. Crisostomo L, Molina VV. Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management. *Int J Occup Environ Health* 2002;8:232–242.

16. Dimich-Ward H, Hertzman C, Teschke K, Hershler R, Marion SA, Ostry A et al. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry.[comment][erratum appears in *Scand J Work Environ Health*. 1998 Oct;24(5):416]. *Scand J Work Environ Health* 1996;22:267–273.

II. Methodology Studies

17. Olsen J, Torsten S. Design options and methodological fallacies in the studies of reproductive failures. *Environ Health Perspec* 1993;101:145–152.

18. O'Rahilly R, Muller F. *Human Embryology and Teratology*. New York: Wiley-Liss; 2001.

19. Wessels D, Barr DB, Mendola P. Use of biomarkers to indicate exposure of children to organophosphate pesticides: implications for a longitudinal study of children's environmental health. *Environ Health Perspec* 2003;111(16):1939–1946. Epub 2003 Sept 11.

20. Chapin RE, Robbins WA, Schieve LA, Sweeney AM, Tabacova SA, Tomashek KM. Off to a good start: the influence of pre-and peri-conceptional exposures, parental fertility, and nutrition on children's health. *Environ Health Perspec* 2004;112(1):69–78. Epub 2003 Sept 24.

21. Landrigan P, Garg A, Droller DB. Assessing the effects of endocrine disruptors in the National Children's Study. *Environ Health Perspect* 2003;111:1678–1682.

22. Longnecker MP, Bellinger DC, Crews D, Eskenazi B, Silbergeld EK, Woodruff TJ et al. An approach to assessment of endocrine disruption in the National Children's Study. *Environ Health Perspect* 2003;111:1691–1697.

23. Hooper K, Clark GC. Workshop on perinatal exposure to dioxin-like compounds. VI. Role of Biomarkers. *Environ Health Perspec* 1995;103:161–167.

III. Time to Pregnancy

24. Abell A, Juul S, Bonde JP. Time to pregnancy among female greenhouse workers. *Scand J Work Environ Health* 2000;26:131–136.

25. Larsen SB, Joffe M, Bonde JP. Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. *Occup Environ Med* 1998;55:278–283.

26. Thonneau P, Larsen SB, Abell A, Clavert A, Bonde JP, Ducot B et al. Time to pregnancy and paternal exposure to pesticides in preliminary results from Danish and French studies. Asclepios. *Scand J Work Environ Health* 1999;25 Suppl 1:62–63.

27. Thonneau P, Abell A, Larsen SB, Bonde JP, Joffe M, Clavert A et al. Effects of pesticide exposure on time to pregnancy: results of a multicenter study in France and Denmark. ASCLEPIOS Study Group. *Am J Epidemiol* 1999;150:157–163.

28. Sallmen M, Liesivuori J, Taskinen H, Lindbohm ML, Anttila A, Aalto L et al. Time to pregnancy among the wives of Finnish greenhouse workers. *Scand J Work Environ Health* 2003;29:85–93.

29. Petrelli G, Figa-Talamanca I. Reduction in fertility in male greenhouse workers exposed to pesticides. *Eur J Epidemiol* 2001;17:675–677.

30. de Cock J, Westveer K, Heederik D, te VE, van Kooij R. Time to pregnancy and occupational exposure to pesticides in fruit growers in The Netherlands. *Occup Environ Med* 1994;51:693–699.

31. Curtis KM, Savitz DA, Weinberg CR, Arbuckle TE. The effect of pesticide exposure on time to pregnancy. *Epidemiology* 1999;10:112–117.

IV. Fertility

32. Tielemans E, Burdorf A, te Velde ER, Weber RF, van Kooij RJ, Veulemans H et al. Occupationally related exposures and reduced semen quality: a case-control study. *Fertil Steril* 1999;71:690–696.

33. Tielemans E, van Kooij R, Looman C, Burdorf A, te VE, Heederik D. Paternal occupational exposures and embryo implantation rates after IVF. *Fertil Steril* 2000;74:690–695.

34. Smith EM, Hammonds-Ehlers M, Clark MK, Kirchner HL, Fuortes L. Occupational exposures and risk of female infertility. *J Occup Environ Med* 1997;39:138–147.

35. Tomenson JA, Taves DR, Cockett AT, McCusker J, Barraj L, Francis M et al. An assessment of fertility in male workers exposed to molinate. *J Occup Environ Med* 1999;41:771–787.

36. Abell A, Ernst E, Bonde JP. Semen quality and sexual hormones in greenhouse workers. *Scand J Work Environ Health* 2000;26:492–500.

37. Harkonen K, Viitanen T, Larsen SB, Bonde JP, ASCLEPIOS., Lahdetie J. Aneuploidy in sperm and exposure to fungicides and lifestyle factors. *Environ Mol Mutagen* 1999;34:39–46.

38. Larsen SB, Spano M, Giwercman A, Bonde J. Semen quality and sex hormones among organic traditional Danish farmers. *Occup Environ Med* 1999;56:144.

39. Potashnik G, Porath A. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. *J Occup Environ Med* 1995;37:1287–1292.

40. Recio R, Robbins WA, Borja-Aburto V, Moran-Martinez J, Froines JR, Hernandez RM et al. Organophosphorous pesticide exposure increases the frequency of sperm sex null aneuploidy. *Environ Health Perspec* 2001;109:1237–1240.

41. Oliva A, Giami A, Multigner L. Environmental agents and erectile dysfunction: a study in a consulting population. *J Androl* 2002;23:546–550.

42. Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. *Hum Reprod* 2001;16:1768–1776.

43. Padungtod C, Hassold TJ, Millie E, Ryan LM, Savitz DA, Christinani DC et al. Sperm aneuploidy among Chinese pesticide factory workers: scoring by the FISH method. *Am J Ind Med* 1999;36:230–238.

44. Greenlee AR, Arbuckle TE, Chyou PH. Risk factors for female infertility in an agricultural region. *Epidemiology* 2003;14:429–436.

45. Heacock H, Hogg R, Marion SA, Hershler R, Teschke K, Dimich-Ward H et al. Fertility among a cohort of male sawmill workers exposed to chlorophenate fungicides. *Epidemiology* 1998;9:56–60.

V. Altered Growth

46. Barker D, Eriksson JG, Forsen T, Osmone D. Fetal origins of adult disease: strength of effect and biological basis. *Int J Epidemiol* 2002;31:1235–1239.

47. Dabrowski S, Hanke W, Polanska K, Makowiec-Dabrowska T, Sobala W. Pesticide exposure and birthweight: an epidemiological study in Central Poland. *Int J Occup Med Environ Health* 2003;16:31–39.

48. Hanke W, Romitti P, Fuortes L, Sobala W, Mikulski M. The use of pesticides in a Polish rural population and its effect on birth weight. *Int Arch Occup Environ Health* 2003;76:614–620.

49. Karmaus W, Wolf N. Reduced birthweight and length in the offspring of females exposed to PCDFs, PCP, and lindane. *Environ Health Perspect* 1995;103:1120–1125.

50. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967–1991. *Am J Epidemiol* 1997;146:329–338.

51. Hourani L, Hilton S. Occupational and environmental exposure corrleates of adverse live-birth outcomes among 1032 US Navy women. *J Occup Environ Med* 2000;42:1165.

52. Munger R, Isacson P, Kramer M, Hanson J, Burns T, Cherryholmes K et al. Birth defects and pesticide-contaminated water supplies in Iowa. *Am J Epidemiol* 1992;136:959.

53. Levario-Carrillo M, Amato D, Ostroski P, Gonzalez-Horta C, Corona Y, Sanin LH. Relation between pesticide exposure and intrauterine growth retardation. *Chemosphere* Nov. 2003(in press).

54. Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect* 2003;111:201–205.

VI. Fetal Death

55. Arbuckle TE, Savitz DA, Mery LS, Curtis KM. Exposure to phenoxy herbicides and the risk of spontaneous abortion. *Epidemiology* 1999;10:752–760.

56. Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspec* 2001;109:851–857.

57. Jarrell J, Gocmen A, Foster W, Brant R, Chan S, Sevcik M. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in southeastern Turkey in the 1950s. *Reprod Toxicol* 1998;12:469–476.

58. Petrelli G, Figa-Talamanca I, Tropeano R, Tangucci M, Cini C, Aquilani S et al. Reproductive male-mediated risk: spontaneous abortion among wives of pesticide applicators. *Eur J Epidemiol* 2000;16:391–393.

59. Savitz DA, Arbuckle TE, Kaczor D, Curtis KM. Male pesticide exposure and pregnancy outcome. *Am J Epidemiol* 1997;146:1025–1036.

60. Bell EM, Hertz-Picciotto I, Beaumont JJ. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *Am J Epidemiol* 2001;154:702–710.

61. Pastore LM, Hertz-Picciotto I, Beaumont JJ. Risk of stillbirth from occupational and residential exposures. *Occup Environ Med* 1997;54:511–518.

62. Gerhard I, Daniel V, Link S, Monga B, Runnebaum B. Chlorinated hydrocarbons in women with repeated miscarriages. *Environ Health Perspect* 1998;106:675–681.

VII. Mixed Outcomes

63. Gerhard I, Frick A, Monga B, Runnebaum B. Pentachlorophenol exposure in women with gynecological and endocrine dysfunction. *Environ Res* 1999;80:383–388.

64. Levario-Carrillo M, Feria-Velasco A, De Celis R, Ramos-Martinez E, Cordova-Fierro L, Solis FJ. Parathion, a cholinesterase-inhibiting plaguicide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study. *Gynecol Obstet Invest* 2001;52:269–275.

65. Jarrell JF, Gocmen A, Akyol D, Brant R. Hexachlorobenzene exposure and the proportion of male births in Turkey 1935–1990. *Reprod Toxicol* 2002;16:65–70.

66. McGready R, Simpson JA, Htway M, White NJ, Nosten F, Lindsay SW. A double blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy. *Trans R Soc Trop Med Hyg* 2001;95:137–138.

67. Zeljezic D, Garaj-Vrhovac V. Chromosomal aberration and single cell gel electrophoresis (Comet) assay in the longitudinal risk assessment of occupational exposure to pesticides. *Mutagenesis* 2001;16:359–363.

Chapter references not listed above:

68. Baird DD, Wilcox AJ, Weinberg CR. Use of time to pregnancy to study environmental exposures. *Am J Epidemiol* 1986;124:470–480.

69. Berkowitz, G.S, Wetmur, J.G., Birman-Deych, E., Obel, J., Lapinski, R.H., Godbold, J.H., Holzman, I.R., Wolff, M.S. In utero pesticide exposure, maternal paroxonase activity, and head circumference. *Environ Health Perspect* 2004;112(3):388–391.

70. Berkowitz, GS, Obel J, Deych E, Lapinski, R, Godbold J, Liu Z, Landrigan PJ, Wolff MS. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. *Environ Health Perspect* 2003;111(1):79–84.

71. Chen J, Kumar M, Chan W, Berkowitz G, Wetmur JG. Increased influence of genetic variation on PON1 activity in neonates. *Environ Health Perspect* 2003;111(11):1403–1410.

72. Joffe M, Villard L, Li Z, Plowman R, Vessey M. A time to pregnancy questionnaire designed for long term recall: validity in Oxford, England. *J Epidemiol Community Health* 1995;49:314–319.

73. Maroni M, Fait 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.

74. Martorell, R. Results and implications of the INC AP follow-up study. *J Nutr* 1995;125:1127S–1138S.

75. Ruel MT, Neufeld L, Habicht J-P, Martorell R. Stunting at birth: a simple indicator that predicts both risk and benefit among stunted populations. *FASEB J* 1996; Abstr 1664;3:289A.

76. Sanín LH, Restrepo M. Ed. Defectos al nacer y pesticidas en Colombia. [Birth defects and pesticides in Colombia] In: Metodología Epidemiológica aplicada a estudios de Salud Ambiental. México: Instituto Nacional de Salud Pública/OMS; 2000. p. 59–74. ISBN 968-6502-48-3.

77. Witter FR. Perinatal mortality and Intrauterine growth retardation. *Curr Opin Obstet Gynecol* 1993;5(1):56–59.

Chapter 9 — Reproductive outcomes

Summary Tables

Table 1 Congenital Malformations

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Engel,L.S., O'Meara,E.S. & Schwartz,S.M. 2000. Maternal occupation in agriculture and risk of limb defects in Washington State, 1980-1993. *Scandinavian Journal of Work, Environment & Health.* **26,** 193–198	**USA** 14466 births from exposed women and two non exposed groups (1), one named "non agricultural" group (2) with 23512 births and another named "paternal agricultural" group (3) with 5994 births. **Retrospective Cohort**	No specific names or type. Occupational data; Job title. Records (Occupation registered in Birth Records) Groups: Maternal agricultural work. Group 2: Maternal work outside house in other occupations. Group 3, the same that group 2, but father working in agricultural work.	Maternal age, marital status, birth place, smoking and alcohol during pregnancy, prenatal care, parity, ethnicity, gestational age, gender of the baby.	Limb defects: Syndactyly, polydactyly, adactyly, and other "limb reductions." Birth Records (Clinical assessment)	Prevalence ratios. Unconditional logistic regression. Statistical interactions were assessed on a multiplicative scale.	OR for risk of limb deffects. With group2: OR: 2.6 (1.1-5.8) and with group 3 OR: 2.6 (0.7-9.5). No seasonal trend in risk of limb-reduction defects.	5,4=4.5 Potential misclassification of occupation. Lack of data on some potential confounders. defects.
Garcia-Rodriguez,J., Garcia-Martin,M., Nogueras-Ocana,M., de Dios Luna-del-Castillo, Espigares, G.M., Olea,N. & Lardelli-Claret,P. 1996 Exposure to	Granada, **Spain.** 274 cases of Orchidopexy and 514 Inpatients. **Ecological Study**	Provinces categorized in four exposure levels (according pesticide use). Records	Age, date of admission, city or town where he habitual resided.	Cases of Orchidopexy. Clinical Diagnosis, records.	Orchidopexy rates and Inpatient control rates OR and Incidence Control Rates ratio. Logistic Regression and Poisson regression Poisson homogeneity test	OR: 2.54, 4.29 and 5.74 for levels 1,2, 3, respectively. ICrates ratio: 8.8. 7.2 and 6.7 for the same levels respectively.	4,4=4 Ecological Bias. Selection bias may have been introduced by including only patients with surgery (50% of all cases, excluded). Possible misclassification of municipalities. Use

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
pesticides and cryptorchidism: geographical evidence of a possible association. *Environmental Health Perspectives.* **104,** 1090–1095					for differences between strata.		of hospital services favored by geographical proximity.
Garcia,A.M., Fletcher,T., Benavides,F.G. & Orts,E. 1999. Parental agricultural work and selected congenital malformations. *American Journal of Epidemiology.* **149,** 64–74	**Spain** 261 cases and 261 controls. **Case-Control**	Two main exposure periods. Acute risk period (Father: 3 months prior to conception and/or 1st trimester of pregnancy; Mother: 1 month prior to conception and/or 1st trimester) and "Nonacute risk period " . Questionnaire	Age, cigarette smoking, alcohol consumption, drug use, medical history for both parents and reproductive history for mother.	Congenital Malformation (ICD-9), nervous system defects, cardiovascular defects, oral clefts, hypospadias/epispadias, musculoskeletal defects and multiple and unspecified defects. Clinical Records.	Crude and adjusted OR. Conditional Logistic Regression	Adjusted OR for mothers involved in agricultural activities during "Acute risk period": 3.16(1.1-9.0). Fathers who reported ever handling pesticides had an adjusted OR= 1.49 (0.94-2.35) mainly related to an increased risk for nervous system and musculoskelatal defects.	5,4=4.5 An association was seen between maternal agriculture work in the acute risk period and birth defects. Power was limited. Only infants born alive and admited to hospital were included, possible selection bias. Maybe information bias for differencial diagnosis (hospitals).
Garcia,A.M., Benavides, F.G., Fletcher,T. & Orts,E. 1998.	**Spain** 261 cases and 261 controls.	Expert's exposure assessment. Probability and intensity of exposure with a mark for confidence in that	Paternal – industrial worker, age > 40 Maternal -	Congenital Malformation (ICD-9), nervous system defects, cardiovascular	Proportion of exposure (with different methods) in each group.	Dichotomous analysis of exposure (absent, present) showed some	5,5=5 Low power. Potential misclassification of

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Paternal exposure to pesticides and congenital malformations.[comment]. *Scandinavian Journal of Work, Environment & Health.* **24,** 473–480	**Case-Control**	scores (based in Agriculture work, characteristics of agriculture work, specific chemical use obtained in questionnaire).	spontaneous abortion, twins, drug consumption, heavy smoking, education	defects, oral clefts, hypospadias/epispadias, musculoskeletal defects and multiple and unspecified defects. Clinical Records.	Crude and adjusted Ors, logistic Regression	increased risks for aliphatic hydrocarbons: adjusted OR: 2.05 (0.62–6.80), inorganic compounds: adj OR 2.02(0.53–7.72) and glufosinate : adj OR 2.45(0.78–7.70), and a significant association for pyridil derivatives: adj OR 2.77 (1.19–6.44)	exposure. Impossible to measure independent contribution of different chemicals. Interactions not evaluated.
Garry,V.F., Harkins,M.E., Erickson,L.L., Long-Simpson,L.K., Holland,S.E. & Burroughs,B.L. 2002. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota,	**USA** 695 families: 228 male (spouse only), 90 female (Spose), 377 couples. 1532 children **Cross-sectional Survey with retrospective information**	Current and past pesticide use, product name, (herbicide, glyphosate, fungicide, etc), years, Number of days per year, type of crop, use of protective equipment, use of pesticides by spouses. Self reported questionnaire (validation of quest., two times)	mother's age, smoking status, alcohol use, season of conception and residence (rural or not rural).	Congenital anomalies, grouped according to major organ system 1968–1998. Questionnaire, clinical records (follow-up).	Crude and adjusted OR	First year of life has a rate of 31.3/1000 birth defects in 3 years or more was 47.0/1000. Conception in spring: 7.6% Vs 3.7%. Adverse neurological and neurobehavioral developmental effects among the children born to applicators of the fumenigant phosphate OR 248 (1.2–5.1)	6,4=5 5 (Reviewed) Possible Bias introduced by differences in the reproductive rate family. Two different classes of pesticides seem to have adverse effects on different reproductive outcomes. Confirmatory studies are needed.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
USA. *Environmental Health Perspectives.* **110,** Suppl-9						Use of herbicide glyphosate yielded an OR of 3.6 (1.3–9.6) in the neurobehavioral category.	
Garry,V.F., Schreinemachers,D., Harkins,M.E. & Griffith,J. 1996. Pesticide appliers, biocides, and birth defects in rural Minnesota. *Environmental Health Perspectives.* **104,** 394–399	**USA** 4,935 births from exposed group (34,772 pesticide appliers) and 210,723 births from general population. **Cross-Sectional**	No specific kind of pesticide. Exposure levels by areas. Pesticide use survey data base	County of residence, parental age, date of Birth, pregnancy riek factors, race.	Birth deffects. Reports on Birth Deffects Identified at birth by Health Professionals (Birth Records)	Proportion of birth anomalies in each group. Crude and adjusted Ors by Mantel-Haenszel Method, and Logistic regression	Western Minnesota, showed the highest rate of birth anomalies per/1000 live births;30.0 for private appliers versus 26.9 for the general population in the same region. The lower rates, 23.7/1000 and 18.3/1000, occurred in non crops region.The male/female sex ratio for the four birth anomaly categories was 2.8 vs 1.5 in western Minnesota and 2.1 vs 1.7 in the non crops region. Adjusted OR for all anomalies was 1.41 (1.18–	5,4=4.5 Fungicide use and exposure are diffcicult to estimate. A lot of strengths. These findings suggest exposure-related effects.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
						1.69) comparing with general population.	
Kristensen,P., Irgens,L.M., Andersen,A., Bye,A.S. & Sundheim,L. 1997. Birth defects among offspring of Norwegian farmers, 1967–1991. *Epidemiology.* **8,** 537-544	**Norway** 192,417 births (E) from farmer parents, 61,351 (NE) from non-farmer parents. **Cross-sectional** (retrosp.inf)	Agricuture census. Two indicators of pesticide exposure: Pesticide exposure information based on amount of money spent on pesticides on the farm in 1968 & tractor pesticide spraying equipment on the farm. Census closest to birth.	Year of birth, maternal age, geographical region, parenteral consanguinity. Animal husbandry.	Specific birth defects: central nervous system (CNSD), neural tube defects (NTDs), orofacial clefts(OC), limb reduction defects (LD), cryptorchidism, hypospadias. Medical Birth Register of Norway and clinical records	Crude and adjusted Ors. Logistic regression.	Spina bifida OR: 2.76 (1.07–7.13), hydrocephaly OR:3.49 (1.34–9.09), limb reduction defects OR: 2.50 (1.06–5.90). They also found an association with pesticide and cryptorchidism and hypospadias.	5,4=4.5 Possible misclassification of exposure maybe with a secular pattern. No couple information (farm information). Lack of registration of therapeutic abortion (subregistration of Down and anencephaly). Incomplete ascertaiment of birth defects in some cases.
Loffredo,C.A., Silbergeld,E.K., Ferencz,C. & Zhang,J. 2001. Association of transposition of the great arteries (TGA) in infants with maternal exposures to herbicides and rodenticides. *American Journal of*	**USA** 1832 cases of congenital hearth defects, with 66TGA and 114 non-TGA. 771 control infants. **Case-Control**	Type of exposure, mode of exposure, places where the exposure occurred, frequency of exposure, and time of exposure by trimester. They constructed 4 exposure groups. First trimester of pregnancy and the preceding 3 months. Questionnaire	Race of infant, socioeconomic status score, maternal age, maternal smoking and alcohol use categories, family history of heart defects, maternal diabetes, maternal solvent exposures, and paternal	Structural heart disease. TGA was defined as transposition of great arteries with or without other defects. The non-TGA group of cardiac outflow tract anomalies consisted of an aortic-pulmonary window, a supracristal ventricular septal	Crude and adjusted Ors. Logistic Regression.	OR for association between TGA and maternal exposure to any pesticide during first trimester 2.0 (1.2–3.3). Maternal exposure to pesticides OR: 2.8 (1.3–7.2), Rodenticides OR: 4.7 (1.4–12.1) and Insecticides	6,5=5.5 Lack of data on specific products. Thay analyzed each possible bias, one by one saying that they were minimized in this study, eventhough recall bias. Many strengths.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Epidemiology. **153,** 529–536			pesticide exposures.	defect, a double-outlet right ventricle, a common arterial trunk, and tetralogy of Fallot. Clinical Records and diagnosis confirmed by cardiologist.		OR: 1.5 (0.9–2.6). There were no significant interactions.	
Medina-Carrilo,L., Rivas-Solis,F. & Fernandez-Arguelles,R. 2002. [In Process Citation]. *Ginecologia y Obstetricia de Mexico.* 70:538–44	**Mexico** Cases (Ca)=93 Controls (Co)=186 **Case-Control**	They consider as exposure any type of contact with any of the agrochemicals used as pesticides. They constructed 9 exposure categories. Questionnaire.	Maternal age, illness during pregnancy, radiation, drug use, medical and reproductive history.	Congenital malformation: Central nervous, face, genital, hip, foot or finger congenital malformations (IDC-10), diagnosed at delivery by physician.	Crude and adjusted Ors. Logistic regression.	Exposed mothers had high rids of having a malformed child (OR=3.5, CI95% 2.05-6.34, p<0.05). Risk was higher if the mother had occupational exposure to pesticides (OR=6.33, CI95% 2.95-13.7, p<0.0001) and in mothers living near areas under perticides treatment (OR=3.47, CI95% 1.91-6.33, p<0.0001). Among obstetric factors, abortion and early delivery (OR=15.05,	5,5=5 (Donald) Possible selection and ascertainment bias (high report of cryptorchidism). Low power.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
						CI95% 1.82-124.30, p<0.01) were significant.	
Nurminen,T., Rantala,K., Kurppa,K. & Holmberg,P.C. 1995. Agricultural work during pregnancy and selected structural malformations in Finland.[comment]. *Epidemiology*. **6,** 23–30	**Finlandia** Cases (Ca): 1306 (581 Oro facial, clefts -OFC; 365 central nervous system defects – CNSD; 360 Skeletal defects – SD), 1306 controls.	Exposure was classified in five levels. Self report questionnaire and Industrial Hygenist Review	Age, birth order, reproductive history, smoking, alcohol intake, drugs and common cold or fever during first trimester.	OFC,CNSD, and SD. Register of Congenital malformations.	Crude and adjusted Ors. Conditional Logistic Regression.	When all birth defects were pooled, the adjusted OR for agricultural work (vs non agricultural work) in the first trimester of pregnancy was 1.4 (0.9–2.0) For OC, adjusted OR was 1.9 (1.1 – 3.5) The occurrence of skeletal deffects was not associated with agricultural work.	5,5=5 Only selected structural malformations. Possible information bias. Sample size was not enough for analysing all exposure categories.
Rojas,A., Ojeda,M.E. & Barraza,X. 2000. [Congenital malformations and pesticide exposure]. [Spanish]. *Revista Medica de Chile*. **128,** 399–404	Chile 453 Cases, 453 Controls? (429 non clear)	Mother labor activity, Father labor activity, House location related with the spaying area. Definition of Exposed: at least 2, Non exposed: none of three. Questionnaire and Geographical area.	Not mentioned in the analysis (They were collected)	Case: Any new born alive or dead with diagnosis of major, minor or multiple congenit malformation. Control: New born alive without malformations with the same sex that born after the case. Clinical specialized diagnosis.	Proportion exposed compared via Chi-square and McNemar test.	Prevalence of 41.2%, Remarkable the number of cases osteomuscular CNS and cromosomopatias. Positive association with pesticides, but was crude. Prevalence of malformations 4% (Very high)	4,5=4.5 (Donald, reviewed) – They did not analize the limitations deeply. – Don't control by possible confounders – Not exhaustive analysis.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
						27.7 of fathers were exposed (casos), and 15% in controls (p,0.01) OR: 2.16 (1.5-3.0) exposed/non exposed. Atribuible fraction 54.5%	
Shaw,G.M., Wasserman,C. R., O'Malley,C.D., Nelson,V. & Jackson,R.J. 1999. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology.* **10,** 60–66	**USA** **Cases (**Ca) Orofacial Clefts (OFC)= 662, Neural Tube defects (NDT) = 265, Cono truncal defects (CTD) = 207, Limb Anomalies (LA) = 165 (n=1299) **Controls** (Co)= 734	Self reported questionnaire Occupational and house hold exposure to pesticides. 4 months (1 month before , and 3 after conception) Validation by an industrial hygienist.	Vitamine use, cigarrete smoking, educational level, ethnicity.	Congenital anomalies: Orofacial Clefts (OFC), Neural Tube defects (NTD), Cono truncal defects (CTD), Limb Anomalies (LA). Clinical records (California Birth defects, monitoring program).	Crude and adjusted ORS, performed for each anomaly. Logistic regression	The OR estimate did not indicate increased risk for any of the studied anomaly groups among exposure women. For exposure father (reported by mother) ORs were elevated for only OFC. Father's OFC: OR= 1.7 (0.9-3.4) Use of pesticide products for gardening , by mothers : OR >/= 1.5 for most of the studied anomalies.	5,5 Exposure reporting errors; sparseness of data with some reported exposures; limited exposure assessment.
Weidner,I.S., Moller,H., Jensen,T.K. & Skakkebaek,N.	**Denmark** 6117 **Cases** of Cryptorchidism	Data base (Tax authority information sheets, Data in the Danish National Patient Register, Fertility	Gestational age, parity, twin birth reproductive history, parental	Diagnosis of cryptorchidism (CC) or hypospadias (HP),	OR crude and adjusted. Restriction contingency	OR: 1.38 (95% CI 1.10-1.73) Combined OR: 1.67 (95%	6.5,5=5.75 Uncertainties in exposure

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
E. 1998. Cryptorchidism and hypospadias in sons of gardeners and farmers. *Environmental Health Perspectives.* 106: 793–796	1345 Cases of Hypospadias 23273 **Controls**	Data Base and Statistics Denmark). Occupational status during the year of conception (Farming, gardening or both)	age, nationality and professional status (self employed, salaried etc..), year of birth.	and all variants of both conditions defined by WHO ICD-8th and 10th revisions. Danish Malformation Register	tables and logistic regression.	CI 1.14-2.47) gardening. Only for CC	assessment. Information Bias nondifferenciate. Bias toward nule value.
* **Crisostomo**, L. & Molina, V.V. 2002. Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management. *International Journal of Occupational & Environmental Health.* 8, 232–242	**Philippines** 676 households 345 Conventional Pesticide Users (CPU) 331 Integrated Pest Management (IPM) **Retrospective Cohort** (it seems a cross-sectional, comparative)	Any Pesticide Self-reported CPU households (those who applied pesticides at levels beyond the "spot spraying" method and IPM households (using suitable technologies to maintain pest populations in low levels, criteria are: zero spraying or spot spraying done only as a last resort, when injury level had been reached). Timing: 3 months before conception up to the first three months of pregnancy.	Socio-demographic information (ethinic group, duration of residence in Barangay, family size, marital status, age of the couple, etc.); medical and reproductive history, ingestion of medicines (except vitamines and iron), and life style.	Self-report: Spontaneous abortion, birth defects and preterm delivery.	Chi2, Fisher's test. Crude and adjusted Risk Ratios Logistic Regression	CPU vs. IPM households Adjusted ORs Birth defects: OR=4.56 (1.21–17.09) The conventional pesticide users in this study were four times more at risk for birth defects, than were IPM users.	**4,4=4** Possible misclassification bias; erroneous recall;
***Dimich-Ward,**H., Hertzman,C.,	British Columbia, Canada	Chlorophenate Records, Expert	gender, year of birth	Surveillance Registry: Congenital	Conditional Logistic Regression	a) Eye anomalies CUM1: OR=1.47 (1.1–2.0); CUM2:	**5,5=5** Possible

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Teschke,K., Hershler,R., Marion,S.A., Ostry,A. & Kelly,S. 1996. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. *Scandinavian Journal of Work, Environment & Health.* 22, 267–273	19675 births from 9512 fathers, saw mill workers **Retrospective Cohort**	estimation 1. exposure up to three months prior to conception (CUM1) 2. exposures in the three months prior to conception (CUM2), and 3. exposures through the entire period of pregnancy (CUM3). Was based on experts' raters estimations of hours of exposure applied to specific time windows prior to birth. They categorized this continuos variables in quartiles.		anomalies. Prematurity, low birth weight, small for gestational age (SGA), stillbirth and neonatal mortality.		OR=2.87 (1.5–5.5); CUM3: OR=2.6(1.4–4.8) Maximum exposure OR= 1.4 (0.7–2.9)	misclassification (non-differential); other exposures in the sawmill such as diesel exhaust, asbestos, sawdust not considered

* The last two papers are repeated in various tables.

Table 2 Time to Pregnancy

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Abell,A., Juul,S. & Bonde,J.P. 2000. Time to pregnancy among female greenhouse workers. *Scandinavian Journal of Work, Environment & Health 26:*131–136.	**Denmark** 492 women **Cross sectional survey** (with retrospective information). (They said: Retrospective Cohort)	Questionnaire (telephone interview) Manual handling of cultures (hours per week) – use of gloves – spraying of pesticides (combined, 4 categories) At the time when the couple started trying to conceive.	Couple smoking, age, caffeine, education, parity, use of contraceptives methods.	TTP Months taking to get pregnancy without control. Censored 13 months. Questionnaire Most recent pregnancy.	Measure of Effect: Time to pregnancy (TTP) in months. Adjusted Hazard Radios. (aFR) Proportional Hazard regresion. Stratified analysis (Use of contraceptive methods)	The aFR for workers in flower greenhouses vs other union members was 1.11 (0.90 - 1.36) Among workers in flower greenhouses the handling of cultures many hours per week, the spraying of pesticides, and the non-use of gloves was related to reduced fecundability. (Adjusted fecundability ratio 0.69 (0.47–1.03),0.78 (0.59–1.06), and 0.67 (0.46–0.98), respectively).	5, 3 =4. Reviewed. Possible selection Bias toward nule value. Crude exposure assessment based on several indirect indicators of exposure. Exposure to pesticides among women working in flower greenhouses may lead to reduced fucundability and that exposure to pesticides may be part of the casual chain.
Larsen,S.B., Joffe,M. & Bonde,J.P. 1998. Time to pregnancy and	**Denmark** selected 904 (523 traditional (80%) final 522	Equipment and use of it – Number of hectars – Type of crops. Construction of index and levels.	Female age, male and female smoking, recent use of oral contraceptives	TTP: Months to get pregnant without using any method of birth control.	Measures of Effect: TTP in months. Censored at 12 m. Feccundability	fOR adjusted for traditional farmers using pesticides was 1.03 (CI 95%	6,4=5 Reviewed Lack of exact exposure measurement.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. *Occupational & Environmental Medicine.* 55, 278–283	vs 381 Organic (90%) final 160. **Cross sectional survey** (with retrospective information).	Questionnaire. Telephone interview.	and female primiparity.	Questionnaire. Youngest child.	odd ratio (fOR) crude and adjusted. Discrete analogue of the Cox's regression model	0.75–1.40). No significant difference in TTP between traditional farmers who used pesticides and organics farmers.	Selection bias if traditional farmers who had difficulty conceiving were less motivated to particpate Exclusions from analysis
Petrelli,G. & Figa-Talamanca,I. 2001. Reduction in fertility in male greenhouse workers exposed to pesticides. *European Journal of Epidemiology*. 17, 675–677	**Italy** 127 Greenhouse workers and 173 Controls (Administarative workers) **Cross sectional survey** (with retrospective information).	Less and more than 100 pesticides application per year (two exposure groups) Questionnaire. Personal interview.	Reproductive history, demographic characteristics, smoking and drinking habits.	Time to pregnancy defined as 'the time interval between the strat of unprotected intercourse and a clinically recognizable pregnancy'. First pregnancy	TTP in months with cut at 6 months Crude and adjusted OR. Logistic Regression. life table, Mantel-Cox test..	The mean TTP was 5.4 months (for the greenhouse workers and 3.9 months (SD: 3.1) for the control population. OR adjusted for high exposure grup 2.4 (CI 95% 1.2 – 5.1)	5,4=4.5 Degree of exposure could not be ascertained so may have misclassification bias.
Sallmen M,Liesivuori,J Taskinen,H,Lindbohm,M.L, Anttila,A, Aalto,L & Hemminki,K. 2003. Time to pregnancy among the wives of Finnish	**Finland** 578 couples (489 wives, 85.5% response rate) The author named the design " **Synthethic prospective study conditional on**	Questionnaire and data gathered from enterprise. An experienced occupational hygienist conducted the exposure assesment (without knowledge of outcome). Exposure ranked: high, moderate, low.Worker considered unexposed it he did not report any	Smoking, alcohol, reproductive history, age, other exposures, marital status, last method of contraception.	Time to pregnancy (months taking to get pregnant). First pregnancy during study period.	Time to Pregnancy (TTP) in months. fOR (Fecundability Odd Ratio) crude and adjusted. Discrete proportional Hazard regression	Males exposed to pyrethroids had wives with significantly lower fecundability rates. Marginal with OP and Carbamates. Fecundability was slightly decreased for	5,4=4.5 The main results was based on only 15 highly exposed men. This low number, together with the low participation rate, weaknes the conclusions drawn for this study.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
greenhouse workers. *Scandinavian Journal of Work, Environment & Health. 29(2):85–93.*	**pregnancy**" ?	pesticide application or handling of treated plants.				the exposed greenhouse workers who were inefficiently protected (FOR = 0.67 (CI 95% 0-33-1.35), o.92 (CI 95% 0.45–1.88) and 0.77(CI 95% 0.46–1.29) for high, moderate and low exposure respectively.	
Thonneau,P., Abell,A., Larsen,S.B., Bonde,J.P., Joffe,M., Clavert,A., Ducot,B., Multigner,L. & Danscher,G. 1999. Effects of pesticide exposure on time to pregnancy: results of a multicenter study in France and Denmark. ASCLEPIOS Study Group. *American*	**France and Denmark** 362 French rural workers (142 exposed and 220 controls). 449 Danish farmers (326 conventional (exposed) and 123 controls). **Cross sectional survey** (with retrospective information).	Job title, type of work, pesticide exposure of the man during the year befor pregnancy, list of pesticides. Questionnaire, given to males and they returned by mail.	Age, parity, smoking, contraceptive method used.	Time for pregnancy (TTP) in months. Censored at 13 months. Most recent born child.	TTP in months fOR (Fecundability OR crude and adjusted) Discrete Cox model	France: FOR adjusted: 1.17 (CI 95% 0.89 - 1.55) Denmark: Pesticide exposure fOR = 1.09 (CI95% 0.82 - 1.43) Green house worker fOR = 0.83 (CI 95% 0.69 - 1.18)	5,4=4.5 Lacking of precise exposure measurements. The crude fecundability ratio for exposure to pesticides did not differ from 1 in any population.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Journal of Epidemiology. 150, 157-163.							
Thonneau,P., Larsen,S.B., Abell,A., Clavert,A., Bonde,J.P., Ducot,B. & Multigner,L. 1999. Time to pregnancy and paternal exposure to pesticides in preliminary results from Danish and French studies. Asclepios. *Scandinavian Journal of Work, Environment & Health.* 25, Suppl-3.	**France and Denmark** 362 French rural workers (142 exposed and 220 controls). 449 Danish farmers (326 conventional (exposed) and 123 controls.) **Cross sectional survey** (with retrospective information).	Job title, type of work, pesticide exposure of the man during the year befor pregnancy, list of pesticides. Questionnaire, given to males and they returned by mail.	Age, parity, smoking, contraceptive method used.	Time for pregnancy (TTP) in months. Censored at 13 months.	TTP in months. fOR (Fecundability OR crude and adjusted). Discrete Cox model	France: FOR adjusted: 1.17 (CI 95% 0.89 – 1.55) Denmark: Pesticide exposure fOR = 1.09 (CI95% 0.82 - 1.43) Green house worker fOR = 0.83 (CI 95% 0.69 - 1.18)	4 Reviewd (discuss exclusion) It doesn't give any new information, it's like a repetition of the same paper published in *Scandinavian Journal of Work, Environment & Health and American Journal of Epidemiology.*
De Cock J, Westveer K, Heederik D, te Velde E, van Kooij R. Time to pregnancy and occupational exposure to pesticides in	**Netherlands** 43 couples (91 pregnancies) **Cross sectional survey** (with retrospective information).	Farm characteristics – Changes – Types of fruit grown – farm size – sprayer equipment – time spent. Questionnaire. Validation using Captan as a sentinel chemical.: Dermal exposure (skin pads)	Age, contraceptive method, nursing, smoking, alcohol, general and reproductive health.	TTP Censored at 12 months (all pregnacies)	Measure of Effect: TTP in months. Kaplan – Meier curves (univariate).	FOR for spraying velocity (low) 0.47 (0.29 – 076) FOR for application solely by owner 0.46 (0.28–0.77) High exposed farmers who	6 They analized each kind of Bias for concluding the study has a higher internal validity. Good paper.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
fruit growers in The Netherlands. Occup Environ Med 1994; 51:693–699		Respiratory exposure (personal air sample)				tried to conceive during the spraying season show a TTP twice as long as the other categories (Crude analysis – curves)	
Curtis KM, Savitz DA, Weinberg CR, Arbuckle TE. The effect of pesticide exposure on time to pregnancy. *Epidemiology* 1999; 10:112–117.	**Ontario, Canada** 2012 planned pregnancies. **Retrospective cohort**	They build a monthly pesticide use hystory for each farm. Exposure. "pesticide use on the farm during the month of trying to conceive or at any time during the prior two months." Questionnaire and telephone calls.	Age, ethnicity, education, income, smoking, caffeine consumption, alcohol use, diseases or drugs, other hazardous jobs, reproductive history.	TTP Months or menstrual cycles taken to become pregnant. All pregnancies.	Measures of effect: Time to Pregnancy (TTP), censored at 13 months. Conditional Fecundability Ratios (CFR). Analog of Cox proportional hazards model, modified for discrete time.	Six from 13 pesticides showed adjusted CFRs<1.0 among exposure windows in which the couple was engaged in pesticides activities. (A decrease of 20% or more)	6 Very sophisticated classification of exposures. They don't stimate sample power but is avery powerful sample size. Pesticide exposure assesment better than in other studies but remains an area of concerns.

Table 3 Fertility (Male and Female)

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Abell et al. 2000. Semen quality and sexual hormones in greenhouse workers. *Scandinavian Journal of Work, Environment & Health.* 26, 492–50	**Denmark** 122 male, age 18–45 years, normal puberty. **Cross-sectional**	Self-report, records, dermal exposure	Period of continence, febrile illness and spillage during collection. Alcohol, tobacco and caffeine consumption, BMI, age.	Semen quality and sexual hormones measurement	Difference of means and proportions. Multiple Linear Regression, test for trend.	Sperm concentration and the proportion of normal spermatozoa were 60% and 14% lower in the high-level exposure group. The age adjusted testosterone/sex-hormone-binding globulin ratio declined 1.9% (CI 0.4–3.4%) per year of work.	**5,5=5** The results are compatible with the hypothesis that semen quality is reduced by exposure to pesticides in greenhouses but caution is necessary in the interpretation. Limitations on the exposure assessment.
Greenlee et al. 2003. Risk factors for female infertility in an agricultural region. *Epidemiology*. 14(4):429–36	**USA** 322 cases (Ca) and 322 Controls (Co) **Case-control**	Occupational and Home exposures, Self-report	Education, income, Smoking status, alcohol consumption, time spent reviewing exposure lists, weight pattern, male partner's age, woman's age at menarche, and number of sexual partners	Infertility, defined as 12 months of unprotected intercourse without conceiving a pregnancy ending in live birth. (Medical diagnoses of endometriosos, anovulation, pituitary-hypothalamic disfunction, and female infertility of tubal, uterine, cervical or vaginal origin, or other specified or unspecified origin).	Conditional Logistic Regression. Crude and adjusted ORs.	OR: 27 (1.9–380) for women participating in mixing and applying herbicides, and OR: 3.3 (0.8–13)for women exposed to fungicides, both , prior to attempting conception. Residing on farm, ranch or rural area was protective OR: 0.6 (0.4–0.8). Having a male partner over the age of 40 was risk, smoke and alcohol consumption were risk factors and drink more than three glasses of milk per day was protective.	**6,4=5** These results suggest that certain agricultural, residencial and life style choices may modify the risk of female infertility. Association with milk consumption must be confirmed in other studies. Maybe errors in recall , but they minimized them through several strategies. maybe differences in medical diagnoses.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Harkonen et al. 1999. Aneuploidy in sperm and exposure to fungicides and lifestyle factors. ASCLEPIOS. A European Concerted Action on Occupational Hazards to Male Reproductive Capability. *Environmental & Molecular Mutagenesis*. 34, 39–46.	**Denmark** 30 Healthy Danish Farmers 29–49 years Occupationally exposed to fungicides Donate semen specimens **Prospective cohort**	Occupational exposure to fungicides before season and after. Total hours sprayed with only fungicides, hours sprayed with all agricultural chemicals. Within time window (35–50 days before sperm sample) hours sprayed with fungicides, with all pesticides	Age and sperm concentration, life style factors	Disomy (sperm with 1-1-7 or 1-7-7 chromosome complement) and diploidy (1-1-7-7) in each category and pooled as the sum of aneuploid sperm cells Fluorescence In Situ Hybriditazion (FISH)	Poison regression. Sum of hyperploid sperm before and after exposure. Sign test, Mann-Whitney U-test, Spearman rank order, Pearson correlation.	The mean frequencies of aneuploid sperm in the study population were 0.12% for disomy 1-1-7, 0,05% for disomy 1-7-7, and 0.11%(before exposure) and 0.9% (after exposure) for diploidy 1-1-7-7.	**4,4=4** Exposure to fungicides was not associated with sperm aneuploidy. Smoking was significantly associated with sperm carrying and extra chromosome 1 and with diploid sperm as well as with the aggregate frequency of aneuploid sperm.
Heacock et al. 1998. Fertility among a cohort of male sawmill workers exposed to chlorophenate fungicides. *Epidemiology*. 9, 56–60	**Canada** Exposed: 23829; Non Exposed: 2658 (All of them sawmill workers.) **Retrospective cohort.**	Occupational exposure: Self-report, records Index of cumulative chlorphenate exposure duration for each workers, based on job history	Age, calendar year	Fertility rate for each year (Average number of live births per year per 1000 men)	Poison regression	RR for E: 0.89 (0.84–0.93) Crude SFR according five categories of exposure (combined comparison) 0.79 (<120h), 0.71 (120–1999), 0.74 (2000–3999), 0.78 (4000–9999), 0.76 (>9999). Male / female ratio for E: 1.06 (provincial norm 1.05)	**6,4=5** There is little evidence for a reduction in fertility among chlorophenates exposed sawmill workers in British Columbia. The analyses indicate the importance of time since hire, as a potentially strong confounder in this type

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
							of investigation.
Larsen et al. 1999. Semen quality and sex hormones among organic and traditional Danish farmers. ASCLEPIOS Study Group. *Occupational & Environmental Medicine*. 56, 139–144	**Denmark** 171 traditional farmers and 85 organic farmers. **Cross-sectional**	Self-reported Total years working as a traditional or organic farmer, total number of years of exposure to pesticides, last date of exposure	Age, semen spillage, sexual abstinence, fever, alcohol intake, self reported reproductive disease.	Semen quality: Volume, concentration, total count, percentages (non-vital, normal, with tail, etc), curved line velocity, straight line velocity. Reproductive hormone levels (Testosterone, FSH, LH, Inhibin B). Chromatin structure of the spermatozoa	Multiple Linear regression, Logistic Regression	The median sperm concentration for traditional and organic farmers was 58 million/ml and 64 million/ml respectively.	**6,4=5** After adjustment for several confounders, sperm concentration, total count, proportion of non vital spermatozooa, sperm chromatin structure, and motility variables did not differ significantly between the two groups.
Oliva et al. 2002. Environmental agents and erectile dysfunction: a study in a consulting population. *Journal of Andrology*. 23, 546–550	**Argentina** 199 men To consult andrology unit of one of three private institutions for erectil dysfunction **Cross-sectional**	Occupational, self-report, industrial hygienist Industrial hygienist verified correlation between jobs and declared exposures	age, BMI, annual income, smoking habits, alcohol consumption, diabetes, hypertension, cardiovascular disease, previous trauma, and past or present use of therapeutic drugs that may affect sexual function	Erectile dysfunction (nonorganic, organic, and flat pattern)	Logistic Regression	OR for pesticides and irregular erectile pattern: 1.8, for flat erectile pattern: 7.1 and 8.4 for men who were frequently exposed.	**5,4=4.5** This study supports the hypothesis that active environmental substances may cause erectile dysfunction. Low power. Selected population. Possible misclassification of the type of exposure.
Oliva et al. 2001. Contribution of environmental factors to the	**Argentina** 225 Male partners from couples having	Occupational, Self-report, industrial hygienist	Age, weight, height, time trying to conceive with the present partner,	Semen quality (volume, concentration, total output, motility, percentage of	Logistic Regression	OR for the relationship between seminal characteristics and pesticide exposure:	**5,5=5** Exposure to pesticide and solvent significantly associated

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
risk of male infertility. *Human Reproduction*. 16, 1768–1776	their first infertility consultation **Cross-sectional**	Past and present jobs and lifestyle habits, contact with chemical substances or physical agents. Industrial hygienist verified correlation between job and declared exposures	intercourse frequency, length of abstinence, and testicular volume. BMI, season, annual income, smoking, alcohol consumption	normal espermatozoa), and concentration of reproductive hormones.		seminal volume 6.6 (1.4-31.4), sperm concentration 1.8, sperm output 1.8, sperm motility 5.8 (1.0-32.7). There was a significantly higher oestradiol/testosterone ratio in the pesticide-exposed group.	with sperm threshold value well below the limit for male fertility, in men with both primary and secondary infertility. Selected population, possible selection bias. Low Power.
Padungtod et al. 1999. Sperm aneuploidy among Chinese pesticide factory workers: scoring by the FISH method. *American Journal of Industrial Medicine*. 36, 230–238.	**China** 32 (exposed) from a large pesticide manufacturing plant and 43 (unexposed) from textile factory free from pesticides. **Cross-sectional**	Occupational, self-report, biological sampling Exposed: Production line workers from pesticide factory plant that manufactures organophosphate pesticides (3 months prior to sample collection). Pesticide residues over an entire 8 hr shift by attachment of 5x5 gauze to nine body areas	Inter-technician effect, age, duration of employment, duration of marriage, number of pregnancies fathered.	Sperm aneuploidy Numerically abnormal count or proportion of sperm exhibiting aneuploidy divided by total number of three disomy types by the number of sperm being scored for each person	Nonparmetric Wilcoxon rank-sum test Poison Regression	Exposed vs. Unexposed (including 1OL) Disomy: XY (chi2=2.6, p=0.10), XX (chi2=1.1, p=0.30), YY (chi2=6.9, p<0.01), 18 (chi2=0.00, p=1.000), Total (chi2=2.93, p=0.087) Without 1OL: Disomy: XY (chi2=4.0, p=0.04), XX (ch2=1.4, p=0.24), YY (chi2=9.0, p<0.01), 18 (chi2=0.07, p=0.80), Total (including the 3 types)(chi2=4.4, p=0.04)	**4,4=4** Occupational exposure to organophosphate pesticides moderately increases the prevalence of sperm aneuploidy. Small sample (power), not study of important confounders like smoke and design.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		and a personal pump of subjects' shirt. Urinary & semen metabolites				RR=1.66 (1.16–2.33) by Poisson Regression, adjusted,no OL	
Potashnik et al. 1995. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. *Journal of Occupational & Environmental Medicine.* 37, 1287–1292	**Israel.** 15 men. Last exposition to the DBCP 17-22 years ago. Have had periodical following since initial diagnoses in 1977. **Case-series**	Occupational, records Historical evidence of occupational exposure to DBCP and their effects. (Pregnancies were classified "exposed," "pre-exposed" and "unexposed" in relation with the exposure time of the partner)	Age	Recovery of testicular function measured through the summary of conceptions, semen analyses and hormonal assays. Sex ratio.	Differences of Mean and proportions. Sex ratio differences.T-test.	49 singleton pregnancies conceived after termination of paternal exposure to DBCP were recorded. 41 went to term, culminating in the birth of 40 infants and one antepartum fetal death caused by cord strangulation in an otherwise normal fetus. A low prevalence of male infants conceived during paternal exposure was found as compared with the preexposure period (16.6% vs 52.9%, $p<0.05$). Restoration of fertility was followed by a gradual increase of this value to 41.4%.	**4 ,4=4** This cumulative experience suggest that spermatogenic recovery of production worker exposed to DBCP is most likely to occur within a period of about 5 years, after which time the likelihood is greatly diminished. This exposure is not associated with an increased risk of congenital malformations or with impaired health status of the offspring.
Recio et al. 2001. Organophosphorous pesticide	**Mexico** 9 Healthy men with no history	Occupational, lab diagnosis They measured	Age, alcohol intake, and total sperm concentration	Sperm sex null aneuploidy, defined as an abnormality of the chromosome	Frequency of aneuploidy before and during spraying	The most frequent aneuploidy was the lack of sexual chromosome or sex	**6,4=5** OP metabolites detected ar higher

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
exposure increases the frequency of sperm sex null aneuploidy. *Environmental Health Perspectives*. 109, 1237–1240	of chemotherapy, radiotherapy, or chronic illness. **Cross-sectional**	5 metabolites of OP and calculated total dialkyphosphates (DAP) as the sum of the 5 metabolites. Organochlorine (OC) pesticide were determined.		number. They recorded 12 chromosome patterns. Total aneuploidies included all the abnormal chromosome patterns found.	seasons. They used a generalized estimating equation to account for the lack of independence of observations. They adjusted by difference in urinary concentration ranges for each OP metabolites. Poisson regression.	null (0.19), followed by XY18 (0.15%) and XY18-18 (0.06%). There were no differences in average aneuploidy frequency or urinary metabolite levels berween samples collected before and after exposure. However, Poisson regression analysis adjusted for age, alcohol intake, and sperm concentration showed significant associations between OP metabolite and frequency of sperm aneuploidies.	concentrations were dimethylthiophosphate and diethylphosphate (DEP). Low power. Peculiarities of both exposure and effect precluded a better estimation of the exposure-response relationships. This preliminary work shows a positive association between OP metabolite levels and sex null and total aneuploidy frequencies even after controlling for age and lifestyle factors, playing important roles in aneuploidy induction.
Smith et al. 1997. Occupational exposures and risk of female infertility. *Journal of Occupational & Environmental Medicine.* 39, 138–147.	**USA** Cases (Ca) 281 unfertile women Controls (Co): 216 fertile women. **Case-control**	Occupational, self-report Jobs held for a period of 6 months or longer, only responses for which the participant indicated direct chemical contact were evaluated Volatile organic	index age, history of smoking/ alcohol and caffeine use, reproductive and medical history	Infertility. Defined as inability to conceive or failure to deliver a live born child after 12 months of unprotected intercourse. Female infertility diagnoses were identified as Ovulatory dysfunction, cervical factor, tubal factor,	Logistic Regression Interaction was tested with Breslow-Day homogeneity test..	Four chemical exposures were associated with increased ORs for infertility in the unadjusted analyses: Volatile organic compounds, dusts, pesticides, and non ionizing radiation (VDTs). Adjusted OR for relation between infertility and Pesticides 3.02 (1.1–	**6,4=5** Results suggest that among women with a medical confirmed diagnosis, fertility may be adversely affected by a variety of occupational chemical exposures. Probably problems in diagnosis. Although they had low power to test risk associated

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		solvents, dusts, metals, gases, pesticides, ionizing radiation, and other. An index age of exposure was developed. Only events experienced before the onset of infertility or conception were considered relevant exposures.		endometriosis, and idiopathic disease.		8.29). Among the medical diagnosed causes of infertility, the adjusted risk associated with having an ovulatory factor increased among those women exposed to pesticides OR 3.82 (1.28–11.42).	with specificall diagnosis, it's interesting that they found an increased risk for some exposures and some specific diagnosis.
Tielemans et al. 1999. Occupationally related exposures and reduced semen quality: a case-control study. *Fertility & Sterility*. 71, 690–696	**The Netherlands** Cases A (Ca A)=692, Cases (Ca B)=267, Cases C (Ca C)=61, Controls (Co)=207. Subsamples for laboratory analyses. All consulting for infertility. **Case-control ?** Using three case groups	Occupational, self report. Information about job characteristics permited them to classify subjects as ocupationally nonexposed or potentially exposed to organic solvents, metals, or pesticides. Pesticides were classified in three	Socio-demographic characteristics, lifestyle habits, medical and "reproductive" history, time triying to conceive, abstinence period.	Semen quality (concentration, motility, morfology) Cases A: sperm concentrations <20 million, <50% sperm motility or < 14 % normal forms; Cases B) Stricter case definition: sperm concentration < 5 million, <10% motile sperm, <5% normal forms: Cases C) Rigid definition: indviduals with azoospermia.	Semen quality in porcentages (motility, concentration) for each group). % of Normality forms in each group. Crude and adjusted ORs. Logistic Regression	Adjusted OR for relation between pesticides and semen quality were 1.7, 2.5 and 1.4 for herbicides, fungicides and insecticides respectively and 1.1 for all, none of them was significative.	**6,4=5** Association with pesticides was NEGATIVE. Possible selection bias.Only one semen sample by subject. Selected population

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
	based on different cutoff values for semen parameters and one stand reference group	categories: Herbicides, Fungicides, Insecticides. Job exposure matrix for solvents Sample urine in a subsample randomly selected for metals and solvents.		Controls: subjects with a sperm concentration of >=20 million, >=50% motile sperm, >=14 normal forms.			
Tielemans et al. 2000. Paternal occupational exposures and embryo implantation rates after IVF. *Fertility & Sterility*. 74, 690–695	**The Netherlands** 726 couples pursuing In vitro fertilization (IVF) treatment (from 836 selected at first) **Prospective Cohort**	Occupational, self-report Each individual was assigned one of three mutually exclusive exposures groups for organic solvents, metal dust or fumes, and pesticides : presumably low or none exposed, moderately exposed, and highly exposed. An additional, strict classification	Cycle rank number, age of woman, number of oocytes retrieved, number of oocytes fertilized, number of embryos replaced, and number of gestational sacs at ultrasonography after 6–7 weeks. Number of embryos transferred in each treatment cycle ranged from one to four. Lifestyle factors, educational	Implantation Rate. Measured as the number of gestational sacs seen with ultrasound at 6-7 weeks of pregnancy, divided by the number of embryos replaced.	Implantation rates in each group. Williams procedure for dependency was used to correct the over dispersion phenomenon Crude and adjusted ORs by Logistic Regression	Adjusted OR for implantation success (lenient): 3.31(1.25–8.80), strict: 1.57 (0.33–7.44). Only 7 couples were exposed to pesticides in the restricted population.	**5,4=4.5** Pesticide exposure was associated with INCREASED implantation rates. ?? when a lenient classification criterion was applied but decreased and did not remain significant when strict exposure classification criterion was applied. The “inverse” association with pesticides must be considered and treated caution.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		scheme was used in which only presumably highly exposed subjects were considered to be exposed.	levels				
Tomenson et al. 1999. An assessment of fertility in male workers exposed to molinate. *Journal of Occupational & Environmental Medicine.* 41, 771–787.	**USA** 272 at three plants for semen samples, 222 provided reproductive history. **Prospective Cohort**	Occupational, industrial hygienist review. Determined for industrial hygiene measurements, estimates of number of hours.Hours of exposure in the spermatide stage (30-60 days before sample). The exposure for each period was calculated by multiplication of the geometric mean exposure to molinate vapour by the number of hours of molinate exposure mcg/m3*hours.	Sex, race, marital status, birth date, number of children, education level , smoking history, exposure to warm (sauna, fever), illness (mumps), etc.	Sperm parameters (volume, viscosity, concentration, motility, presence of white blood cells and Mg and Zn levels) and serum hormone levels (FSH, LH and testosterone). Number of children.	Mean of the three replicate samples collected in each period. Mean levels of sperm parameters. log Transformations for hormone levels. Standardized fertility analyses for SFR. GEE (Generalized Estimating Equations) for each period.	Workers' mean exposures to molinate during the monitoring periods ranged from 12.7 mcg/m3 to 210.9 mcg/m3. The only regression findings that might be interpreted as evidence of a molinate-related effect were the falls in sperm concentration and motility score (and the corresponding increase in percent non-motile sperm) at Richmond as exposure increased in the second monitoring period.	**6,4=5** There was litlle evidence that sperm and serum hormone levels at the start of the study were related to the total number of hours of exposure to molinate before the study.The analysis the changes over the four monitoring periods also did not indicate an effect of molinate exposure. Possible selection Bias. Intraindividuality variability in sperm parameters. Design, samples collection and power are strenghts.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		Categorised in none, low and high levels.					

Table 4 Altered Growth – Low Birth weight, Intrauterine Growth Retardation (IUGR or SGA), preterm delivery

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Dabrowski,S.,Hanke,WPolanska,K.,Makowiec-Dabrowska,T. & Sobala,W. 2003. Pesticide exposure and birthweight: an epidemiological study in Central Poland. *International Journal of Occupational Medicine & Environmental Health.* 16, 31–39	**Poland** They said that the design is C and C, but it seems a cross-sectional study (comparative). It's confuse. 117 infants with low birth weight (LBW) 377 infants with BW>=2500g, in analyses they handle the data like cross-sectional. **Confused design**	No specific names or type. Use of pesticide in each of pregnancy trimesters. Occupational (direct and indirect exposure). Questionnaire. 6-12 months after delivery an interviewer visit the husbands of women who reported pesticide use.	baby gender, maternal prepregnancy weight, height, smoking during pregnancy, calendar year of birth and involvement in field work, place of residence	Low Birth Weight. Less than 2.500 g. Clinical Records.	Measures of effect: Means, proportions. Crude and adjusted regression coefficient (beta). Crude and adjusted OR. Multiple linear Regression and Logistic regression. Stratified analyses (place of residence).	Adjusting for gestational age, women exposed to pesticides have infants with BW lower + or - 100g (p=0.06) than non exposed women. Adjusted OR for exposure to pesticides (yes/no) and LBW (yes/no) was 5.84 (3.61-9.47). Infants born to women exposed to pesticides in 1st or 2nd trimester had BW lower by 189 g than that of infants of the non exposed women. Women exposed to pesticides, delivered half a week earlier than no exposed (adjusted).	**4,4=4** cons: Small sample size prevented adequate control of confounding for exposure to specfic pesticides. Pros: verified pesticide exposure with husband and looked at timing of exposures.
Levario-Carrillo M, Amato D, Ostrosky P, Gonzalez-Horta C, Corona Y and Sanin LH. Relation between pesticide	**Mexico** 371 mother/newborn pairs: 79 IUGR (cases) , 292 without (controls)	Area with intensive use of pesticides mainly from cholinesterase inhibiting group: Chlorpyrifos, diazinon, dimethoate, malathion, monocrotophos and Metil-Parathion.	Mother's age, maternal anemia, history of urinary tract infections, maternal nutrition, baby gender, maternal body	Case group: newborns with weight for gestational age <10th percentile (without apparent congenital malformations, or intrauterine	Crude and adjusted OR. Logistic Regression.	Odds of IUGR Pesticide exposure: OR=2.3 (1.0-5.3) Acetlycholiesterase activity (U/ml): IUGR=3.67 +/-1 Healthy	**6,4=5** Exposure assessment to pesticides done through questionnaire but good control for counfounders.

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
exposure and intrauterine growth retardation. Chemosphere 2003	**Case-Controls**	Two of the following criteria: 1) positive history of prenatal exposure to pesticides determined by living 1 km or less from crop areas and usage of pesticides during the gestational period 2) a spouse or relative living in the same residence who used or handled pesticides, 3) a spouse working in agriculture. Questionnaire Also measured AChE activity in newborns . Each criteria was proofed alone and combined.	composition, maternal anthropometry, tobacco addiction, occupation, parity, placental weight (g), IgM antibodies against rubell virus, T. gondii and cytomegalovirus .	infection). Control group: formed with newborns with weight for gestational age >10th percentile. Clinical diagnosis.		infants=4.01 +/-1 p<0.01 The results showed that women exposed to pesticides were more likely to have a child with IUGR and IUGR children had lower AChe levels.	Outcomes clinically asessed.
Hanke W, Romitti P, Fuortes L, Sobala W and Mikulski M. The use of pesticides in a Polish rural population and its effect on birthweight. *Int Arch Occup Environ Health* 2003;76(8): 614–620	**Poland** 104 women participating. **Cross-sectional with retrospective information**.	Based on maternal reporters confirmed by the person directly involved in the application a history of pesticides exposure in the 3 months preceding the conception and the 3 trimesters of pregnancy was reconstructed. Field work and trade name of pesticides were established.	Pregnancy duration, infant gender, maternal age, pre-pregnancy weight, smoking during pregnancy, calendar year of birth (for trend)	Birth weight in grams. Clinical Records.	t-test Multiple Linear Regression.	Field work involvement & birth weight No field work: 3 347.0 Field work: 3 587.5 p=0.044 Linear regression birth eight and 1st or 2nd trimester exposure to pyrethroids synthetic pryrethroids:	**4,5=4.5** Possible misclassification bias, recall bias,

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
		History of pesticide use on the farm, names and active ingredients identified from a database of registered pesticides in Poland.				adjusted coefficient: ------- 233.3 p=0.02. Reduction in birth weight and maternal expousre to **pyrethroids** in 1st and 2nd trimester of pregnancy - this effectmay have been related to a slower paceof foetal development. exposure	
Karmaus,W. & Wolf,N. 1995. Reduced birthweight and length in the offspring of females exposed to PCDFs, PCP, and lindane. *Environmental Health Perspectives.* **103,** 1120–1125	**Germany** 221 exposed (E); 189 non exposed (NE). **Cross-sectional** (Comparative with retrospective data)	Exposure during pregnancy. Pentachlorophenol (PCP) and lidone dioxins dibenzofuranol. Measures in wood and indoor air . Exposure matrix (Job history and exposure information of each centre. Various groups. Exposed if employee worked in any of 24 exposed facilities at any time during her pregnancy).	Smoking, age, gestational age, occupational history, parity, maternal height and weight.	Adverse health outcomes (abortion, miscarriage, stillbirth, etc) Birth weight in g and Length in cm.	Proportions, means Gestational age was put in to the models as square values. Multiple Linear Regression. Beta-coefficient (crude and adjusted)	B= -217 g in exposed pregnances (all), and - 2 cm in length. When the analysis was restricted to validate observations, B for weight was - 259 grs. Controlling for confounders, the results show a significantly reduced birth weight and lenght in exposed pregnances.	**6,4=5** Some association with working in day cares with wood panelling and reduced birth weight. Study cons: cross-sectional design, indirect exposure measurement; pros: looked at exposures during pregnancy.
Kristensen,P., Irgens,L.M.,	**Norway**	Pesticide exposure indicators: amount of	Year of birth, location,	Gestational age, perinatal death and	Logistic Regression. OR.	There was not a signficant	**5,4=4.5**

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Andersen,A., Bye,A.S. & Sundheim,L. 1997. Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967–1991. *American Journal of Epidemiology.* 146, 329–338	192, 417 "farmer's births" and 61351 "non farmers births" **Cross-sectional**	money spent on pesticides in 1968 (1969 census) and on pesticide spraying equipment (1979 census). The amount of time between the year of birth and the closest census (avalaible information) was <3 years for 53% and <5 y for 80% .Kind of farm. They stratified by season. Census. Records (Data-base)	maternal age, married status, birth order, baby gender, kind of delivery.	birth weight. Medical Birth Registry of Norway	Contingency tables.	association with pesticide purchase however farmers' wives were more likely to have late-term abortions, birth weight <1000g and gestational age <28 weeks. Farming was protective against pre-term delivery, small for gestational age, and stillbirth.	Data are not in accordance with associations previously reported between parenteral exposure to pesticides and IGR, preterm birth, and stillbirth.Crude proxy measures for pesticide exposure; However, medical registry used for birth outcomes and census data on exposures was thought to be complete by all farmers in Norway.
Munger,R., Isacson,P., Hu,S., Burns,T., Hanson,J., Lynch,C.F., Cherryholmes,K., Van Dorpe,P. & Hausler,W.J., Jr. 1997. Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies.[erratu	**USA** 13 communities & 856 Iowa municipal drinking water supplies. **Ecological**	Exposure to drinking water contaminants assigned to mothers by relating the drinking water data by municipality to maternal residence at time of giving birth. Data reviewed for elevated levles of specific chemicals. residence at time of giving birth	Median income, previous mean parity, and following proportions: women in the workforce, schoolarity, tobacco habit, mothers with poor prenatal care, births with missing date of Last Menstrual Period (LMP).	Birthweight obtained from Birth certificate data obtained from state vital records: IUGR defined as weight less than 10th percentile for gestational age (Califronia standards for non-Hispanic whites). Outcome: age-adjusted community rate of IUGR.	Multiple Linear Regression.	The Rathburn communities (whose water system was found to contain elevated levels of Triazine herbicide) had a greater risk of Intrauterine Growth Retardation (IUGR) than southern communities RR=1.8(1.3-2.7). MLR: levels atrazine, metolachlor and cyanazine were each one	4,4=4 Community level rather than individual level data; exposure based on residence, possible misclassification bias; did not measure use of bottled water; Definition of IUGR based on birth certificate data; medical complications during pregnancy not known; many

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
m appears in Environ Health Perspect 1997 Jun;105(6):570]. *Environmental Health Perspectives.* **105,** 308–314						predictors of IUGR.	other contaminants not studied.
*** Dimich-Ward,**H., Hertzman,C., Teschke,K., Hershler,R., Marion,S.A., Ostry,A. & Kelly,S. 1996. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. *Scandinavian Journal of Work, Environment & Health.* 22, 267-273.	British Columbia, Canada 19675 births from 9512 fathers, saw mill workers **Retrospective Cohort**	Chlorophenate Records, Expert estimation 1. exposure up to three months prior to conception (CUM1)2. exposures in the three months prior to conception (CUM2), and 3. exposures through the entire period of pregnancy (CUM3). Was based on experts' raters estimations of hours of exposure.	Gender, year of birth	Surveillance Registry: Congenital anomalies. Prematurity, low birth weight, small for gestational age (SGA), stillbirth and neonatal mortality.	Conditional Logistic Regression	No associations were found for LBW, IUGR (SGA), or prematurity. (all around 1.0 in all levels of exposure)	**5,5=5** No association with prematurity in any category of exposure. Possible misclassification (non-differential); other exposures in the sawmill such as diesel exhaust, asbestos, sawdust not considered
Hourani,L. & Hilton,S. 2000. Occupational and environmental exposure correlates of	**U.S.A.** (San Diego, California, Portsmouth, Virgina, Jacksonville Florida)	Any Pesticide Mother-reported maternal and paternal occupational exposure at work and home.	Race, maternal age, marital status, pay grade, parity, reproductive and medical history, , life style	Clinical Records: Small for gestational age, birth defect, fetal distress, preterm birth, and low birth weight.	Logistic regression Chi-square	Paternal , but not maternal, exposure to pesticides at work generated Odds ratios >2 with preterm delivery. Adjusted OR: 2.52	**5,4=4.5** The limited number of exposure effects in the present study may be a result of observing only low-

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
adverse live-birth outcomes among 1032 US Navy women. *Journal of Occupational & Environmental Medicine. 42, 1156-1165*	1032 Navy active-duty women in their reproductive years **Cross-sectional**	Timing: 3 months preceding conception	behaviors, emotional stress.			(1.05-6.01).	exposure outcomes. Other potential risk factors not controlled for, low response rate
* **Perera**,F.P., Rauh,V., Tsai,W.Y., Kinney,P., Camann,D., Barr,D., Bernert,T., Garfinkel,R., Tu,Y.H., Diaz,D., Dietrich,J. & Whyatt,R.M. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environmental Health Perspectives. 111, 201–205*	New York, USA 263 non-smoking African-American and Dominican women residing **Cross-sectional**	pesticides (CPF like proxi of organophophate pesticide), Prenatal personal monitoring data on PAHs, Maternal blood collected within 1 day postpartum; umbilical cord blood collected at delivery.	Maternal body mass index, parity, gestational age, infant sex, income, alcohol consumption, maternal age.	Clinical records: Fetal growth: birthweight, birth length, head circumference	Multiple regression	CPF was associated with decreased birth weight, and birth length overall ($p<0.01$), and lower birth weight among African-Americans ($p<0.05$), and reduced birth length in Dominican ($p<0.01$)	**6,5=5.5** PAHs and CPF appear to be significant independent determinants of birth outcomes. Mean birth weight, birth length, and head circumference were lower and there was greater variability in these outcomes among African-Americans than in Dominican infants. Modest sample size, biomarkers measured at a single point in time.

* Papers asterisked were considered in various tables.

Table 5 Fetal Death

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Arbuckle,T.E., Lin,Z. & Mery,L.S. 2001. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environmental Health Perspectives.* 109, 851–857	**Canada** 2110 women, 3936 pregnancies, 395 spontaneous abortions **Retrospective Cohort** (Cross-sectional with retrospective information?)	17 pesticides variables analyzed separately for each level (use class, chemical family, and active ingredient). They use to "exposure windows": Pre and postconceptional. Related with the loss. Information from farm operator and construction of exposure history (by month!!) with the couple. (Records and data base)	21 possible risk factors for abortion (ex.: maternal and paternal age, education, smoking status, family income, alcohol and caffeine consumption).	Abortion, divided in two groups: <12 weeks and 12–20 weeks. All but five of the abortions were medically confirmed !!	Crude and adjusted OR. Logistic Regression. Classification and Regression Tree (CART)	Preconceptional exposures (PE) and early abortions: Phenoxy acetic and herbicides OR 1.5 (1.1–2.1), triazines OR: 1.4 (1.0–2.0), and any herbicide OR: 1.4 (1.1–1.9). PE and late abortions: glyphosate: OR:1.7 (1.0–2.9), Thiocarbamates OR: 1.8 (1.1–3.0). Maternal age (>34y) was the stronger risk factor. Several interactions in the older group with CART.	**7,5=6** Moderate increases in the risk of early abortions for preconceptional exposures . Post conception exposures were generally associated with late spontaneous abortions. Many methodological contributions in relation with exposure assessment and analysis.
Arbuckle,T.E., Savitz,D.A., Mery,L.S. & Curtis,K.M. 1999. Exposure to phenoxy herbicides and the risk of spontaneous abortion. E*pidemiology.* **10,** 752–760	**Canada** 3936 pregnancies **Retrospective Cohort** (Cross-sectional with retrospective information?). Same group that paper above.	17 pesticides variables analyzed separately for each level (use class, chemical family, and active ingredient). They use to "exposure windows": Pre and postconceptional. Related with the loss. Questionnaire. Information from farm operator and	Maternal and paternal age, education, off-farm employment, alcohol, tobacco and caffeine consumption, per capita income, parity, BMI, I diabetes, mother's age	Spontaneous abortion(SA) at <20 weeks, and 12–19 weeks as reported by the mother.	Logistic regression, generalized estimating equations	Preconception exposure was weakly associated with SA adjOR=1.1(0.6–1.9),when the analyses was restricted to SA,12 weeks, the risk was more than double. The results suggest a possible role of	**5,5=5** Examined critical periods of exposure and farm operator provided most of pesticide infromation, mother provided reproductive history so unlikely there is recall bias. Also time

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
		construction of exposure history (by month!!) with the couple. (Records and data base) **In this paper analyses was focused on phenoxy herbicides (PH) and the risk of spontaneous abortion**	at menarche, number of years mother lived on a farm, number of months between marriage and conception date, language preference (English or French).			preconception (maybe paternal) exposures to PH in the risk of early spontaneous abortions.	windows of exposure examined and separted late vs. early spontaneous abortions.
Gerhard,I., Daniel,V., Link,S., Monga,B. & Runnebaum,B. 1998. Chlorinated hydrocarbons in women with repeated miscarriages. *Environmental Health Perspectives.* 106, 675-681	**Germany** 89 women with history of miscarriage and "reference population" **Cross-sectional. Comparative.**	The blood levels of CHS (Chlorinated hydrocarbons): pentachlorophenol, hexachlorocyclohexane, hexachlorobenzene, DDT group and polychlorinated biphenyls) were determined. An index (6-24) was created. Laboratory.	Age, occupation, reproductive history, chromosomal, uterine, medical, or immunological causes of miscarriages. Hormone determinations (FSH, LH, TSH, etc.)	Repeated Miscarriages (primary, secondary, early and late). Clinical records.	Levels of different CHC according different miscarriages status. Spearman Correlations. Wilcoxon test Spearman Correlations. None model, only "Partial Analysis" (Stratified?)	In more than 20% of the women, at least one of the CHC levels exceeded the reference range. Correlations between chlorinated hydrocarbon score and hormonal parameters between -0.23 to 0.22, with $p<0.05$.	**4,4=4** An exploratory study. There was no clear control group. They did not control for selection bias because only included women who attended a reproductive endocrinology clinic.
Petrelli,G., Figa-Talamanca,I., Tropeano,R., Tangucci M., Cini,C., Aquilani,S., Gasperini,L. & Meli,P. 2000. Reproductive male-mediated	**Italy** Exposed (E)=32 pesticide applicators, Non-exposed (NE)=51 food retailers. **Cross-sectional**	For each product used the following information was abstracted: active ingredients, company, period of use, and formulation. Questionnaire and	Registers of the desinfestation centre.	Spontaneous abortion. (They didn't give an operational definition of outcome). Self reported.	Proportion of spontaneous abortion in each group. Ratio of abortion proportion. Crude and adjusted ORs.Logistic Regression. Interaction	The ratio of abortions/pregnancies for applicators was 0.27 and for retailers 0.07. OR for spontaneous abortion adjusted for age of wife and smoking of parents is 3.8 vs control	**5,4=4.5** The results allows the authors to hypothesise that occupational exposure to pesticides may harm the fetus. Low power.

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
risk: spontaneous abortion among wives of pesticide applicators. *European Journal of Epidemiology*. 16:391-393.	**with retrospective information.**	Registers of the desinfestation centre.			effects were tested (but they didn't describe which interactions were tested)	population in the logistic regression model and 7.6 times with interaction effects model.	Differences in recall accuracy may be related to educational level. Pesticides applicators had a lower educational level.
Pastore,L.M., Hertz-Picciotto,I and Beaumont,J.J. 1997. Risk of stillbirth from occupational and residential exposures *Occupational & Environmental Medicine.* 54, 511–518.	**USA** Cases (Ca)=630, Controls (Co)=642 **Case-control**	Extreme temperatures, pesticides, and video display terminals. By month and by trimester. Self-reported, questionnaire.	Smoking, alcohol use, maternal race and ethnicity, maternal age, county of residence, earlier pregnancy loss. Season of conception for pesticides.	Stillbirths(>20 w of gestation) and neonatal deaths (24 hours), restricted to two causes of death: Congenital anomalies and complications of the placenta, cord, or membranes (ICD-9). Birth and fetal death certificates (data Base)	Proportion of exposures in each group. The case control data were transformed into a case cohort study desing to calculate the risk estimates. Logistic regression and proportional hazard models. OR and RR.	Occupational expose to pesticide during the first two months of gestation was positively associated with stillbirths due congenital annomalies. OR: 2.4 (1.0 to 5.9), and during the first and second trimesters with stillbirths due to all causes of death. RR: 1.3-1.4 (1.0 to 1.7) and stillbirths due to complications of the placenta, cord, and membranes. RR: 1.6-1.7 (1.1 to 2.3).	**7,4=5** Occupational exposure to pesticides in the 1st and 2nd trimester of pregnancy showed significant increases in the risk of stillbirth. Occupational exposure to pesticides in the 1st and 2nd trimester of pregnancy showed significant increases in the risk of stillbirth.
Bell,E.M., Hertz-Picciotto,I. & Beaumont,J.J. 2001. Case-cohort analysis of agricultural pesticide applications near maternal	**USA** 319 cases, 611 noncases. **Case-Control**	Chemical used (5 classes), amount applied, and date and location of each application. Location was specific to the level of town, range and section (TRS). They used county	Race, gender, trimester prenatal care began, season of conception, and prior fetal loss.	Fetal Death (20 weeks and up). California State Vital Statistics Registry	Exposure prevalence en cases and noncases. OR and hazard ratios. Multivariate proportional hazard models.	Risks were elevated 30-40% for several pesticide classes when exposure occurred in the second trim: Halogenated hydrocarbons, carbamates,	**5,5=5** Ecological assignation of exposure. Lack of questionnaire data on potential confounders for almost 45% of the

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
residence and selected causes of fetal death.[comment]. *American Journal of Epidemiology. 154:702-710*		maps to locate the TRS for each maternal address. Pesticide exposure was determined by linking the maternal TRS to the TRS of each pesticide application, two levels of exposure were identified.			Stratified analysis.	estrogenic pesticides, and carbamate ache inhibitors, with hazard ratios of 1.3 (1.0-1.8), 1.3 (1.0-1.8), 1.4 (0.8-2.5), and 1.3 (1.0-1.8) respectively.	study participants. Underreporting of fetal deaths between 20-27 weeks. Error?? in matching by maternal age.
* **Crisostomo**,L. & Molina,V.V. 2002. Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management. *International Journal of Occupational & Environmental Health.* 8, 232-242.	**Philippines** 676 households 345 Conventional Pesticide Users (CPU) 331 Integrated Pest Management (IPM) **Retrospective Cohort** (it seems a cross-sectional, comparative)	Any Pesticide Self-reported CPU households (those who applied pesticides at levels beyond the "spot spraying" method and IPM households (using suitable technologies to maintain pest populations in low levels, criteria are: zero spraying or spot spraying done only as a last resort, when injury level had been reached). Timing: 3 months before conception up to the first three months of pregnancy.	Socio-demographic information (ethinic group, duration of residence in Barangay, family size, marital status, age of the couple, etc.); medical and reproductive history, ingestion of medicines (except vitamines and iron), and life style.	Self-report: Spontaneous abortion, birth defects and preterm delivery.	Chi2, Fisher's test. Crude and adjusted Risk Ratios Logistic Regression	The conventional pesticide users in this study were six times more at risk for spontaneous abortion than were IPM users. Abortion: OR=6.17 (1.37–27.86) Preterm: OR=0.37 (0.10–1.37)	**4,4=4** Probably misclassification bias, names and dose depend upon recall.
* **Dimich-**	British Columbia,	Chlorophenate	gender, year of	Surveillance	Conditional	Stillborn(SB)	**5,5=5**

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Ward,H., Hertzman,C., Teschke,K., Hershler,R., Marion,S.A., Ostry,A. & Kelly,S. 1996. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. *Scandinavian Journal of Work, Environment & Health.* 22, 267–273.	Canada 19675 births from 9512 fathers, saw mill workers **Retrospective Cohort**	Records, Expert estimation 1. exposure up to three months prior to conception (CUM1)2. exposures in the three months prior to conception (CUM2), and 3. exposures through the entire period of pregnancy (CUM3). Was based on experts' raters estimations of hours of exposure.	birth	Registry: Congenital anomalies. Prematurity, low birth weight, small for gestational age (SGA), stillbirth and neonatal mortality.	Logistic Regression	OR=1.00 (0.97-1.06); OR=1.08 (0.94-1.15) OR=1.00 (0.96-1.04); OR=1.01 (0.98-1.08); Neonatal death OR=1.00 (0.99-1.001); OR=1.02 (0.89-1.17); OR=1.02 (0.98-1.06); OR=1.00 (0.96-1.02); for CUM1, CUM2, CUM3 and maximal exposure respectively.	No association with, stillborn, or neonatal death in any category of exposure. Possible misclassification (non-differential); other exposures in the sawmill such as diesel exhaust, asbestos, sawdust not considered
*** Garry,**V.F., Harkins,M., Lyubimov,A., Erickson,L. & Long,L. 2002. Reproductive outcomes in the women of the Red River Valley of the north. I. The spouses of pesticide applicators: pregnancy loss, age at menarche, and exposures to pesticides.	**Minnesota (Red River Valley), USA** Pregnancies fathered by 522 pesticide applicators. **Cross-sectional**	Herbicides, Insecticides, Fungicides, Organotin, Trazole, EBDC, Substituted aromatics, Benzimidazoles, Imidizolinone, Oxphenoxy, Mixtures Self-reported of current and past pesticide use by father and mother Note: phone call 6	Residence place (rural or urban), maternal age, smoking status, alcohol consumption.	Self-report: Fetal loss (28 weeks or less), stillbirths (>28 weeks) and deaths due to premature birth (28–37 weeks). Miscarriage rate and sex ratio.	Logistic Regression Crude and adjusted ORs Pregnancy loss and Pesticide Use group: Herbicide only: (reference) Herbicide/insecticide/fungicide OR=1.64 (1.01–2.67) Other:1.04 (0.49–2.17)	ORs for Pregnancy Loss and Specific Fungicide Use: Organotin: 1.55 (1.01–2.37) EBDC:1.77 (1.11–2.83) Miscarriages in Herbicide use by applicator (father) Sulfonylurea: OR=2.11 (1.09–4.09); Imidizolinone: OR=2.56 (1.11–5.87);	**4.5=4.5** Maternal exposure: Personal pesticide use & fetal loss: OR=1.81 (1.04–3.12). Adj OR for miscarriages: 1.68 (1.02–2.70). The overall reproductive toxicity observed in this population is, for the greater part, a male-mediated event.

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
Journal of Toxicology & Environmental Health Part A. 65, 769-786		mo. later to validate pesticide use for father				Mixture 9100 chlorophenoxy+sulfonylurea+benzothidiazole): OR=2.94 (1.40–6.16)	Both exposure and outcomes were self-reported and there was no exposure window.
*** Jarrell,** J., Gocmen,A., Foster,W., Brant,R., Chan,S. & Sevcik,M. 1998. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in southeastern Turkey in the 1950s. *Reproductive Toxicology. 12, 469-476*	**Southeastern Turkey** 126 women, three groups of 42 each one. Group1(G1): Those with confirmed porphyria cutanea tarda (PCT), G2, controls for the region G3, controls for the country. **"Retrospective controlled cohort comparison study".**	Exposed: individuals with clinically confirmed porphyria cutanea tarda (PCT) who had been studied in previous follow-up reports 25-30 yrs prior that doctors presumed was related to HCB exposure in contaminated seed grains. Unexposed: absense of known exposure to HCB in the tainted grain in 1955–57 Exposure was categorized in 4 levels, lowest=0 and highest: >=1ng/L	Age, geographical region.	Self-reported: Number of Pregnancies, live births, spontaneous abortions, still births and sex of live babies (for sex ratio). Estradiol, FSH, beta-inhibin.	Correlated response logistic regression model	Beta coefficient for spontaneous abortion: 2.88, p<0.01 with logistic transformation and 4.09 without transformation for highest level of HCB	**6,5=5.5** Exposure was categorized in 4 levels, lowest=0 and highest: >=1ng/L Possible selection bias in exposed group, ubiquitous nature of HCB.
*** Savitz**,D.A., Arbuckle,T., Kaczor,D. & Curtis,K.M. 1997. Male pesticide exposure and pregnancy outcome. *American Journal*	**Ontario, Canada** 1,898 farm couples, 3,984 pregnancies. **Retrospective Cohort**	Pesticide classes, families and active ingredients. Self-reported Timing: Paternal of the father was involved in pesticide activities during the critical window (3	Mothers and fathers age, education, occupation, consumptions, mothers language, ethnicity, religion,	Mother-reported: Miscarriage, preterm delivery, small for gestational age (SGA), and sex ratio.	Crude and Adjusted ORs Logistic regression	Combinations of activities with a variety of chemicals (atrazine, glyphosate, organophosphates, 4-[2,4-dichlorophenoxy] butyric acid, and	**5,5=5.5** Possible exposure misclassification, limited power; lengthy recall

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
of Epidemiology. 146, 1025-1036		months before conception and first month of pregnancy).	reproductive story, and the month of conception.			insecticides) generated OR of two or greater.	

* Papers asterisked are repeated in various tables.

Table 6 Other Reproductive Outcomes

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Garry,V.F., Harkins,M., Lyubimov,A., Erickson,L. & Long,L. 2002. Reproductive outcomes in the women of the Red River Valley of the north. I. The spouses of pesticide applicators: pregnancy loss, age at menarche, and exposures to pesticides. *Journal of Toxicology & Environmental Health Part A. 65, 769-786*	**Minnesota (Red River Valley), USA** Pregnancies fathered by 522 pesticide applicators. Cross-sectional	Herbicides, Insecticides, Fungicides, Organotin, Trazole, EBDC, Substituted aromatics, Benzimidazoles, Imidizolinone, Oxphenoxy, Mixtures Self-reported of current and past pesticide use by father and mother Note: phone call 6 mo. later to validate pesticide use for father:	Residence place (rural or urban), maternal age, smoking status, alcohol consumption.	Self-report: Fetal loss (28 weeks or less), stillbirths (>28 weeks) and deaths due to premature birth (28-37 weeks). Miscarriage rate and sex ratio.	Logistic Regression Crude and adjusted ORs	Pregnancy loss and Pesticide Use group: Herbicide only: (reference) Herbicide/insecticide/fungicideOR=1.64 (1.01-2.67) Other: OR=1.04 (0.49-2.17) Pregnancy Loss and Specific Fungicide Use: No fungicide: reference Organotin: OR=1.55 (1.01-2.37) EBDC: OR=1.77 (1.11-2.83) Miscarriages in Herbicide use by applicator (father) Sulfonylurea: OR=2.11 (1.09-4.09); Imidizolinone: OR=2.56 (1.11-5.87); Mixture 9100 chlorophenoxy+sulfonylurea+benzothidiazole): OR=2.94 (1.40-6.16) Maternal exposure: Personal pesticide use & fetal loss: OR=1.81 (1.04-3.12). Approximately 21% fewer boys than girls were born to families fathered for an applicator applying fungicides, insecticides and herbicides (compared to the referent group: herbicide only).	4.5 Both exposure and outcomes were self-reported and there was no exposure window determined.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Gerhard,I., Frick,A., Monga,B. & Runnebaum,B. 1999. Pentachlorophenol exposure in women with gynecological and endocrine dysfunction. *Environmental* Research*. 80, 383-388*	**Heidelberg, Germany** exposed=65, unexposed=106 Women with a history of at least two miscarriages Cross-sectional	Chorinated hydorcarbons determined including:α-hexachlorocyclohexane (α-HCH), β-HCH, γ-HCH (lindane), hexachlorobenzene (HCB), pentachlorophenol (PCP), Blood collected after an overnight fast.	Age (matching), underlying condition, and geographical region (matching) Height and weight (no differences)	Lab Diagnosis: Hormonal levels: FSH, LH, Prolactina, Estradiol, Progesterone, TSH, T3, T4, cortisol, 17-Hydroxyprogesterone, 21-deoxicortisol, DHEA, DHEAS, Androstenedione, Testosterone, Dihydrotestosterone.	Crude differences of proportions and means. Spearman partial correlation. Kruskal-Wallis test, Mann-Whitney-Wilcoxon test.	Luteal insufficiency: 62.7% exposed vs 50.6% unexposed. Euthyroid goiter 50% vs 30%. Increased 21 – deoxycortisol levels were higher in exposed group than in control group: 59.3% vs 30.6%	4 There was no clear control group (compared women with 4 or more miscarriages to women with 2 or more).
***Jarrell,** J., Gocmen,A., Foster,W., Brant,R., Chan,S. & Sevcik,M. 1998. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in southeastern Turkey in the 1950s. *Reproductive Toxicology. 12, 469-476*	**Southeastern Turkey** 126 women, three groups of 42 each one. Group1(G1): Those with confirmed porphyria cutanea tarda (PCT), Group 2 (G2), controls for the region and group 3 (G3), controls for the country of Turkey.	Exposed: individuals with clinically confirmed porphyria cutanea tarda (PCT) who had been studied in previous follow-up reports 25-30 yrs prior that doctors presumed was related to HCB exposure in contaminated seed grains. Unexposed: absense of known exposure to HCB in the tainted grain in 1955–57 Control groups 1: individuals age-matched & living in same region as those who had clinically confirmed PCT. Control group 2: age matched subjects selected from	Age, geographical region.	Self-reported: Number of Pregnancies, live births, spontaneous abortions, still births and sex of live babies (for sex ratio). Estradiol, FSH, beta-inhibin.	Correlated response logistic regression model	Beta coefficient for spontaneous abortion: 2.88, $p<0.01$ with logistic transformation and 4.09 without transformation for highest level of HCB	5 Possible selection bias in exposed group, ubiquitous nature of HCB.

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		the capital city 700 km away. 25-30 years prior to study					
Jarrell, J.F., Gocmen, A., Akyol, D. & Brant, R. 2002. Hexachlorobenzene exposure and the proportion of male births in Turkey 1935-1990. *Reproductive Toxicology. 16, 65-70.*	Turkey 126 women Retrospective Cohort	Hexachlorobenzene exposure 40 years ago Exposed=42 women who had had confirmed porphyria cutanea tarda from HCB exposure 40 years ago; Control 1=no history of exposure to treated grain or prophyria cutanea tarda; Control 2=subjects who had lived 900 km from exposed area - no known exposure	year of exposure spontaneous abortion rate	Self-reported: Sex ratio and proportion of male births of individual subjects who had survived.	Binary logistic regression Chi-squared, ANOVA	Signficant change in calcualted sex ratio among children 0-4 years of age between 1935 and 1990 in Turkey (F=11.62, p=0.007). Sex ratio G1= 0.92, G2=1.24, G3=1.03. Subject % male G1=50.17%, G2=53.12%, G3=54.22% Males born to exposed women vs. controls - no signficant differnce in either the sex ratio between groups or the means of the proportio of males by subject. Factors predicting the proportion of male births among exposed subjects: year of exposure (p=0.03); year of exposure + spontaneous abortion rate (p=0.013)	4.5 Possible recall bias; results subject to modelling asumptions;
Levario-Carrillo,M., Feria-Velasco,A., De Celis,R., Ramos-Martinez,E., Cordova-Fierro,L. & Solis,F.J. 2001.	**Chihuahua, Mexico** 10 placentas from women living in agricultural region (exposed) and 10 placentas from	Parathion during pregnancy Geographical area, agricultural activities and Cholinesterase activity	age, gestational age	Lab Diagnosis: Morphological study of placentas (descriptive)	Descriptive Fisher's test	Blood cholinesterase activity U/ml significantly difference p<0.01 between exposed and unexposed: 4.34 +/-0.3 (exposed); 5.54+/-0.8 (unexposed) Placental weight 616 g in exposed and 554 in	4 Qualitative study, low power

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Parathion, a cholinesterase-inhibiting plaguicide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study. *Gynecologic & Obstetric Investigation. 52, 269-275.*	women living in a urban area. Cross-sectional					unexposed, diameter 17.5*16.4 cm and 19*16cm respectively Qualitative results: Placental characteristic a) surface aspect: Velvet appearance in exposed and unexposed b) surface texture: nonhomogenous (exposed); homogenous & finely granular (unexposed) c) characteristics of tertiary villi: bulous or fungiform ending with incomplete sulci and numerous plaquest of frbrinoid material (exposed); normal (unexposed) d) presence of microvilli: some areas devoid of microvilli (exposed); all villi covered by microvill (unexposed) e) characterstics of miscrovilli: some microvilli showed bullous ending and others were bifurcated (exposed); normal (unexposed).	
Levario-Carrillo M, Chavez-Corral D, Ramos-Martinez E, Solis F, Gonzalez-Horta C, Sanin LH. Exposicion de mujeres a	Chihuahua, Mexico 300 women, and subset of 68 with microscopic assay Cross-sectional	Lab diagnosis, self-report AChe level, also agricultureal vs urban community, and <5 km from fields	maternal nutrition via: pre-pregnancy weight/height2 or BMI, body composition post partum (amount of fat)	Lab diagnosis: macroscopic placental characteristics: weight, diameter, presence of infarction, etc.	multivariate logistic regression t-test for descriptives, Odds ratio	OR for placental ischaemia or infarction 3.5 (2.1-5.85) for rural vs urban OR for AChe units/gm hemoglobin depression (i.e. <43.14 at least 25% less than "normal", about lower two tertiles) approximately 2.2	5.5 Lack of bio-marker for sub-chronic exposure. (Geographic and ACHE activity

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
plaguicidas organofosforados durante el embarazo y alteraciones en la placenta. *Rev Bras Toxicol 2002; 15(2): 79–85*						(1.2-4.3) adjusted	based in own model)
* **Savitz**,D.A., Arbuckle,T., Kaczor,D. & Curtis,K.M. 1997. Male pesticide exposure and pregnancy outcome. *American Journal of Epidemiology. 146, 1025-1036*	Ontario, Canada 1,898 farm couples, 3,984 pregnancies. Retrospective Cohort	Pesticide classes, families and active ingredients. Self-reported Timing: Paternal pesticide Exposure if reported use of a specific chemical on the farm and the father was involved in pesticide activities during the critical window (3 months before conception and first month of pregnancy). Unexposed group: those with no chemical activity or no farm or chemical activity.	Mothers and fathers age, education, jobs outside the farm, tobacco, alcohol, and caffeine use, mothers language, ethnicity, religion, parity, income, child's sex, interval between conception and the survey and the month of conception.	Mother-reported: Miscarriage, preterm delivery, small for gestational age (SGA), and sex ratio.	Crude and Adjusted ORs Logistic regression	Risk of Miscarriage A) Crop herbicide: Herbicides OR=1.4 (1.0-2.0); Thiocarbamates OR=1.9 (1.1-3.3); Carbaryl OR=1.9 (1.1-3.1) B) Crop insecticides or fungicides: Insecticides OR=1.6 (1.1-2.4); Carbaryl OR=2.1 (1.1-4.1); C) Yard herbicides: OR=2.1 (1.0-4.4) i) use of protective equipment: OR=2.5 (1.1-5.8) ii) Chemicals used on farm: triazines OR=3.2 (1.2-8.9); 2,4-DB OR=3.5 (1.2-9.9); No associations were found between farm chemicals and small-for-gestational-age births or altered sex ratio.	5.5 Possible exposure misclassification, limited power; lengthy recall

* Papers marked with an asterisk were considered in other tables.

Chapter 10 — Pesticide Health Effects and Children

Children are ubiquitously exposed to low levels of pesticides in their food and environment, yet there has been a paucity of studies on the long-term health effects of these exposures (10, 26, 32). Many pesticides persist in the environment, are often transferred long distances from their original area of application, are routinely detected in human tissue, and are transferred across the placenta and via breast milk (1, 19).

Relative to adults, children eat more in proportion to their body weight, resulting in more concentrated exposures. Intakes by children of the four primary pesticides (chlorpyrifos, malathion, diazinon, and atrazine) appear to come primarily from the ingestion of solid food (2). Another common exposure source is indoor and outdoor home pesticide applications, where children may be exposed by playing on floors, treated lawns and play areas, or by handling treated pets (8). Agricultural uses of pesticides may expose children inadvertently from spray drift or farm work (31).

Children present a number of unique characteristics with regard to risks from exposure to pesticides and other environmental pollutants. The most vulnerable time is during fetal development when the brain is known to be subject to environmental influences at all phases of development, with critical windows at different points (6). Since in the female, ova are formed in the fetal stage, and environmental contaminants have been found in follicular fluid, the next generation of children born may be affected by their grandmother's exposures (6). The newborn child has low levels of the enzyme paraoxanase-1, which detoxifies organophosphate pesticides (7).

Environmental contaminants may pose a greater risk to children than adults for another reason: children have a longer life expectancy in which to develop diseases with long latency periods. For example, if a 70-year-old adult and a 5-year-old child are exposed to a carcinogen with a 40-year latency period, the child has a much higher lifetime risk of developing adverse health consequences (20).

Studies in children have so far demonstrated subtle neurotoxic effects of low level, intrauterine, or early childhood exposures to a variety of environmental agents including lead, methyl mercury, and PCBs. While studies of pesticide health effects in children are still lacking, it is possible that a parallel model may emerge for low-level exposures to pesticides, some of which are by design neurotoxic (28, 32, 33). A range of developmental disabilities including learning disabilities, attention deficit hyperactivity disorder, developmental delays, autism, and behavioural disorders are of great importance due to possibly increasing incidence, and personal and public health costs. (12, 17, 18, 33). These are disorders of unknown etiology with a link between genetic susceptibility and environmental factors, perhaps including pesticides in some small proportion of cases (18, 27). Research is urgently needed to fill in the many gaps in this area.

Summary of Findings Concerning Children

The few studies we found which addressed children's health effects from exposures to pesticides have been discussed in detail in each relevant chapter and will be summarized here.

Several studies found associations between pesticide exposures and solid tumours in children. An elevated rate of kidney cancer was associated with paternal pesticide exposure through

agriculture (11). Four studies found associations with brain cancer: two found associations with indoor household use of pesticides (9, 30), one with parental farming occupation (16), and one with parental occupational exposure to pesticides (34).

Several studies in this review implicate pesticides as a cause of hematologic tumours in children. One study found an association with childhood non-Hodgkin's lymphoma (5), and several studies found elevated childhood leukemia rates with pesticide exposure (16, 21, 23, 24). An excellent study by Ma (23) showed an association between maternal pesticide exposure and childhood leukemia. More detailed information on these studies is in Chapters 3–5.

In the genotoxicity or immunotoxicity area (Chapter 6) there were two studies relevant to children. In the first, children with poor metabolizer polypmorphisms, genotyped at birth and representing just over 40% of the Montreal study group, had overall increased risk of acute lymphocytic leukemia if exposed to pesticides in utero or during childhood, especially for exposure to repellents and sprays for outdoor insects during pregnancy, and exposure to mite and spider killers during pregnancy or between birth and leukemia diagnosis. Herbicide use (mainly 2,4-D), both during pregnancy and in childhood, showed a consistent interaction with poor metabolizer genes and was associated with a 2-fold increase in leukemia incidence (14). Phillips (29) found that children exposed to chlordane and/or heptachlor had more cytokine panel abnormalities than matched controls.

Neurodevelopmental effects (Chapter 8) were found in pre-school children in pervasive pesticide exposure situations in Mexican valley agriculture, and likely resulted from maternal, in-utero, and early childhood exposures (13). The only other study of effects on children (15) found substantially higher proportions of residents — including adolescents — exposed to pesticides from aerial spraying drift to have mental and emotional symptoms compared to those not exposed by aerial spraying, consistent with other studies of broader nervous system function.

In the reproductive review (Chapter 9), findings suggested that occupational exposure to agricultural chemicals including pesticides may cause intrauterine growth retardation, and may increase a woman's risk of giving birth to children with congenital anomalies, such as limb defects, nervous system and musculoskeletal defects, cryptorchidism and hypospadias, cardiovascular defects, oral clefts, and other multiple and specific defects. The adverse reproductive effects that are non-fatal produce future risks for the individual and for the next generation. Intrauterine growth retardation has been shown to increase susceptibility in later life to hypertension, type 2 diabetes, heart disease, and breast and prostate cancer (3, 4). Men with birth defects are twice as likely to produce children with birth defects (22).

Future Studies

There have been some plans to develop a parallel Canadian cohort study that would be complementary to the US National Children's Study, a study that will follow a cohort of 100,000 children from the prenatal period to adulthood to study environmental influences on health and development. Scientists from Health Canada were involved in the planning along with the US National Institute of Child Health and Human Development, the US Environmental Protection Agency, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences. The Canadian involvement is dependent on federal funding which as of February 2004 is still uncommitted. Such a large and comprehensive prospective study is vital and would finally provide sufficient data to inform whatever policy decisions are necessary to protect our children and their futures.

Chapter 10 — Children

References

1. Anderson HA, Wolff MS. Environmental contaminants in human milk. *J Expo Anal Environ Epidemiol* 2000;10 Suppl 6:755–760.
2. Andrew Clayton C, Pellizzari ED, Whitmore RW, Quackenboss JJ, Adgate J, Sefton K. Distributions, associations, and partial aggregate exposure to pesticides and polynuclear hydrocarbons in the Minnesota Children's Pesticide Exposure Study (MNCPES). *J Expo Anal Environ Epidemiol* 2003;13(2):100–111.
3. Barker DJP, Eriksson JF, Forsen T, Osmond C. Fetal origins of adult diseases. *Int J Epidemiol* 2002;31:235–239.
4. Barker DJP. The developmental origins of adult disease. *Eur J Epidemiol* 2003;18(8):733–736.
5. Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer* 2000;89:2315–2321.
6. Chance GW, Harmsen E. Children are Different: Environmental Contaminants and Children's Health. *Can J Public Health* 1998;89 Suppl 1:S9–S19.
7. Chen J, Kumar M, Chan W, Berkowitz G, Wetmur JG. Increased Influence of Genetic Variation on PON1 Activity in Neonates. *Environ Health Perspect* 2003 Aug;111(11):1403–1410.
8. Cooper K, Vanderlinden L, McClenaghan T, Keenan K, Khatter K, Muldoon P, Abelsohn A. Children's Health Project: Environmental Standard Setting and Children's Health [report on the Internet]. Toronto: Canadian Environmental Law Association, Ontario College of Family Physicians Environmental Health Committee; 2000 [cited 30 March 2004]. Available from http://www.cela.ca/ch_health/titlepg.htm
9. Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer [comment]. *Arch Environ Contam Toxicol* 1993;24:87–92.
10. Eskenazi B, Bradman A, Castorina R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ Health Perspect* 1999;107 Suppl 3:409–419.
11. Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture: the role of pesticides. *Br J Cancer* 1998;77:825–829.
12. Goldman LR, Koduru S. Chemicals in the environment and developmental toxicity to children: a public health and policy perspective. *Environ Health Perspect* 2000;108 Suppl 3:443–448.
13. Guillette EA. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. *Environ Health Perspect* 1998;106(6):347–353.
14. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 1999;10(5):481–487.
15. Keifer M, Rivas F, Moon JD, Checkoway H. Symptoms and cholinesterase activity among rural residents living near cotton fields in Nicaragua. *Occup Environ Med* 1996;53:726–729.

16. 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;65:39–50.

17. Landrigan P, Kimmel C, Correa A, Eskenazi B. Children's health and the environment: Public health issues and challenges to risk assessment. *Environ Health Perspect* 2004;112(2):257–265.

18. Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. Environmental Pollutants and Disease in American Children: Estimates of Morbidity, Mortality, and Costs for Lead Poisoning, Asthma, Cancer and Developmental Disabilities. *Environ Health Perspect* 2002;110(7):721–728.

19. Landrigan PJ, Sonawane B, Mattison D, McCally M, Garg A. Chemical Contaminants in Breast Milk and Their Impacts on Children's Health: An Overview. *Environ Health Perspect* 2002;110(6):A313–A315.

20. Landrigan, PJ, JE Carlson, CF Bearer, JS Cranmer, RD Bullard, RA Etzel, J Groopman, JA McLachlan, FP Perera, JR Reigard, L Robison, L Schell, WA Suk. Children's health and the environment: A new agenda for prevention research. *Environ Health Perspec* 1998;106 Suppl 3:787–794.

21. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study [comment]. *Am J Public Health* 1995;85(2):249–252.

22. Lie RT, Wilcox AJ and Skjærven R. Survival and reproduction among males with birth defects and risk of recurrence in their children. *JAMA* 2001;285:755–760.

23. Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, Reynolds P. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspec* 2002;110(9):955–960.

24. 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:1943–1948.

25. 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(7):639–646.

26. National Research Council. *Pesticides in the Diets of Infants and Children*. Washington DC: National Academy Press; 1993.

27. National Research Council. *Scientific Frontiers in Developmental Toxicology and Risk Assessment*. Washington DC: National Academy Press; 2000.

28. Needleman HL. Childhood lead poisoning: the promise and abandonment of primary prevention. *Am J Public Health* 1998;88(12):1871–1877.

29. Phillips TM. Assessing environmental exposure in children: immunotoxicology screening. *J Expo Anal Environ Epidemiol* 2000;10 Suppl 6:769–775.

30. Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environ Health Perspec* 1997;105(11):1214–1220.

31. Pollack SH. Adolescent occupational esposures and pediatric-adolescent take-home exposures. *Pediatr Clin North Am* 2001;48(5):1267–1289.

32. Rice DC. Issues in Developmental Neurotoxiclogy: Interpretations and Implications of the Data. *Can J Public Health* 1998;89 Suppl 1:S31–S39.

33. Schettler T. Toxic Threats to Neurological Development. *Can J Public Health* 2001;109 Suppl 6:813–816.

34. 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):989–997.

Chapter 11 — Implications of the Review for Family Physicians

This systematic review of pesticide health effects was undertaken to help family physicians and their patients interpret the large body of literature in this area and make effective decisions about prevention efforts. These include patient education, identification of vulnerable groups, risk assessment, and clinical problem solving. We also identified areas where existing information is insufficient to inform clinical decision-making.

Family physicians, and other health professionals who are points of entry for health care, have at least three kinds of responsibilities in dealing with possible pesticide health effects.

A. Patient Inquiry

Patients ask questions about their concerns relating to pesticide exposure and potential health consequences. Their concerns may be related to occupational, home, or environmental exposures. We need good evidence-based information, distilled from methodologically acceptable studies, to answer these concerns, and to provide reassurance, educational intervention, or direction for further investigation into links between exposures and disease or illness. The information in this review is reported by health effect and will be useful in determining whether patients' concerns about specific health effects may be related to pesticide exposure. Because most human studies are of multiple pesticide exposures, the health effects of specific pesticides are still difficult to infer from the literature.

B. Health Screening

Patients also come to us for routine preventive care, giving us the opportunity for early intervention if their pesticide exposures are at a level that may cause significant health problems. Routine functional enquiries on farmers, pesticide applicators, professional gardeners, homeowners with lawns or gardens, floriculturists, and greenhouse workers should include specific questions about frequency, duration, and type of pesticide exposure, as well as about the use of protective gear, and any patient concerns about these exposures. Many studies document neurological, reproductive, genotoxic, and carcinogenic effects of pesticides, both in occupational and domestic settings, and preventive action is warranted for patients who are specifically vulnerable.

C. Case Finding: Relationship to ill-defined symptoms?

Finally, patients present with non-specific symptoms—for example, fatigue, dizziness, low energy, rashes, weakness, sleep problems, anxiety, and depression. An important step in diagnosing such non-specific symptoms is to take an exposure history (1) including pesticide exposures (2). There have been no studies of incidence of pesticide-related illnesses in primary care settings. Many of the studies in this review measure health effects that are subclinical, such as chromosome aberrations. There is a high level of consistency in results to indicate a wide range of pesticide-related clinical and subclinical health effects. Reviewing the literature since 1992, most studies of pesticides as a cause of health effects show a positive association. This is true across diverse areas including hematologic cancers, solid tumours, birth defects, increased time to pregnancy (a measure of couple fertility), neurological diseases, skin reactions, and genotoxic effects on lymphocytes.

Which pesticides are most harmful?

The results of the systematic review do not help indicate which pesticides are particularly harmful. Exposure to all the commonly used pesticides — phenoxyherbicides, organophosphates, carbamates, and pyrethrins — has shown positive associations with adverse health effects. The literature does not support the concept that some pesticides are safer than others; it simply points to different health effects with different latency periods for the different classes. Triazine herbicides increased breast cancer risk (3). Carbamate and phenoxyherbicide exposure increased lung cancer risk (4). Spraying of an organophosphate during pregnancy caused deterioration in placentas (5). Indoor use of insecticides was associated with brain cancer and acute lymphocytic leukemia in children (6, 7). Six pesticides, including 2,4-D and Dicamba, were associated with increased time to pregnancy (8). Fungicide exposure had positive associations with dermatitis (9, 10, 11).

Some more surprising positive associations were found for pesticides that are considered less toxic in acute poisoning settings. For example, pyrethrins were associated with chronic psychiatric effects (12), chromosome aberrations (13), rashes in licensed pet groomers (14), and intrauterine growth retardation, which is a major determinant of health in the first year of life (15). The herbicides glyphosate and glufosinate had associations with congenital malformations (16, 17). Parental preconception exposure to glyphosate was associated with late abortion (18).

Reducing exposure is the best advice

Given the wide range of commonly used home and garden products associated with health effects, our message to patients should focus on reduction of exposure to all pesticides, rather than targeting specific pesticides or classes. Such exposure reduction efforts could include: supplying information about organic methods of lawn and garden care and indoor pest control, education about the high skin absorption of pesticides, and instruction in the use of respirators for home and occupational exposures. For patients with occupational exposures, the history should include use of personal protective equipment, and timing of re-entry into recently sprayed work settings (19, 20). Information from a number of studies suggests that the use of protective equipment reduces exposure and health effects.

Vulnerable patient groups for pesticide health effects

Pregnant women are a special risk group, given the findings showing increased risk of childhood acute lymphocytic leukemia when women use pesticides in the home and garden during pregnancy (7). Women who intend to become pregnant need specific information about avoiding pesticide use in their homes, gardens, and workplaces.

Children are another very important group with specific vulnerability to pesticides. Family doctors need to consider possible pesticide exposures, which can occur by take-home exposures from a parent's workplace, use of pesticides on lawns, gardens, schoolyards, and parks, or by treating/spraying pets or homes (see Chapter 10 for a more detailed discussion of the vulnerability of children).

We have reported on many studies showing excess cancer risk in children exposed directly or indirectly to pesticides. These associated cancers include: brain cancer (6, 21), kidney cancer in offspring of occupationally exposed men (22), and excess acute lymphocytic leukemia in children whose mothers used pesticides in homes and gardens during pregnancy (7). In spite of

the important concern that pesticides may be toxic to the developing nervous system, only two studies (both positive) specifically examined neurological effects in children (12, 23). Reproductive effects of concern include increased miscarriage, fetal death, infertility, IUGR, and birth defects (see Chapter 9).

The elderly also have chronic neurological diseases that have been related to long-term pesticide exposure. These include Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease (Chapter 8). All these diseases are difficult to treat, which highlights the importance of prevention by reducing lifetime pesticide exposure.

Prevention and education opportunities for family doctors

Making a correct diagnosis that leads to effective treatment is still one of the enduring rewards of family practice. Consider pesticide exposure in your differential for recurring rashes and other non-specific symptoms, and that satisfaction may be yours.

There is little satisfaction for a family doctor in knowing that a patient's infertility, tumour, or Parkinson's disease was probably caused by pesticide exposure. The severity of many pesticide-related illnesses is a reason to focus on prevention rather than diagnosis.

Patients trust family doctors as a source of information on environmental questions (24). We need to earn this trust by informing ourselves: first about high-risk groups in our practices, then about methods to reduce pesticide exposure for women of childbearing age, occupationally exposed patients, and most importantly, children. Our offices can be used to promote reduction of pesticide use by our patients, and improved use of personal protection for those who choose to work with pesticides. We can promote community-based solutions by involving ourselves in the promotion of municipal bylaws aimed at reducing the cosmetic use of pesticides. Our concerns about health effects of pesticides can be transmitted to politicians who are making regulatory decisions which impact public health. We can be an important voice in encouraging our hospitals to stop using pesticides on lawns, and our schools to stop spraying areas where children play. We can promote the use of the precautionary principle in the area of pesticide use. This principle asserts "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully understood" (25).

What we can do

1. Correctly diagnose and treat acute and chronic pesticide health effects.
2. Emphasize prevention vs. retrospective case-finding for chronic or terminal disease
3. Inform ourselves about pesticide health effects and consider high-risk groups in our practices.
4. Advocate reduction of risk to or use by individual patients.
5. Advocate reduction of use in the community, schools, hospitals, and to governments.

Why we should do it

Very few of our patients willingly expose themselves to harmful chemicals, but information about pesticide health effects is not common knowledge, and we are in an excellent position to make it so. Strong one-to-one messages from health care providers about the potential harm from

pesticide exposure are an effective way to inform our patients. The evidence for harm is strong, and just as the public became aware of the health risks of smoking over decades of education, we now have an important role in heightening awareness of the risks of pesticide exposure.

In 2003, well-known non-Hodgkin's lymphoma researchers Hardell and Erikson (26) published a careful analysis of the decline in this disease in countries where the herbicide 2,4-D has been banned for over ten years. Their analysis concluded that 5% (3.0–7.7%) of NHL is attributable to chlorphenoxy herbicide and chlorophenol exposure. If this level of attributable risk is similar for even some of the other tumour–pesticide associations, it is clear that a concerted effort by physicians to reduce patients' pesticide exposures could produce measurable reductions in cancer. Stronger intervention at the regulatory level, such as the province-wide cosmetic pesticide ban instituted by the Government of Quebec in 2003, could well prove to provide important cost savings to the health care system. Even in the absence of cost reductions, the smallest reduction in incidence of non-Hodgkin's lymphoma, childhood leukemia, or brain cancer would reduce human costs and be a cause for celebration.

Chapter 11—Implications for Family Doctors

References

1. Marshall L, Weir E, Abelsohn A, Sanborn MD. Identifying and managing adverse environmental health effects:1. Taking an exposure history. *CMAJ* 2002;166(8):1049–1055.
2. Sanborn MD, Cole D, Abelsohn A, Weir E. Identifying and managing adverse environmental health effects: 4. Pesticides. *CMAJ* 2002;166(11):1431–1436.
3. 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;42:127–136.
4. 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;5:310–318.
5. Levario-Carillo M, Feria-Velasco A, De Celis R, Ramos-Martinez E, Cordova-Fierro L , Solis FJ. Parathion, a cholinesterase-inhibiting pesticide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study. *Gynecol Obstet Invest* 2001;52:269–275.
6. Pogoda, JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environ Health Perspec* 1997;105(11):1214–1220.
7. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms [comment]. *Epidemiology* 1999;10:481–487.
8. Arbuckle TE, Savitz DA, Mery LS, Curtis KM. Exposure to phenoxy herbicides and the risk of spontaneous abortion. *Epidemiology* 1999;10:752–760.
9. Cole DC, Carpio F, Math JJ, Leon N. Dermatitis in Ecuadorean farm workers. *Contact Dermatitis* 1997;37:1–8.
10. Paulsen E. Occupational dermatitis in Danish gardeners and greenhouse workers (II). Etiological factors. *Contact Dermatitis* 1998;38:14–19.
11. Rademaker M. Occupational contact dermatitis among New Zealand farmers. *Australas J Dermatol* 1998;39:164–167.
12. Keifer M, Rivas F, Moon JD, Checkoway H. Symptoms and cholinesterase activity among rural residents living near cotton fields in Nicaragua. *Occup Environ Med* 1996;53:726–729.
13. Mohammad O, Walid AA, Ghada K. 1995. Chromosomal aberrations in human lymphocytes from two groups of workers occupationally exposed to pesticides in Syria. *Environ Res* 1995;70:24–29.
14. Bukowski J, Brown C, Korn LR, Meyer LW. Prevalence of and potential risk factors for symptoms associated with insecticide use among animal groomers. *J Occup Environ Med* 1996;38:528–534.
15. Hanke W, Romitti P, Fuortes L, Sobala W, Mikulski M. The use of pesticides in a Polish rural population and its effect on birthweight. *Int Arch Occup Environ Health* 2003;76(8):614–620.

16. Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environ Health Perspec* 2002;110 Suppl 9:441–449.
17. Garcia AM, Benavides FG, Fletcher T, Orts E. Paternal exposure to pesticides and congenital malformations. *Scand J Work Environ Health* 1998;24:473–480.
18. Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspec* 2001;109:851–857.
19. Duell EJ, Millikan RC, Savitz DA, Newman B, Smith JC, Schell MJ, Sandler DP. A population-based case-control study of farming and breast cancer in North Carolina. *Epidemiology* 2000;11:523–531.
20. Lander BF, Knudsen LE, Gamborg MO, Jarventaus H, Norppa H. Chromosome aberrations in pesticide-exposed greenhouse workers. *Scand J Work Environ Health* 2000;26:436–442.
21. 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;65:39–50.
22. Fear NT, Roman E, Reeves G, Pannett, B. Childhood cancer and paternal employment in agriculture: the role of pesticides. *Br J Cancer* 1998;77:825–829.
23. Guillette EA, Meza MM, Aquilar MG, Soto AD, Garcia IE. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. *Environ Health Perspec* 1998;106(6):347–353
24. Health Canada. An investigation of the attitudes of Canadians on issues related to health and the environment. Ottawa: Decima Research; 1992.
25. Raffensperger C, Schettler T, Myers N. Precaution: Belief, regulatory system, and overarching principle. *Int J Occup Environ Health* 2000;6:266–269.
26. Hardell M, Eriksson M. Is the decline of the increasing incidence of non-Hodgkin lymphoma in Sweden and other countries a result of cancer preventive measures? *Env Health Perspect* 2003;111(14):1704–1706.

Appendix 1

Pesticides Literature Review

Form for Review Papers

Health Outcome Subject:_____

Reviewer's Name: _____

Date: _____

Complete Reference:_____

_____

Objective:_____

_____

_____

_____

Search Strategy: _____

_____

_____

_____

Inclusion and Exclusion Criteria: _____

_____

_____

_____

Number of Papers:

(a) Identified _____

(b) Relevant _____

(c) Assessed for Quality _____

Data Extracted: _____

_____

_____

Populations: _____

_____

_____

Description of Exposure: _____

_____

_____

_____

_____

Limitations: _____

_____

_____

_____

_____

_____

Observations: _____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Appendix 2

Pesticides Literature Review

Data Extraction Form

INSTRUCTIONS TO COMPLETE THIS AUTOMATIC FORM

1. Use the tab button to jump fields
2. Use the mouse or the space bar to check boxes
3. Save the file with the name “First author_year of publication_your intitials”
   For example: Arbuckle_1998_KB
4. Press F1 and you will see some instructions (not for all fields)

Reviewer name: Choose your name from the list:

Date:

Article:

Health Effect:

INCLUSION VERIFICATION

Does this study meet all the inclusion criteria?
☐ It is a study of health effects related to pesticide exposure in human populations
☐ This study was published between 1992 – present
☐ This paper is peer-reviewed
Conclusion
☐ Included ☐ Excluded
☐ Not sure (Please discuss with Marg Sanborn or Kate Bassil before you continue)

METHODS

Study design

☐ Retrospective cohort ☐ Prospective cohort
☐ Case control ☐ Case report, case series
☐ Cross-sectional survey ☐ Other

Study objective

Geographical region (city, country)

POPULATION

Number of individuals included in the study

Selection Method

☐ Random sample ☐ Other
☐ Convenience sample

Any matching used? Stratification? ☐ Yes ☐ No ☐ Don't know

Inclusion criteria

Exclusion criteria

Demographics

Age:

Sex:

Ethnicity:

Employment:

Other demographics:

DATA

Description of exposure

Type of exposure: ☐ Occupational ☐ Home ☐ Para-occupational Other

Length of exposure:

Timing of exposure:

Other information regarding exposure:

Exposure Assessment Method

☐ Self-report/questionnaire
☐ Biological monitoring
☐ Records (work, use, farm receipts, etc.)
☐ Lab diagnosis
☐ Database
☐ Other test (ex. skin patch)

Other

Quality control (i.e. systematic checks for errors, inconsistencies, rechecking of procedures, etc.)

☐ Yes ☐ No ☐ Don't know

Was the exposure assessment method blinded to the outcome?

☐ Yes ☐ No ☐ Don't know

Outcome Description

Outcome Assessment Method

☐ Self-report / questionnaire
☐ Clinical diagnosis / assessment
☐ Clinical records
☐ Lab diagnosis
☐ Database
☐ Other test (ex. skin patch,)

Other

Quality control?

☐ Yes ☐ No ☐ Don't know

Was the outcome assessment method blinded to the exposure?

☐ Yes ☐ No ☐ Don't know

Covariates
Description Quality control? ☐ Yes ☐ No ☐ Don't know Adjust for confounding (i.e. stratified analysis, adjustment): ☐ Yes ☐ No ☐ Don't know
Method of data analysis, statistical tests
Measures of effect: Measure of association Model of association Other Power: ☐ Estimated ☐ Not estimated

RESULTS

General
Quantitative results (Associate measurements)
Analysis (Limitations indicated by the authors)
Authors Conclusions

METHODOLOGICAL QUALITY ASSESSMENT

Were the methods and questions clearly stated?	☐ Yes ☐ No ☐ Don't know
Were the setting, population, and selection criteria clearly described?	☐ Yes ☐ No ☐ Don't know
Were the analyses appropriate?	☐ Yes ☐ No ☐ Don't know
Was bias avoided: Selection bias? Ascertainment bias? Confounding?	 ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know ☐ Yes ☐ No ☐ Don't know
Were all selected subjects included in the analysis?	☐ Yes ☐ No ☐ Don't know
Was the follow-up complete?	☐ Yes ☐ No ☐ Don't know
Were there exclusions from the analysis?	☐ Yes ☐ No ☐ Don't know
Did the researchers control for potential confounders?	☐ Yes ☐ No ☐ Don't know
Did the researchers account for any heterogeneity in results?	☐ Yes ☐ No ☐ Don't know

Rank on the Global Assessment Scale
(1-very poor, 2-poor, 3-unsatisfactory, 4-satisfactory, 5-good, 6-very good, 7-excellent):

Conclusions:

Is there any additional information you would like to add?

Is there any additional study in the reference list of this article that might be included in our review? Which reference(s)?

Please, after completion of this form return it to Kate Bassil by email (kate.bassil@utoronto.ca)