Pesticides and Human Health

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Pesticides and human health

Part 1: Systematic Review

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3.1 Introduction

Agricultural plays a large part in the land use and economy of Prince Edward Island (PEI). Productive conventional agriculture requires the use of a significant amount of pesticides to maintain high quality yields. Given the common use of pesticides in PEI for both agricultural and domestic purposes, it is important to understand the human health effects of pesticide exposure.

Pesticide use in PEI is primarily (60-80%) fungicides (F) applied to crops, with the balance made up of insecticides (I) and herbicides (H). Pesticides can be grouped according to their class of intended action (i.e. insecticide, herbicide or fungicide). They can also be grouped by type with compounds of similar chemical properties. In PEI, pesticide types used in quantities of more than 10,000 kg in 2008 included chloronitiriles (F), carbamates (F), pipyridyliums (H), aryloxyalkanoic acids (H), triazonines (H) and organophosphates (I).

Exposure can occur through oral ingestion, dermal absorption and inhalation. Pesticides can travel from one location to another on crops, clothing and footwear. Children are more vulnerable to pesticide exposure due to their high food consumption to weight ratio, absorptive skin, less effective livers and behaviors that put them in contact with floor and ground surfaces.Given the potential exposure of the entire population to both residential and agricultural pesticides, the human health effects of chronic pesticide exposure is an important topic of scientific research that is highly relevant to the PEI population.

3.2 Methods

We conducted an exhaustive literature review of published scientific papers in the area of pesticides and human health effects. Using a defined and focused PubMed search strategy, we retrieved relevant papers for each health effect. We explored the epidemiological research in reproductive, neurologic and neurodevelopmental, oncologic, respiratory, endocrine and other health outcome areas. Included in this review are meta-analyses, reviews, case-control and cohort studies and cross-sectional and descriptive analyses published from 2004 to 2015. Each article was reviewed and relevant information from the article was entered into the tables found in Appendix 1.

3.3 Results

Using the tables from Appendix 1, we described each study and graded the relationship between pesticide exposures and health outcomes using a letter grade system. The full guide to the letter grade system is presented in Table 6in the Methods section. In this summary section, we present only those relationships that achieved a letter grade of A in any category in Table 1. A letter Grade of A was assigned to those outcomes where the author concludes that there is **good** evidence to recommend that pesticides or the named pesticide or pesticide class **is** a contributing

factor to the human health effect under consideration. This evidence comes from several well-done observational studies or a well-done meta-analysis.

Much of the evidence is based on research studies of occupational pesticide exposures. Although these studies provide some indication of the possible health effects of a specific pesticide exposure, we cannot be certain that they transfer to a general population level of exposure to a specific pesticide. All results presented must be interpreted with this in mind and we have not presented occupational and other exposures separately in this summary. The reader should refer to the subject area of interest for the specific nature of the exposure associated with the outcome.

Many areas of pesticide exposure research comprise only one or a few studies. Given this limited evidence, in many instances it is difficult to conclude that there does not exist a significant relationship between a pesticide exposure and a health outcome.

In describing the results of the literature review, many reproductive outcomes and any outcomes involving children specify a particular exposure time frame (i.e. pre-conceptual, prenatal or during childhood). In order to simplify the presentation of the results, we have not included these risk periods in the summary tables. The reader should refer to the subject area of interest for critical periods of vulnerability.

3.3.1 Reproductive outcomes

There is good evidence to suggest that cleft palate is associated with any pesticide exposure(Table 1).

3.3.2 Neurological outcomes

Significant neurological outcomes were prominent in the research evidence (Table 1). There was good evidence for an association between any pesticide exposure and Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS).There was also good evidence that solvents, paraquat and maneb/mancozeb were associated with Parkinson's disease. Organophosphates were implicated in an increased number of abnormal reflexes in newborns.

3.3.3 Cancer outcomes

Cancer was the largest outcome area with a large volume of research into multiple different outcomes (Table 1). There was good evidence for significant associations between NHL and any pesticide, organophosphates, organochlorines, carbamates, triazine and triazonines, thiocarbamates, phenoxys and a number of specific pesticides (Table 1). In adults, any pesticide use was associated with any LHC, some types of leukemia and cutaneous melanoma. In children, any pesticide use was associated with lymphoma, brain cancer, Ewing's sarcoma, neuroblastoma and leukemia. Insecticides and fungicide exposure was associated with lymphoma and brain cancer in children. Insecticide and herbicide exposure was associated with leukemia in children. Hepatachlor was associated with breast cancer. Employment as an agricultural worker was also associated with leukemia.

3.3.4 Respiratory outcomes

There were no respiratory outcomes associated with pesticide exposure with good evidence.

3.3.5 Endocrine outcomes

There was good evidence that the specific organochlorines trans-nonachlor and oxychlordane were associated with diabetes..

3.3.6 Other outcomes

There were no other outcomes associated with pesticide exposure with good evidence.

3.3.7 Conclusion

Categorizing the human health effects of pesticides is a complex topic with many different possible exposures and outcomes. Several pesticides exposures have been shown to have significant human health effects. Many other pesticide exposure and outcome relationships lack sufficient well-designed epidemiological studies to enable the determination of their effect on human health. Recommendations that reduce the use of and exposure to pesticides for the general population and for vulnerable groups (i.e. pregnant women and children) are indicated based on the state of the research evidence at this time. In addition, educational supports for the reduction of and the safe use of agricultural pesticides are important to reduce the risks associated with pesticides in this occupationally exposed group.

Table 1. Grade A research findings for any pesticide, pesticide class or pesticide type.

Exposure		Outcome	
Any pesticide	Any	Cleft palate	NHL in adults
		PD	Lymphoma, brain cancer, Ewing's sarcoma & neuroblastoma in children
		ALS	
		ML in adults	AML in children
		CML in adult men	Childhood leukemia
		LHC in adults	Cutaneous melanoma
Pesticide class	Insecticide	Lymphoma & brain cancer	Childhood leukemia
	Herbicide	Childhood leukemia	
	Fungicide	Lymphoma & brain cancer	
	Solvents	PD	
Pesticide type	Organophosphates	Increased number of abnormal reflexes in newborns	NHL
	Organochlorines	NHL	
	Carbamates	NHL	
	Triazines and triazonines	NHL	
	Thiocarbamates	NHL	
	Phenoxys	NHL	
Specific pesticides or applications	Paraquat	PD	
	Maneb/mancozeb	PD	
	Heptachlor	Breast cancer	
	Lindane	NHL	
	Dicambia	NHL	
	2,4-D	NHL	
	Carbaryl	NHL	
	Carbofuran	NHL	
	Glyphosphate	NHL	
	Diazinon	NHL	
	Malathion	NHL	
	Pentachlorophenol	STS	
	Trans-nonachlor	Diabetes	
	Oxychlordane	Diabetes	
	Specific application (agricultural worker)	Leukemia	

PD: Parkinson's Disease ALS: Amyotrophic Lateral Sclerosis ML: Myeloid leukemia CML: Chronic Myeloid Leukemia LHC: Lymphohematopoietic Cancer NHL: Non-Hodgkin Lymphoma AML: Acute Myeloid Leukemia STS: Soft Tissue Sarcoma

4. Introduction

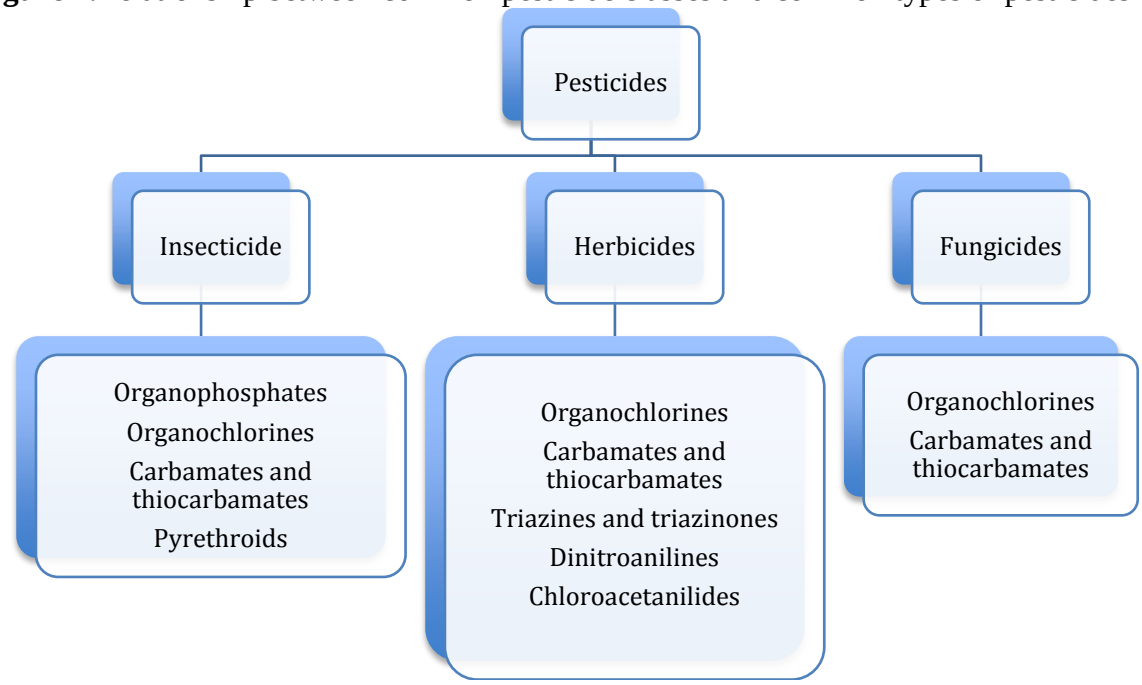
The use of pesticides has been of huge public benefit during the second half of the 21st century by significantly boosting agricultural yields and assisting in the control of many diseases. The PEI Department of Agriculture and Forestry advises that in a given year in PEI, between 60 and 80 percent of pesticides applied are fungicides with greater applications in years with more moisture to control potato blight. Insecticides and herbicides complete the remaining pesticide use in PEI in approximately equal proportions.(1) Given the large part agriculture plays in the economy and land use in PEI, it is important to understand and define the human health effects of pesticide exposure for Islanders.

Pesticides are a broad group of chemicals that are used to kill insects, weeds, fungi and rodents. Pesticides can be grouped by action into classes of herbicides, insecticides, fungicides and fumigants. These pesticide classes group diverse chemicals by their intended use. Herbicides are designed to repel weeds. Insecticides are meant to prevent and control insect infestation. Fungicides are intended to prevent fungus from growing and crop spoilage. Fumigants are pesticides that fill an area with a gaseous substance to suffocate target pests. Pesticides can also be grouped by type with compounds of similar chemical properties. Figure 1 describes the relationship between pesticide class and type.(2,3)

The most recent available 2008 PEI annual sales figures report that over 680 thousand kilograms (kg) of active pesticides were sold to applicators in the province. Of these pesticides, the vast majority were fungicides, at over 556 thousand kg. Much smaller volumes of herbicides and insecticides were sold, at 96 thousand and 27 thousand kg respectively. Recent trends have shown an increase in herbicide sales and a decrease in insecticide sales when compared to previous years. In 2008, Group A pesticides (sales of more than 50,000 kg) included the fungicides chlorothalonil (a chloronitrile), mancozeb and metiram (carbamates). Group B pesticides (sales of 10,001 to 50,000 kg) included the herbicides diquat (a pipyridyliums), MCPA (an aryloxyalkanoic acid), hexazinone (a triazonines) and the insecticide phorate (an organophosphate). All other products had sales less than 10,000 kg.(3,4)

A 2009 study of downwind potato pesticide drift in PEI focused on sample air levels of diquat, methamidophos, carbofuran and mancozeb during spraying and one and three hours post-spray. The air samples were collected at zero, 10, 30 and 100m downwind from the field. Concentrations of diquat, carbofuran and mancozeb were highest during spraying and were reduced or undetectable within one hour of spraying. Methamidophos was also reduced after spraying but took longer to dissipate, persisting at levels above the Texas Commission on Environmental Quality (CEQ) screening level up to three hours post-spray within 10m of the field. The CEQ screening level is a one-hour human health based effect screening level.

Figure 1. Relationship between common pesticide classes and common types of pesticides



Further information about the class and type of specific pesticides named in this report can be found in the glossary of pesticides and health outcomes (Section 15).

Exposure to pesticides can occur via oral ingestion, dermal absorption and inhalation. Residential pesticide exposures include pesticide use on lawns and gardens and in homes. Residential pesticides are used to control weeds, protect homes from infestations of wasps, cockroaches and ants and in pet and human treatments for scabies and lice. Pesticides applied in residential settings can be tracked into homes on clothing and vehicles, exposing the entire family.(5)

Agricultural pesticides are used on crops and their mixing and application are occupational pesticide exposures. Despite the initial application and mixing being occupational pesticide exposures, drift from spraying operations and runoff from fields into water sources can cause exposure of residential populations to agricultural pesticides. As well, consumers may ingestpesticides and/or pesticide residues when eating food items produced using these substances.(5)

Children are particularly vulnerable to high levels of exposure because they eat and drink more per kilogram than adults. Their skin absorbs pesticides more easily and their livers do not filter them out as quickly. They often put hands and non-food items in their mouths and play on the ground indoors and outdoors. Pesticides that may have quickly degraded outdoors may degrade slowly once brought inside on footwear and clothing. Men and women of reproductive age are also vulnerable to the pre-conceptual and prenatal effects of pesticide exposure on embryonic and fetal development. Pre-conceptual and prenatal pesticide exposure can also affect the risk of developing disease in childhood.(5)

Given the potential exposure of the entire population to both residential and agricultural pesticides, the human health effects of chronic pesticide exposure has been an important topic of scientific research. The scientific research in the area of pesticides and human health effects is vast. In collaboration with the PHAS, we have endeavored to limit the scope of the review to only the most relevant research for the situation in PEI. The focus of the review is on human health effects identified in recent comprehensive reviews.

5. Methods

The vast scope of research into the human health effects of agricultural and residential pesticide exposures meant that a focused strategy was necessary to complete a relevant review of the research.

5.1 Inclusion and exclusion criteria

The focus of the review was on determining the human health effects of pesticide exposures in the general population. To this end, several exclusion criteria were applied to the research articles retrieved using the search strategy. The specific exclusion criteria and their rationale are detailed in Table 2.

Table 2. Exclusion criteria and rationale

Criteria	Rationale
Involve exposures of cells in a laboratory	Focus of review is epidemiological studies in humans
Involve rats or other animal exposures	Focus of review is epidemiological studies in humans
Validate exposure testing for pesticides	This was not the focus of our efforts.
Involve non-agricultural occupational exposure and commercial applicators of pesticides	Occupational exposures outside of the agricultural sector are unlikely in PEI as there is no pesticide manufacturing facilities. Agriculture pesticide application can also result in contamination to the air, soil and water sources, and these are relevant to the general population health.
Studies not occurring in North America or Europe or Japan	Application of pesticides in other areas of the world is subject to fewer regulations regarding the substances used and the use of PPE during their application.
Case or case series descriptions	These do not provide quantitative assessments of the human health effects of pesticides.
Genotype studies	Although interesting, our focus is on the effect of pesticides on the health of the general population.
Specific subtypes of outcomes	Studies on rare subtype of outcomes are limited, involve small sample sizes and are not relevant to overall population health.
Studies and study results of DDT exposure	No use on PEI since 1960. Any DDT still in the environment is acting as a background exposure for the general population.
Off-label exposures	Studies examining accidental or intentional pesticide poisoning were not the focus of the review.

PEI: Prince Edward Island PPE: Personal Protective Equipment

When a well-done meta-analysis was retrieved for a specific subject area, studies that would have met the inclusion criteria were excluded from the review. For example, if the meta-analysis covered articles on paternal occupational pesticide exposure and childhood leukemia from 1999 to 2009, then only articles published from 2009 onwards on paternal occupational pesticide exposure and leukemia were included in this review to ensure that studies were not included multiple times.

5.2 Search strategy

The search strategy used for this review was based on methods used by Sanborn et al. (2012).(6) The PubMed database was searched for relevant articles using the search terms listed in Table 3 to Table 5. Articles were limited to those published about humans in English from 2004 to 2015. After locating the initial articles for each section, the titles were screened for relevancy. Articles that passed this screening had their abstracts reviewed and those that met all the inclusion criteria were retained. Any uncertainty regarding whether an article met inclusion criteria was resolved in consultation with the PHAS.

Table 3. Neurological, reproductive and endocrine PubMed search terms

Pesticide term used in all searches: pesticid* OR fungicid* OR herbicid* OR insecticid* OR molluscacid* OR rodenticid*

Human health effect area	Health effect	Search terms	Initial article count	Article count after title screening	Final number of articles included
Neurological	Parkinson's disease	Parkinson disease[majr] OR Parkinsonian Disorders[majr]	322	7	6
	ALS	ALS[majr]	25	3	2
	Memory disorders	Memory disorders	18	6	10[3]
	Depression	Depression[majr] OR Depressive Disorder[majr]	14	10	7
	Neurologic outcomes in children	Childhood Behaviour Disorders OR Nervous System Diseases[majr]) NOT Neoplasms	197	17	15
	Pervasive development disorder	Child development disorders, pervasive	19	7	4
	Attention deficit disorder	Attention deficit and disruptive behavior disorders	24	11	7
	Learning disorders	Learning disorders OR Developmental disabilities, mental retardation	14	4	4
Reproductive	Congenital abnormality[1]	congenital abnormality [majr] OR chromosomal aberration[majr]	54	49	24
	Fetal growth[2]	fetal development[majr] OR fetal growth retardation[majr] OR low birth weight[majr] OR gestational age[majr]	43	18	13
	Fetal loss and spontaneous abortion	spontaneous abortion[majr] OR stillbirth[majr] OR fetal death[majr]	23	6	1
	Infertility	fertility[majr] OR infertility[majr] OR female infertility[majr] OR sperm analysis[majr] OR sex distribution[majr]	132	35	17
	Preterm birth	Infant, Low birth weight [majr] OR Obstetric Labor, Premature[majr] OR Gestational Age [majr]	35	15	7
Endocrine	Diabetes	diabetes[majr] OR impaired glucose tolerance[majr]	73	29	13
	Other endocrine	endocrine system diseases[majr] NOT diabetes[majr] OR impaired glucose tolerance[majr]	140	48[4]	8
	Nutritional and metabolic disorders	nutritional and metabolic diseases	3	2	1

[1]For male genital defects only meta-analyses and studies done in North America were used due to the large number of studies in this area. Four articles were also eliminated due to being ranked low quality by Sanborn et al. (2012).(6)
[2]Reviews over five years old not pulled for this section
[3]Two articles from child neurological outcomes section
[4]One article to pancreatic cancer, 16 articles to congenital defects, five articles to testicular cancer and one article to ovarian cancer
ALS: Amyotrophic lateral sclerosis

Table 4. Respiratory, skin and other PubMed search terms

Pesticide term used in all searches: pesticid* OR fungicid* OR herbicid* OR insecticid* OR molluscacid* OR rodenticid*

Human health effect area	Health effect	Search terms	Initial article count	Article count after title screening	Final number of articles included
Respiratory	Asthma	asthma[majr] OR wheezing[majr]	33	14	12[1]
	COPD	chronic obstructive lung disease[majr] OR emphysema[majr] OR lung emphysema[majr] OR bronchitis[majr]	44	3	3
	Lung function	forced expiratory volume [majr] OR lung function test[majr] OR respiratory failure[majr] OR lung parenchyma OR bronchial reactivity AND Forced Expiratory Volume[majr] OR Respiratory Function Tests[majr] OR Respiratory physiological phenomena[majr] OR respiratory insufficiency[majr] OR bronchial hyperreactivity[majr]	72	3	3
	Respiratory tract infections	recurrent infection AND lung infection OR coughing[majr] AND chronic OR persistent	1	1	0
	Interstitial lung disease	Interstitial Lung Diseases[majr] OR Pulmonary Eosinophilia[majr] OR Bronchiolitis Obliterans[majr] OR Bronchiolitis[majr] OR Respiratory Hypersensitivity[majr] OR Extrinsic Allergic Alveolitis[majr] OR Pulmonary Fibrosis[majr] OR Pulmonary Sarcoidosis[majr] OR Sarcoidosis[majr] OR Granulomatous Disease[majr] OR Chronic Granuloma[majr] OR Respiratory Tract Bronchitis[majr] OR Emphysema[majr] OR Pulmonary Emphysema[majr] OR Bronchiectasis[majr]	97	2	2
Skin and other	Dermatitis	dermatitis	98	8	2
	Other health effects	NA[2]	NA[2]	NA[2]	13

[1]One article to lymphoma and two articles to chronic bronchitis and one extra article retrieved from Sanborn et al. (2012) (6)
[2] Articles for the other health effect section came from other categories when they fit the inclusion criteria but not explicitly into a health effect already defined
COPD: Chronic Obstructive Pulmonary Disease

Table 5. Cancer PubMed search terms

Pesticide term used in all searches: pesticid* OR fungicid* OR herbicid* OR insecticid* OR molluscacid* OR rodenticid*

Human health effect area	Health effect	Search terms	Initial article count	Article count after title screening	Final number of articles included
Cancer	General cancer	NA[1]	NA[1]	NA[1]	38
	Bone cancer	NA[1]	NA[1]	NA[1]	2
	Brain cancer	Central Nervous System Neoplasms[majr]	14	9	8
	Breast cancer	Breast Neoplasms[majr]	118	37	24
	Gastrointestinal cancer	Stomach neoplasms[majr]	18	6	5
	Kidney cancer	Kidney Neoplasms[majr]	11	5	1
	Leukemia	Leukemia[majr] OR Hematologic Neoplasms[majr]	35	16	7
	Liver cancer	Liver neoplasms [majr]	36	3	2
	Respiratory cancer	Respiratory tract neoplasms[majr]	48	4	4
	Lymphoma	Lymphoma[majr]	86	55	30
	Ovarian cancer	ovarian neoplasms[majr]	14	2	2
	Pancreatic cancer	Pancreatic neoplasms[majr]	21	10	8
	Prostate cancer	Prostatic Neoplasms[majr]	93	31	17
	Skin cancer	Skin Neoplasms[majr]):	31	9	7
	Testicular cancer	Testicular Neoplasms[majr]	14	9	7
	Other cancer	NOT Leukemia[majr] OR Hematologic Neoplasms[majr] OR Lymphoma[majr] OR Central Nervous System Neoplasms[majr] OR Kidney Neoplasms[majr] OR Breast Neoplasms[majr] OR Prostatic Neoplasms[majr] OR Liver neoplasms[majr] OR Respiratory tract neoplasms[majr] OR Skin Neoplasms[majr]	236[1]	83[1]	3
Children	General cancer	NA[1]	NA[1]	NA[1]	10
	Brain cancer	Central Nervous System Neoplasms [majr]	20	15	5
	Leukemia	Leukemia[majr] OR Hematologic Neoplasms[majr]	51	20	13
	Wilms' tumor	Wilms tumor[majr]	4	4	3
	Other cancer	NA[1]	NA[1]	NA[1]	3

[1] All articles retrieved for these categories came from the other cancer search
NA: Not applicable

Due to the sheer number of articles retrieved, the goal was to summarize the relevant results for each outcome category. Confounders were not explicitly listed in the outcome tables due to their number and time constraints. However, the risk estimate listed is always the most adjusted estimate (i.e. the estimate that adjusted for the largest number of confounders) provided by the authors of the article. Quality scoring was attempted for the articles but was dropped due to the volume of articles and the similarity of the quality scores between articles.

When presenting the results of the literature review, we included mainly significant results. Because many studies examined large numbers of pesticides or outcomes, it was unwieldy to provide long lists of negative results particularly for specific pesticides. This means that all significant positive results have been carefully listed but that negative results are not necessarily included in the review.

5.3 Type of studies considered

Two main types of articles were retrieved using the search strategy. The first type consisted of review articles and meta-analyses.

Review articles summarized the state of research but did not provide quantitative aggregate risk estimates for the specific pesticides exposure and health outcome. The review articles retrieved were of varying quality with some providing a systematic review of the evidence with table listing quantitative risk estimates and others providing only basic study descriptions and written summaries.

Meta-analyses provided much of the same information as the review articles but summarized the individual risk estimates from studies into a meta risk estimate. These meta-analysis, where they were available, were generally of high quality and presented the best available evidence of the human health effects of a specific pesticide exposure. Many health outcomes had an insufficient number of studies or studies that were too heterogeneous to allow this approach to be applied.

The second type of article reviewed consisted of individual studies. Because pesticide exposure is considered hazardous, the gold standard of a randomized controlled trial is not ethical and we must rely on epidemiological evidence to reach conclusions about the health effects of pesticides. Cross-sectional, case-control, cohort and ecological studies were included in this review and there were all levels of quality within each type of study.

When examining results for the review, only those results that reached statistical significance were included in the report. Statistical significance was defined at a p value of less than 0.05 and a lower end confidence interval that did not include the null value (i.e. 1.0 for an Odds Ratio or Risk Ratio and 0 for a continuous difference measure). Many studies reported findings as significant when they had confidence intervals that included the null value and these findings were not included in the review. All risk estimates reported are the maximum adjusted risk estimates for the available confounders. Crude risk estimates are identified as such.

Each article was reviewed and relevant information from the article was entered into the tables found inAppendix 1. These tables form the basis for the rest of the project.

5.4 Evaluation of studies

Once the studies had been retrieved and examined, we required a suitable framework to evaluate the evidence for each pesticide and health outcome. Given the complexity of the task, with multiple pesticides and multiple possible outcomes, an explicit means of evaluation was required. In consultation with the PHAS, the Public Health Agency of Canada's National Advisory Committee on Immunization's evidence grading guidelines were modified to suit our needs.(7) Our modified grading system is presented in Table 6.

We applied a strict hierarchy of exposures and outcomes when entering studies into our letter grade tables to improve clarity and interpretation.

Hierarchy of exposure:

1) Any pesticide
2) Pesticide class (i.e. insecticide, fungicide, etc...)
3) Pesticide type (i.e. organophosphate, organochlorine, etc...)
4) Carcingenicity category (i.e. probable, possible, etc...)
5) Specific pesticide (i.e. metam sodium)
6) Specific application (i.e. metam sodium with gloves on)

Hierarchy of outcomes:

1) Primary outcome (i.e. leukemia)
2) Primary outcome by subgroup (i.e. leukemia in males under 18)
3) Secondary outcome (i.e. Acute Lymphocytic Leukemia (ALL))
4) Secondary outcome by subgroup (i.e. Acute Lymphocytic Leukemia (ALL) in males under 18)

Table 6. Evidence grading

Grade	Description
A	The author concludes that there is **good** evidence to recommend that pesticides or the named pesticide or pesticide class **is** a contributing factor to the human health effect under consideration. This evidence comes from several well-done observational studies or a well-done meta-analysis.
B	The author concludes that there is **moderate** evidence to recommend that pesticides or the named pesticide or pesticide class **is** a contributing factor to the human health effect under consideration. This evidence comes from one or a few observational studies of variable quality.
B-	The author concludes that there is **fair** evidence to recommend that pesticides or the named pesticide or pesticide class **is** a contributing factor to the human health effect under consideration. This evidence comes from one or a few observational studies of poor quality.
C	The author concludes that there is **inconsistent** evidence to recommend that pesticides or the named pesticide or pesticide class **is or is not** a contributing factor to the human health effect under consideration. Several well-done observational studies or a meta-analysis are presenting conflicting results.
D	The author concludes that there is **fair** evidence to recommend that pesticides or the named pesticide or pesticide class **is not** a contributing factor to the human health effect under consideration. This evidence comes from one or a few observational studies of variable quality.
E	The author concludes that there is **good** evidence to recommend that pesticides or the named pesticide or pesticide class **is not** a contributing factor to the human health effect under consideration. This evidence comes from several well-done observational studies or a well-done meta-analysis.
I	The author concludes that there is **insufficient** evidence to recommend that pesticides or the named pesticide or pesticide class **is or is not** a contributing factor to the human health effect under consideration. There are no or limited studies in the subject area.

There are considerable methodological challenges in assessing the human health effects of pesticides and we can present these based on the study design.

Exposure assessment is a problem for all studies of pesticides and human health. Biomarker testing is the gold standard for exposure assessment. Aside from organochlorine pesticides that accumulate in body tissues, pesticides have a short half-life inside the human body. Many pesticides lack commercially available biomarker testing methods. Even for those pesticides for which biomarker testing is available, the timing of biomarker assessment is important. Pesticides are applied periodically and the exposure level is not consistent even from day to day. As well, particularly for chronic or long-term outcomes such as diabetes or cancer, there is a long lag time from exposure to the chronic disease or cancer occurring. As a result, alternative exposure assessment methods are required.

Given the rare nature of many outcomes related to pesticide use, case-control studies provide a means of examining relationships between pesticides and human health effects. Unfortunately, the exposures considered in these studies will be for the most part well in the past.

Organochlorine pesticide levels can still be measured but for other pesticides a different means of exposure assessment is required. Recall bias may play a significant part in these results, particularly if the population views pesticides as harmful. This may be particularly true when population controls are used. Other problems with case-control studies include low participation rates, loss to follow-up and low numbers of exposed cases.(5)

Cohort studies have frequently been used to evaluate pesticides. Unfortunately, most cohort studies focus on self-reported exposures among adult males belonging to occupational groups likely to be exposed to high levels of pesticides along with other potentially harmful exposures.(5) Recall has been proven to be fairly accurate within the Agricultural Health Study. Exact agreement was in the range of 80% for pesticide application methods and for specific pesticides used when evaluated one year later. Once more information on the frequency and amount applied was required, exact agreement dropped to 50 to 75%.(8)

Studies that have relied on job exposure matrices or other occupational proxies for exposure are likely underestimating the true effect of the pesticides for a couple of reasons. Using occupation as a proxy for occupational exposure to pesticides in farmers can result in substantial over-estimation of the number of exposed individuals. One study estimated that 78.3% of farm jobs had no likelihood of pesticide exposure but that most jobs with likely pesticide exposure were farm jobs (68.8%).(9) The healthy worker effect is another problem that plagues cohort study. Individuals in the workforce are known to have a lower risk of many conditions. Even if pesticide exposure increased their risk of an outcome to the level of the general population, this difference would be difficult to detect.

Other problems with cohort studies include loss to follow-up, low numbers of exposed cases and difficulties in complete outcome ascertainment. There are significant costs that accompany doing large cohort studies, particularly for exposures that are rare at the population-level and for rare outcomes. This makes the assessment of the health effects of pesticide exposure for the general population difficult.

Finally ecological studies examine aggregate exposure and outcome measures. While these studies can provide interested evidence and generate hypotheses they do not provide evidence for individual-level effect of pesticide exposure.

6. Reproductive health outcomes and pesticide exposure

6.1.1 Fetal growth

Table 7. Pesticide exposure and fetal growth

Grade	Exposure	Outcome
B	Any pesticide (occupational)	Fetal length and placental weight (10)
	Specific pesticide (metochlor)	Low birth weight (11)
	Specific pesticide (carbaryl)	Decreased birth weight (12)
	Specific application (municipalities growing peas)	Reduced head circumference (13)
B -	Specific pesticide (dichloran)	Increased abdominal circumference (11)
C	Specific pesticide (atrazine, late pregnancy)	Small-for-Gestational Age (14–16)
D	Any pesticide	Head circumference (17)
	Any pesticide	Growth restriction (13)
	Any pesticide	Birth weight (12,13,17)
	Any pesticide (occupational)	Fetal weight and head circumference (10)
	Pesticide type (organophosphate)	Birth weight (18)
	Pesticide type (organochlorine)	Birth weight, crown-heel length and head circumference (19,20)
	Specific pesticide (atrazine, late pregnancy)	Low birth weight (16)
	Specific pesticide (chlorpyrifos)	Birth weight, length and head circumference (21)

6.1.1.1.1 Non-organochlorine pesticides

Five studies examined associations between non-organochlorine pesticides and fetal growth. Overall, there is a lack of consistent evidence supporting a strong relationship between environmental non-organochlorine exposure and changes in fetal growth.Some of these studies examined a large number of pesticides and some significant findings would be expected based on chance alone.(11,12) There is limited clinical significance of the change in newborn birth length and head circumference that were associated with environmental pesticide exposure in two of the studies.(10,13)

Barr et al. (2010) examined maternal serum biomarkers for 8 pesticides in a cohort of 150 women having elective cesearean deliveries in New Jersey. They found significant associations only between high (above the 75th percentile) levels of metochlor and low birth weight and high levels dichloran and increased abdominal circumference.(11) Sathyanarayana et al. (2010) examined birth outcomes and first trimester use of pesticides in a cohort 2,246 farmwomen participating the Agricultural Health Study. Only the use of carbaryl was associated with a significant 82g reduction in birth weight.(12) Petit et al. (2012) did not find any associations between birth weight and head circumference and residential or agricultural insecticide exposures in their cohort study of 1,213 French births.(17)Petit et al. (2010) did not find any associations between birth weight and growth restriction and agricultural exposures in their cohort study of 3,421 births, except for a significant reduction of 0.2cm in head circumference in municipalities growing peas.(13) Snijder et al.(2012) examined a cohort of 4,680 women in the Netherlands for occupational pesticide exposure and fetal weight, placental weight, head circumference and fetal length. They found significant reductions in fetal length of 0.035cm and placental weight of 65.90g with occupational pesticide exposure.(10)

6.1.1.1.2 Organophosphates

One study and a review examined associations between organophosphate exposure and fetal growth outcomes.(18,21)There is no consistent evidence supporting an association between changes in fetal growth parameters and organophosphate exposure in the studies included.

Rauch et al. (2012) examined 6 organophosphate urinary metabolites in 306 infant-mother pairs. No significant change in birth weight was found after adjustment for gestational age.(18) Mink et al. (2012) review 4 cohort studies of chlorpyrifos exposure and birth weight, length and head circumference and found no consistent associations.(21)

6.1.1.1.3 Atrazine

The association between atrazine and fetal growth was the subject of three studies.(14–16)The evidence is inconsistent for a possible increase in Small-for-Gestational-Age (SGA) babies with high levels of late pregnancy atrazine exposure.

Migeot et al. (2013) examined 11,446 women-neonate dyads and atrazine and nitrate levels by tertile in community drinking water. No combinations of atrazine levels and nitrate exposure showed significant associations with SGA births.(14)A second cohort study of 24,154 births in Indiana found that atrazine concentration in drinking water above 0.1 μg/L during the third trimester resulted in a 17–19% increase in the prevalence of SGA compared with the non-exposed cohort(below 0.1 μg/L).(15) A third cohort study of 3,510 births in Spain found that there was no overall association between SGA and low birth weight babies and atrazine water levels. (16)

6.1.1.1.4 Organochlorines

Organochlorines and fetal growth outcomes were the subject of two studies that met the inclusion criteria. No associations were found between maternal serum organochlorine levels and birth weight, crown-heel length and head circumference in two cohort studies of 385 and 722 American infants.(19,20)

6.1.2 Congenital abnormalities

Table 8. Pesticide exposure and congenital abnormalities

Grade	Exposure	Outcome
A	Any pesticide (maternal, occupational)	Cleft palate (22)
B	Any pesticide (paternal exposure, housewife and conception Apr-Sept)	Congenital defects (23)
	Any pesticide (maternal, occupational)	Gastrochisis in children of women over age 20 (24)
	Any pesticide (residential, at time of conception)	NTD (25)
	Pesticide class (herbicides or insecticides, maternal periconceptual)	Esophageal atresia (26)
	Pesticide type (petroleum derivatives)	Anencephaly (27)
	Pesticide type (hydroxybenzonitriles)	Spina bifida (27)
	Pesticide type (dinitroanilines and dithiocarbamates)	Cleft lip palate (27)
	Specific pesticides (trifluralin and maneb)	Cleft lip palate (27)
	Specific pesticide (cyanazine and dicambia)	Congenital defects in males(28)
	Specific pesticide (diclofomethyl)	Hypospadias (29)
	Specific pesticide (atrazine)	Hypospadias (30)
	Specific pesticide (atrazine)	Gastrochisis in children of women over age 25 (31)
	Specific pesticide (atrazine)	Choanal stenosis (32)
	Specific pesticide (atrazine)	Congenital defect (30)
	Specific pesticide (hexachlorobenzene)	Cryptorchidism (33)
	Specific pesticide (hexachlorobenzene and chlordane)	Cretinism (34)
	Specific application (maternal work in agriculture around conception)	NTD (35)
	Specific application (potato cultivation)	NTD (36)
	Specific application (napropamide, benomyl, 1,3-dichloropropene, acephate, phloropyrifos, dimethosate, disulfoton, glyphosate, naled, oxydemetonmethyl, fenbutation-oxide, oxyfluorfen and methomyl application within 1,000m of the home)	NTD (37)
	Specific application (paternal farm work over 500 hours per year)	NTD (36)
	Specific application (conception during high pesticide season when mother a housewife)	Stillbirth caused by congenital abnormality (23)
	Specific application (living near cultivated fields)	NTD (25)
	Specific application (high atrazine and pesticide exposure months at conception)	Congenital defects (38)
C	Any pesticide (occupational, maternal or paternal)	Hypospadias (39,40)
D	Any pesticide (maternal, occupational)	Gastrochisis in children of women under age 20 (24)
	Pesticide class (herbicides or insecticides, maternal periconceptual)	Congenital diaphragmatic hernia (26)
	Specific pesticide (atrazine)	Gastrochisis in children of women under age 25 (31)
	Specific application (number of pesticide exposures within 500m of residence)	Hypospadias (29,41)
E	Pesticide type (organochlorine)	Male genital defects (33,42–44)

NTD: Neural Tube Defect

Four articles were identified that examined the risk of congenital abnormalities in general.(23,24,28,38)These studies found an increased risk of birth defects in a subset of paternally exposure fetuses(23), with conception during the highest atrazine and pesticide months(38), with exposure to specific pesticides for male offspring (28) and for gastroschisis in older mothers with occupational pesticide exposure(24).

Two of the articles examined birth outcomes from birth certificates.(23,38) Ronda et al. (2005) examined 587,360 births in Spain for paternal agricultural work as a proxy for pesticide exposure and found a 1.7-fold increase in risk of a congenital abnormality causing stillbirth when the mother was a housewife and the child was conceived in the season of highest pesticide use (April to September).(23) Winchester et al. (2008) examined 30.11 million birth outcomes between 1996 and 2002 for congenital abnormalities in association with monthly nitrate, atrazine and other pesticide levels in water samples. They found that births with conceptual periods during the season of highest agricultural levels (April to July) were more likely to experience 11 of 22 birth defects studied.(38)

The other two articles examined periconceptual pesticide exposures. Weselak et al (2008) examined 3412 pregnancies in Ontario farm families for pre and post conception pesticide exposures. Exposure tocyanazine and dicamba were associated with a respective 5- and 2.4-fold increased risk of birth defects in male offspring only. No other significant associations were found.(28) Kielb et al. (2014) examined maternal occupational pesticide exposure based on job title from one month pre-conception to 3 months post-conception in 817 cases and 2857 controls. Occupational exposure to insecticides, herbicides and fungicide was associated with a gastroschisis among infants of women aged 20 years or older but not for women under age 20.

6.1.2.1 Neurological abnormalities

Five studies met the inclusion criteria and considered neurological abnormalities including neural tube defects in general, and specifically anencephaly and spina bifida.(25,27,35–37)In general, studies reported significant associations between increasing pesticide exposures and/or specific pesticides and the risk of neural tube defects.

Nordby et al. (2005) used a large retrospective cohort of 105,403 female and 131,243 male farmers and their 300,805 children to examine the association between mancozeb exposure and neural tube defects. They used fungal forecasts (a combination of humidity and temperate conditions) and farm production as a proxy for mancozeb exposure. They found an approximate 1.6 fold increase in neural tube defects with potato cultivation and paternal farm work over 500 hours per year.(36) Lacasana et al. (2006) examined 151 cases and 151 controls in Mexico and found that children born to mothers who worked in agriculture between 3 months before and 1 month after their last menstrual period had 4.5 times higher odds of having anencephaly.(35)

Residential proximity of the home to agricultural areas was the focus of the other three studies.(25,27,37) Rull et al. (2006) pooled two case-control studies (731 cases and 940 controls) and found significant increases in the risk of neural tube defects with the application of 13 pesticides within 1,000 meters of the home.(37) Yang et al (2014) examined pesticide application records and the residential proximity of 73 cases of anencephaly, 123 cases of spina bifida and 785 controls in California. They found significant associations for an increased risk of

anencephaly with exposure to petroleum derivatives and 4 specific chemicals and an increased risk of spina bifida with exposure to hydroxybenzonitriles and specifically bromoxynil octanoate.(27) Brender et al. (2010) examined 184 cases of neural tube defects and 225 controls among Mexican American women. They found that after adjustment for significant confounders, the use of pesticides at home and living near cultivated field around the time of conception were associated with 1.8- and 2.7-fold increase in risk of neural tube defects. There was evidence of a dose-response relationship with increasing risk of neural tube defects associated with an increasing number of pesticide sources.(25)

6.1.2.2 Hypospadias and cryptorchidism

The literature examining associations between hypospadias and cryptorchidism and pesticide use is broad and encompasses numerous articles. To limit the scope of this review, only articles that both met the inclusion criteria and involved North American studies were included.

6.1.2.2.1 Non-organochlorines

Four articles and one meta-analysis examined the association between male genital birth defects and exposure to pesticides in general.(29,30,39–41)Occupational exposure to non-organochlorine pesticides in North America showed an inconsistent association with the risk of hypospadias.(39,40) Studies examining environmental exposure to pesticides due to residential proximity to agriculture and male genital defect had mixed results.(29,30,41) Atrazine in drinking water was associated with an increase in hypospadias in one study.(30)

Two of the aforementioned studies considered occupational pesticide exposure. In their 2009 meta-analysis Rocheleau et al. found an elevated risk of hypospadias with both paternal and maternal occupational pesticide exposure when they pooled the results from 9 studies.(39) A study of 647 cases and 1496 controls in the United States by Rocheleau et al. (2011) found no significant increased risk of hypospadias with maternal occupational pesticide exposure in the 1 month prior to conception and the first trimester of pregnancy.(40)

Three studies examined environmental pesticide exposure due to residential proximity to application sites (29,41) or in water (30). Carmichael et al. (2013) examined 690 cases and 2195 controls from California and found no increase in risk of hypospadias with exposure to increasing numbers of pesticides exposures within 500m of the home address. They did find some significant associations between exposures to a number of specific pesticides, representing a 1.9 to 3.4-fold increase in risk (see Appendix1). The authors do note that the a number of significant associations would be expected due to chance as they examined 57 chemical groups and 292 chemicals. As well, there is some evidence for a U-shaped response curve for endocrine disruptors, with larger increases in risk seen at low doses then tapering as the dose increases.(41) Meyer et al (2006) completed a similar analysis of 354 cases and 727 controls in eastern Arkansas where they examined pesticide application within 500m of the home address from gestational weeks 6 to 16. They found an 8% increase in risk of hypospadias with each additional 0.05-pound increase in diclofomethyl used. Despite examining 38 pesticides, no increase in risk of hypospadias was seen with any other chemicals.(29)

Agopian et al. (2013) examined country level estimate of atrazine water levels and the risk of hypospadias, cryptorchidism and small penis in 16,433 cases and county level controls. They found that women with atrazine exposures between the 25th and 90th percentile had a significantly increased risk of having infants with male genital malformations alone. Women with atrazine exposure above the 90th percentile had an increased risk of having infants with male genital malformations in combination with other birth defects.(30)

6.1.2.2.2 Organochlorines

Four articles examined associations between organochlorine pesticides and male genital birth defects. All four articles were case-control studies using maternal serum organochlorine levels and none found any consistent significant associations between male genital defects and organochlorine exposure.(33,42–44) The only exception is the largest case-control study by Pierik et al. (2007) where a 2-fold increase in cryptorchidism was seen with hexachlorobenzene levels between the 50th and 90th percentile.(33)

6.1.2.3 Orofacial abnormalities

Two studies and one meta-analysis examined orofacial defects and pesticide exposure.(22,27,32)Atrazine exposure in drinking water was associated with choanal atresis and stenosis in one study.(32) Maternal occupational pesticide exposure was associated with cleft palate in a meta-analysis study.(22)

Agopian et al. (2013) examined 280 cases of choanal atresis and stenosis and 3720 controls in Texas and their association with county level atrazine drinking water estimates. High levels of atrazine exposure were associated with a 1.8-fold increased risk of choanal atresis and stenosis and there was a trend of increasing risk with increasing atrazine exposure.(32)

Romitti et al. (2007) completed a meta-analysis of 19 studies of the association between cleft palate and exposure to pesticides. They found a significant pooled 1.4-fold increase in risk of clefting with maternal occupational pesticides exposure. There was no increased risk of clefting with paternal occupational pesticide exposure or residential pesticide exposure.(22) Yang et al. (2014) found an increased risk of cleft lip palate with exposure to 2 specific chemical groups and 2 chemicals in their study of 277 cleft lip palate cases and 785 controls in California.(27)

6.1.2.4 Gastrointestinal and endocrine abnormalities

There were significant increases in gastroschisis with atrazine drinking water exposure and in cretinism with increasing hexachlorobenzene and chlordane levels in breastmilk.(31,34)

Agopian et al. (2013) examined the association between gastroschisis and county level atrazine drinking water estimates in 1,161 cases and 8,390 county level controls in Texas. They found a significant 2-fold increase in risk of gastroschisis in the offspring of women over age 25 only.(31) Felix et al. (2008) found that maternal contact with herbicides or insecticides in the 1-month prior to conception to the end of the first trimester was associated with a significant 2-fold increase in esophageal atresia cases in their examination of 47 cases and 202 controls. This Netherlands-based study found no association with congenital diaphragmatic hernia.(26)

Nagayama et al. (2007) examined the association between exposure to organochlorine pesticides and cretinism (congenital hypothyroidism) in 34 cases and 102 controls in Fukuoka, Japan. They found that high levels in hexachlorobenzene and chlordane in breast milk were significantly associated with a respective 22- and 6.6-fold increase in risk of cretinism.(34)

6.1.3 Preterm birth

Table 9. Pesticide exposure and preterm birth

Grade	Exposure	Outcome
B	Pesticide type (organophosphates)	Decreased gestational age at birth (18)
	Specific pesticide (hexachlorobenzene)	Decreased gestational age at birth (20)
B -	Specific pesticide (hexachlorocyclohexane)	Preterm labor (45)
C	Specific pesticide (hexachlorocyclohexane and hexachlorobenzene)	Preterm birth (46)
	Specific application (atrazine in drinking water)	Preterm birth (15,16,47)

6.1.3.1.1 Atrazine

Three studies considered the association between preterm birth and atrazine levels in drinking water.(15,16,47) Two of these studies were discussed in the fetal growth section and found no significant association between drinking water atrazine levels and preterm birth.(15,16) The third study by Rinsky et al. (2012) of 71,768 Kentucky births divided women in 3 exposure groups based on atrazine water levels. They found a 1.2 to 1.3-fold increase in risk of preterm birth in the counties with the highest atrazine levels.(47)

6.1.3.1.2 Organophosphates

Rauch et al. (2012) examined 6 organophosphate urinary metabolites in 306 infant-mother pairs. They found a significant decrease in gestational age of 0.5 weeks for each 10-fold increase in metabolites.(18)

6.1.3.1.3 Organochlorines

Two studies and a review examined organochlorine pesticides and preterm birth.(20,45,46) Cioroiu et al. (2010) did not test for significant differences in the colostrum concentrations of the 63 mother in their study but the sum of hexachlorocyclohexanes isomers was higher in mothers who had experienced preterm labor.(45) Fenster et al. (2006) noted a significant decrease of gestational length of 0.5 weeks with increasing levels of hexachlorobenzene in their California-based cohort study of 385 women. The other seven pesticide maternal serum levels did not have any associations with length of gestation.(20) Ferguson et al. (2013) conducted a comprehensive review of organochlorine pesticides and preterm birth and found that there was insufficient data to make conclusions about hexachlorobenzene or hexachlorocyclohexane and preterm birth at the background levels found in the Unites States. There was an association between preterm birth and these organochlorines but only at levels much higher than those found in the United States.(46)

6.1.4 Infertility

Table 10. Pesticide exposure and infertility

Grade	Exposure	Outcome
B	Any pesticide (occupational)	Time-to-pregnancy (10,48)
	Any pesticide (residential)	Time-to-pregnancy (48)
	Pesticide type (pyrethroids)	Lower sperm motility and sperm motion parameters (49)
	Pesticide type (pyrethroids)	Semen concentration (50)
	Pesticide type (organophosphate)	Sperm quality and count (50,51)
	Specific pesticide (carbaryl/naphthalene)	Below-reference sperm concentration and percent motile sperm (52)
	Specific pesticide (hexachlorobenzene)	Time-to-pregnancy (53,54)
	Specific pesticide (hexachlorobenzene)	Failed implantation at IVF (55)
	Specific pesticide (β-hexachlorocyclohexane and heptachlor epoxide)	Time-to-pregnancy (54)
	Specific pesticide (benzene hexachloride)	Time-to-pregnancy (56)
	Specific pesticide (hexachlorobenzene)	Increased testosterone levels in men (57)
	Specific application (residence within 200 feet of an agricultural field)	Time-to-pregnancy (48)
B -	Any pesticide	Semen quality(58)
	Pesticide type (organochlorine)	Decreased oocyte/embryo quality and implantation rates at IVF (59)
	Specific pesticide (alachlor, diazinon and atrazine)	Low sperm quality (60)
D	Any pesticide (occupational)	Semen quality and infertility (61,62)
	Any pesticide (residential exposure to agricultural pesticide)	Fertility rates (63)
	Pesticide type (organochlorine)	Pregnancy rates after IVF (59)
	Pesticide type (pyrethroid)	Male reproductive hormone levels
	Specific pesticide (chlorpyrifos)	Lower sperm morphology, below reference sperm concentration and motility (52)
	Specific pesticide (carbaryl/naphthalene)	Lower sperm morphology (52)
	Specific pesticide (heptachlor epoxide, in utero or breastmilk exposure)	Any reproductive endpoint (64)
	Specific pesticide (hexachlorobenzene)	Chemical pregnancy or spontaneous abortion (55)

IVF: In Vitro Fertilization

6.1.4.1.1 Semen quality

Three studies and two reviewsexamined the association between pesticide exposure and semen quality and male infertility.(50,58,60–62) Two studies of occupational pesticide exposure, a cohort of 402 men consulting for couples infertility in France and a case-control study of 650 cases and 698 controls in the United States (US), failed to find an association between occupational pesticide exposure and semen quality or male infertility.(61,62) A small US-based case-control study of 25 cases and 25 controls examined urinary pesticides metabolite levels and low sperm quality. Men with higher levels of alachlor and diazinon and atrazine levels above the limit of detection were significantly more likely to have low sperm quality.(60)

Jurewicz et al. (2009) reviewed 19 studies of semen quality and pesticide exposure and found that several pesticides have clear effects on male fertility. However, exposure assessment was weak in most studies and this makes an evaluation of dose response relationships difficult.(58)Martenies et al. (2013) also reviewed 17 studies of sperm parameters and pesticides exposure. They found that most studies reported significant associations between sperm concentration and less frequently sperm motility and exposure to all pesticides. Specifically, exposure to pyrethroids may reduce semen concentration and organophosphate exposure may reduce semen quality.(50)

6.1.4.1.1.1 Organophosphate pesticides

Both studies of organophosphate pesticides were associated with reduced semen quality parameters.(51,52)Recio-Vega et al. (2008) examined the relationship between organophosphate (OP) pesticides and semen quality, concentration and count by dividing 52 Mexican men into 3 groups: non-occupationally exposed, agricultural workers but not OP sprayers and OP sprayers. The lowest sperm quality and count were found among the OP sprayers compared to the other 2 groups. The sperm quality and counts were at their lowest point in the year in the spring when the highest use of OP pesticides occurred and improved in the winter when there was little use of OP pesticides.(51)

Meeker et al. (2004) examined 272 men attending aMassachusetts infertility clinic with no occupational pesticide exposure for associations between semen quality and Carbaryl/Naphthalene (C/N) and Chlorpyrifos (C) urinary metabolites. Increasing concentrations of C/N was associated with increased odds of below-reference sperm concentration and percent motile sperm and lower sperm morphology. Increasing concentrations of C were associated with lower sperm morphology but not below-reference sperm concentration and percent motile sperm.(52)

6.1.4.1.1.2 Pyrethroid pesticides

Meeker et al. (2008) examined the relationship between pyrethroid insecticide urinary metabolite levels and semen quality among 207 men attending a Massachusetts infertility clinic. Higher metabolite levels were associated with significantly lower sperm motility and sperm motion parameters.(49)

6.1.4.1.2 Time-to-Pregnancy

Two studies and one review examined fertility rate and time-to-pregnancy and the relationship with general pesticide exposure. Two of these studies found increase time-to-pregnancy with increasing pesticide exposure.(10,48) The third study was a population level fertility rate comparison and could have been affected by multiple confounders on fertility rates not associated with pesticide use.(63)

Clementi et al. (2008) compared the fertility rates of resident women in three Italian province and low, intermediate and high pesticide exposure based on estimated quantities sprayed. There were no significant differences in fertility rates.(63) Harley et al. (2008) examined the time-to-pregnancy in a cohort of 402 pregnant women in a migrant farm community in California and

self-reported pesticides exposures. Significantly longer time-to-pregnancy was reported with maternal occupational pesticide exposure, home pesticide use and residence within 200 feet of an agricultural field.(48) Snijder et al. (2012) reviewed 7 studies that considered male and female pesticide exposures and found adverse effects on time-to-pregnancy in 6 of the 7 studies considered.(10)

6.1.4.1.2.1 Organochlorines

Four studies and one review considered the relationship between organochlorine pesticides and time-to-pregnancy or female infertility.(53–56,59) Three studies examined time-to-pregnancy and serum organochlorine levels in 501 couples in Michigan and Texas(53), 41 couples in Hamilton, Ontario(56) and 3,421 pregnant women in France(54). Two studies found significantly increased time-to-pregnancy with increasing exposure to hexachlorobenzene.(53,54) Chevrier et al. (2013) also found significantly increased time-to-pregnancy with exposure to β-hexachlorocyclohexane and heptachlor epoxide.(54)Cole et al. (2006) found significantly increased time-to-pregnancy with exposure to benzene hexachloride.(56)

Mahalingaiah et al. (2012) examined in vitro fertilization (IVF) outcomes and maternal serum levels of hexachlorobenzene in 720 women in Boston, Massachusetts. Increasing serum levels of hexachlorobenzene was significantly associated with increased odds of failed implantation but not chemical pregnancy or spontaneous abortion.(55) Kadhel et al. (2012) reviewed 22 studies examining the relationship between organochlorine pesticides and female fertility based on IVF outcomes. Organochlorine levels did not significantly affect pregnancy rates after IVF. There was suggestive evidence that increasing organochlorine levels were associated were decreased oocyte or embryo quality and implantation. Variations in studies protocols made comparisons between studies difficult.(59)

6.1.4.1.3 Reproductive function

Luderer et al. (2013) examined reproductive function in 457 adults who were in utero or nursing during a 15-month period of cow's milk contamination with heptachlor epoxide. No significant changes in reproductive endpoints were found. Some significant changes in age at menarche and menstrual cycle hormone levels were noted in the women exposed to higher levels of heptachlor epoxide.(64)Langer et al. (2014) found significantly increased testosterone levels with increasing serum levels of hexachlorobenzene for males aged 21 to 75 years.(57)

Yoshinga et al. (2014) examined urinary pyrethroid insecticide and serum reproductive hormone levels in 322 male Tokyo university students. They found no relationship between serum levels of reproductive hormones and urinary pyrethroid metabolite levels.(65)

6.1.5 Fetal loss and spontaneous abortion

Table 11. Pesticide exposure and fetal loss and spontaneous abortion

Grade	Exposure	Outcome
B -	Specific application (distance to hazardous waste sites containing pesticides less than 1 mile)	Fetal death (66)

Only one study of fetal loss was identified that met the inclusion criteria. Mueller et al. (2007) examined 7,054 cases of fetal death after 20 weeks and 10 controls per case in Washington State. They examined the distance between identified hazardous waste sites and maternal residence and found a 1.3-fold increase in risk of fetal death with residences located less than one mile from pesticide containing sites.(66) No additional information as to the nature of the pesticides was available in the article.

7. Neurological health outcomes and pesticide exposure

7.1 Neurologic health outcomes in adults

Table 12. Pesticide exposure and neurologic health outcomes

Grade	Exposure	Outcome
A	Any pesticide (occupational)	Reduced attention, visuomotor integration, verbal abstraction and perception (67)
B	Any pesticide (occupational, direct exposure)	Drop in MMSE score (68)
	Any pesticide (occupational, indirect exposure)	Reduced Stroop bad answer score (68)
	Any pesticide (occupational)	Headache, tension, insomnia, irritability, dizziness, numbness in hands or feet, depression, difficulty concentrating, twitches in arms or legs, fast heart rate, poor balance, poor night vision, tremor in hands, blurred double vision, changes in smell or taste, difficulty speaking and loss of consciousness(69)
	Any pesticide (occupational)	Decreased visual memory, attention and memory in men(70)
	Pesticide class (insecticides, fungicides and fumigants)	Experiencing more than 10 of 23 neurological symptoms (69,71)
	Pesticide type (organophosphates, organochlorines, carbamates and pyrethroids)	Experiencing more than 10 of 23 neurological symptoms (69,71)
	Pesticide type (organophosphate, occupational)	Decreased memory, response speed, fine motor control, mental flexibility and strategy making (72)
	Specific pesticide (enthoprop)	Decreased motor speed (73)
	Specific pesticide (malathion)	Decreased visual scanning (73)
	Specific application (more than 65 lifetime days of pesticide use)	Experiencing more than 10 of 23 neurological symptoms (71)
	Specific application (work in agriculture)	Decreased coding, complex function and response speed in women (70)
D	Any pesticide (occupational)	Neurobehavioural performance (73)
	Pesticide class (herbicide)	Experiencing more than 10 of 23 neurological symptoms (71)
	Specific application (work in agriculture)	Decreased coding, complex function and response speed in men (70)

MMSE: Mini Mental State Examination

Six studies and a meta-analysis examined associations between neurobehavioral outcomes and pesticide exposure.(67,68,70,72,73) Ismail et al. (2012) completed a meta-analysis of 17 studies of occupational organophosphate pesticide exposure in agricultural workers. Participants exposed to organophosphate pesticides showed significant reductions in measures of the neurobehavioral functions of attention, visuomotor integration, verbal abstraction and perception constructs.(67)

Baldi et al. (2011) examined 614 farmers who completed neurobehavioral tests several years apart and found a 2 fold increased risk of a 2 point drop in the Mini-Mental State Examination

(MMSE) in directly pesticide exposed participants and a 2-fold increase in risk of a reduced Stroop bad answers score in indirectly exposed participants.(68)

Mackenzie Ross et al. (2010) examined 127 sheep farmers and 78 controls for the effects of occupational exposure to organophosphates and found that exposed subjects performed significantly worse than controls on tests of memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for the effects of mood.(72)

Rohlman et al. (2007) examined the neurobehavioral performance of 119 adults and 56 adolescents who worked in agriculture and their experience handling pesticides. Women but not men performed worse on coding, complex function and response speed measures as the number of years they worked in agriculture increased. Men experienced significantly worse performance on tests of visual memory, attention and memory when they reported handling pesticides. There were no significant differences between adults and adolescents in the results.(70)

Starks et al. (2012) examined the neurobehavioural performance of 701 male pesticide applicators in the Agricultural Health Study and found no strong overall associations between performance and pesticide use. Only entoprop and malathion were associated with significant reductions in performance in motor speed (entoprop) and visual scanning (malathion). Interestingly, use of a number of specific pesticides was associated with improved performance.(73)

Kamel et al. (2007) examined 23 neurological symptoms in 18,782 male Caucasian pesticide applicators enrolled in the Agricultural Health Study. There were significant associations between experiencing more than 10 of the neurological symptoms in the past year and the application of more than 65 lifetime days of pesticides use (1.1 to 1.2-fold), the application of insecticides (1.8-fold), fungicides (1.3-fold) and fumigants (1.3-fold) and the use of organphosphates (1.5-fold), organochlorines (OR 1.7-fold) carbamates (1.4-fold) and pyrethroids (1.3-fold). Herbicides were not associated with having more than 10 neurological symptoms in the past years. There were significant dose-response relationships for insecticides, organophosphates or organochlorines.(71) A second analysis of the same data by Kamel et al. (2005) found significant dose-response associations with increasing cumulative lifetime days of insecticide use. They also found significant associations with, in descending order of strength, organophosphates, organochlorines, carbamates, pyrethroids, fumigants and fungicides. Exposure to any pesticide was significantly associated with headache, tension, insomnia, irritability, dizziness, numbness in hands or feet, depression, difficulty concentrating, twitches in arms or legs, fast heart rate, poor balance, poor night vision, tremor in hands, blurred double vision, changes in smell or taste, difficulty speaking and loss of consciousness.(69)

7.1.1 Parkinson's disease

Table 13. Pesticide exposure and Parkinson's disease

Grade	Exposure	Outcome
A	Any pesticide	PD (74–78)
	Pesticide class (solvents)	PD (74)
	Specific pesticides (paraquat and maneb/mancozeb)	PD (74,78)
B	Any pesticide (occupational, cumulative lifetime days)	Incident PD (79)
	Specific pesticide (trifluralin and 2,4,5-T)	Incident PD (79)
	Specific pesticide (paraquat and cyanazine)	Prevalent PD (79)
C	Pesticide class (herbicides)	PD (74,75,77)
	Pesticide class (insecticides)	PD (74,75)
	Specific application (high pesticide use districts)	PD (80)
D	Any pesticide (occupational, ever use)	PD (79)
E	Pesticide class (fungicide)	PD (74,75,77)

PD: Parkinson's disease

The literature examining connections between Parkinson's Disease (PD) and pesticide use is extensive. There appears to be a consistent association between overall pesticide exposure and an increased risk of PD. There are mixed findings regarding exposure to herbicides and insecticides as pesticide classes. Fungicides as a pesticide class do not appear to be associated with an increased risk of PD. Exposure to solvents, paraquat and maneb/mancozeb specifically appear to increase the risk of PD.

This section examined the results of four meta-analyses, one systematic review, an ecological study and a cohort study. In the four meta-analyses reviewed, there was an estimated 28 to 77% increase in risk of PD with exposure to pesticides in general.(74–77) The systematic review also noted significant associations between PD and general pesticide exposure in the majority of studies reviewed.(78) Parrón et al.'s 2011 ecological study also noted a 30% increase in PD cases in high pesticide use district compared to low pesticide use districts but when age and gender were incorporated the results were no longer significant.(80)

Three meta-analyses examined associations between classes of pesticides and PD with mixed results. Herbicide exposure was associated with a 40% increase in PD risk in two meta-analyses (74,75) but not in a third (77). Exposure to insecticides was associated with a 50% increase in PD in one meta-analysis (75) but a second one failed to find an association (74). Exposure to solvents was associated with a 60% increase in PD in one meta-analysis.(74) Fungicide exposure was not associated with PD in three meta-analyses.(74,75,77)

Specific pesticides exposures and their association with PD were examined in two meta-analyses. Paraquat and maneb/mancozeb exposure were associated with a respective 1.7- and 2.2-fold increase in PD in one meta-analysis.(74) A systematic review by Freire et al. (2012) also noted associations between paraquat and maneb/mancozeb and PD.(78)

Kamel et al. (2006) completed an analysis of 83 prevalent and 78 incident cases of PD within a cohort of 55,931 Agricultural Health Study participants. Neither incident nor prevalent PD was associated with ever pesticide use. There was a significant increase in risk of incident PD with increasing cumulative lifetime days of overall pesticide use (4^{th} quartile versus 1^{st} quartile 2.3-fold) with a significant trend. Incident PD was significantly associated with use of trifluralin (1.7-fold) and 2,4,5-T (1.8-fold). Prevalent PD was not associated with overall pesticide use but was significantly associated with the use of paraquat (1.8-fold) and cyanazine (2.6-fold).(79)

7.1.2 Amyotrophic lateral sclerosis (ALS)

Table 14. Pesticide exposure and ALS

Grade	Exposure	Outcome
A	Any pesticide	ALS (81)
B	Any pesticide (occupational)	ALS (82)
	Pesticide class (herbicide)	ALS (82)

ALS: Amyotrophic Lateral Sclerosis

Two studies examined associations between Amyotrophic Lateral Sclerosis (ALS) and pesticides exposure. Pamphlett et al. (2012) found an increase in risk of ALS of 77% for men and 43% for women with occupational exposure to herbicides or pesticides.(82) Kamel et al. (2012) completed a meta-analysis of published case-control studies and found a 90% increase in risk of ALS with any pesticide exposure but failed to find an association between ALS and pesticide exposure in their own cohort study.(81)

7.1.3 Memory disorders

Table 15. Pesticide exposure and memory disorders

Grade	Exposure	Outcome
B	Any pesticide (occupational)	All-cause dementia and AD (83)
	Pesticide type (organophosphate)	AD (83)
	Specific application (residence in high pesticide use districts)	AD (80)
D	Specific application (residence in high pesticide use districts)	Cerebral degeneration, affective psychosis and polyneuropathies (80)

AD: Alzheimer's Disease

Two studies examined associations between pesticides, dementia and Alzheimer's Disease (AD). Hayden et al. (2010) completed a cohort study of occupational pesticide exposure and found a 38% increased in risk of all-cause dementia and a 42% increase in risk of AD. The increase in risk of AD was higher at 53% with organophosphate exposure than at 49% with organochlorine exposure.(83) Parrón et al. (2011)'s ecological study of hospital discharge diagnoses found a 65% increased risk of AD with residence in high pesticide use districts after adjustment for age and gender. Interestingly, residence in high pesticide districts was protective for cerebral degeneration, affective psychosis and polyneuropathies.(80)

7.1.4 Depression

Table 16. Pesticide exposure and depression

Grade	Exposure	Outcome
B	Any pesticide	Suicide (80,84)
	Any pesticide (occupational, high exposure)	Depression (85)
	Pesticide class (insecticides, fungicides and fumigants)	Depression (85)
	Pesticide type (organochlorine)	Depression (85)
	Pesticide type (organophosphate)	Depression (72,85)
	Specific pesticide (metalaxyl and permethrin)	Depression (86)
B -	Pesticide class (organophosphate)	Anxiety (72)
	Pesticide class (herbicide, long-term or high intensity use)	Depression (87)
C	Pesticide class (insecticide and fungicide)	Depression (87)
D	Any pesticide (occupational)	Depression (86)
	Any pesticide (occupational)	Depression in female spouses of farmers (88)
	Pesticide type (phenoxys and triazines)	Depression (86)
	Specific pesticides (carbofuran, trifluralin, metribuzin, Imazethapyr, cyanazine, atrazine and 2,4-D)	Depression (86)

Six studies examined associations between depression, anxiety and suicide and pesticide use. One study and a systematic review found a possible increased risk of suicide with increasing overall pesticide use. Evidence for an association between overall pesticide use and depression is mixed, although results are suggestive of a possible association with specific classes or products.

A systematic review by Freire et al. (2013) found increased risk of suicide in 9 of 14 studies examined.(84) Parrón et al.'s 2011 ecological study also found 1.8-fold increase in risk of suicide attempt in high pesticide use districts.(80)

Beard et al. (2013) completed a cohort study of 16,893 farm wives from enrollment in 1993-1997 to 2005-2007 and found no association between overall pesticide use by the farm wives or their husbands and self-reported depression. Only metalaxyl and permethrin were associated with respective 1.6- and 1.4-fold increases in the risk of depression. Interestingly, several specific pesticides were inversely associated with depression, which the author's suggested could be related to a healthy worker effect.(86)

Mackenzie Ross et al. (2010) reported that 40% of the organophosphate-exposed cohort of sheep farmers reported anxiety and depression compared to 23% of controls.(72)

After exclusion of those experiencing a pesticide-poisoning event, high lifetime pesticide exposure was associated with a 54% increase in risk of depression in a study of 534 cases and 17,051 controls from the Agricultural Healthy Study. Specific ever use of insecticides, organophosphates, organochlorines, fungicides and fumigants was associated with a 1.3- to 2.0-fold increase in risk of depression.(85) A second analysis of 29,074 female spouses enrolled in

the same study found that there was no association between cumulative lifetime low (up to 225 days) or high (more than 225 days) pesticide exposure and depression.(88)

Weisskoft et al (2013) found an increased risk of self-reported depression among 567 farmers aged 37 to 78 years with long-term or high intensity herbicide use.(87)

7.2 Neurodevelopmental and behavioural health outcomes in children

Table 17. Pesticide exposure and neurodevelopmental and behavioural health outcomes in children

Grade	Exposure	Outcome
A	Pesticide type (organophosphate, newborn period)	Increased number of abnormal reflexes (89–91)
B	Pesticide type (organophosphate, maternal prenatal urinary levels)	Reduced BMDI score (92)
	Pesticide type (organophosphate, maternal prenatal and child urinary levels)	PDD (92)
	Pesticide type (organophosphate, prenatal and childhood exposure)	Decreased short-term memory, increased reaction time and increased risk of impaired mental development or pervasive developmental problems (91)
	Pesticide type (organophosphate, adolescent period)	Increased mental and emotional problems (91)
	Specific pesticide (chlorpyrifos, cord blood)	BPDI and BMDI at age 3 (93)
	Specific pesticide (chlorpyrifos, cord blood)	Increased risk of BPDI and BMDI delays, attention problems, ADHD diagnosis and PDD (93)
	Specific pesticide (chlorpyrifos, cord blood)	Decreased IQ and working memory at age 7 (94)
	Specific pesticide (piperonyl butoxide, prenatal air sample levels)	Decreased BMDI score (95)
	Specific pesticide (hexachlorobenzene, cord blood levels)	Poor SC score (96)
	Specific pesticide (mirex)	Reduced working memory and quantitative scores on the MCSA (97)
B -	Specific pesticide (methyl parathion)	Reduced short-term memory and attention and increased frequency of behavioural and motor skill problems(98)
D	Pesticide type (organophosphate, child urinary levels)	Increased BMDI score (92)
	Specific pesticide (permethrin, maternal and umbilical blood levels)	BSID score (95)
	Specific pesticide (hexachlorobenzene, cord blood levels)	Parent responses to SD questionnaire at age 7 or 8 (99)
	Specific pesticide (hexachlorobenzene, cord blood levels)	Cognitive and psychomotor performance at age 4 (96)
	Specific pesticide (mirex)	Scores in areas of the MCSA other than working memory and quantitative scores (97)
	Specific pesticide (methyl parathion)	Performing lower than expected on the PENTB (98)
E	Pesticide type (organochlorine)	Human neurodevelopment (91,100)

BMDI: Bayley Mental Development Index PDD: Pervasive Development Disorder BPDI: Bayley Psychomotor Development Index
ADHD: Attention Deficit and Hyperactivity Disorder IQ: Intelligence Quotient SC: Social Competence
MCSA: McCarthy Scale of Children's Abilities BSID: Bayley Scales of Infant Development SDQ: Strengths and Difficulties Questionnaire
PENTB: Pediatric Environmental Neurobehavioral Test Battery

Two reviews examined the general association between neurodevelopment and pesticide exposure in children. Korrick et al. (2008) reviewed 12 cohorts studies and found limited evidence for significant effects of organochlorines on human development.(100) Jurewicz et al. (2008) reviewed 18 studies with mixed designs and found that children exposed to

organophosphate pesticides (OP), prenatally and during childhood, may have difficulties with short-term memory, have increased reaction time, and increased risk of impaired mental development or pervasive developmental problems. In newborns, the effects of OP exposure are mainly an increased number of abnormal reflexes. Adolescents show increased mental and emotional problems.(91) Studies investigating the association between exposure to organochlorine pesticides and neurodevelopmental effects have inconsistent results. No consistent impairments in mental and psychomotor functions are reported.(101)

7.2.1 Neurologic outcome in newborns

Two studies examined neurologic outcomes in newborns using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) and organophosphate exposure. Both studies found that increasing levels of maternal urinary organophosphate metabolites were associated with a 1.3- to 5-fold increased risk of a greater number of abnormal reflexes in the post partum period.(89,90)

7.2.2 Neurologic outcomes in children up to age three

Three studies examined pesticide exposure and motor and cognitive development in children up to the age of 3 using the Bayley Scales of Infant Development (BSID). Rauh et al. (2006) found that children with high level of chlorpyrifos in umbilical cord blood had significant reductions in the Bayley Psychomotor and Mental Development Indices (BPDI and BMDI) by age 3. The children with high levels of chlorpyrifos were also at increased risk of BPDI and BMDI delays, attention problems, ADHD diagnosis and pervasive development disorder.(93) Horton et al. (2011) found no association between BSID score and maternal and umbilical blood levels of permethrin. The same study did find a significant reduction in the BMDI score of children highly exposed to piperonyl butoxide in prenatal air samples.(95) Eskenazi et al. (2007) found significant reductions in BMDI score with increasing maternal prenatal urinary organophosphate metabolites but significant increases with increasing levels in child urine samples. Both prenatal and child urinary organophosphate metabolite levels were associated with a respective 2.2-fold and 1.7-fold increase in odds of pervasive development disorder.(92)

7.2.3 Neurologic outcomes in children over age three

Five studies were identified examining neurologic outcomes in children over the age of 3. Three studies examined outcomes after exposure to organochlorines and two after exposure to organophosphates.

Sioen et al. (2013) found no association between cord blood levels of hexachlorobenzene (HCB) and parent responses to the Strengths and Difficulties questionnaire at age 7 or 8 in 270 children.(99) Ribas-Fitó et al. (2007) examined preschool teacher responses to the California Preschool Social Competence Scale and cord blood HCB levels in a 475-person birth cohort. They found children with higher cord blood HCB levels had a 4-fold increased risk of having poor Social Competence scores. There was no association between HCB and the cognitive or psychomotor performance of children at age 4.(96) Puertas et al. (2010) examined mirex placental levels and results at age 4 on the McCarthy Scale of Children's Abilities (MCSA). They found that detectable levels of mirex were associated with reduced working memory and quantitative score areas only. No changes in other areas of the MCSA were found.(97)

Rauh et al. (2011) followed 265 children and compared their umbilical blood levels of chlorpyrifos and their Intelligence Quotient (IQ) scores at age 7. For each standard deviation increase in chlorpyrifos, IQ decreased by 1.4% and Working Memory by 2.8%.(94) Ruckart et al. (2004) administered the Pediatric Environmental Neurobehavioral Test Battery (PENTB) to a cohort of children illegally exposed to methyl parathion as pest control and to unexposed controls. There were no persistent differences between groups performing lower than expected in the 1-year follow-up. Some significant adverse effects were seen for short-term memory and attention and the frequency of behavioural and motor skill problems was higher. This study also used 90% confidence interval to narrow the confidence interval slightly and potentially increase significance of the findings.(98)

7.2.4 Pervasive developmental disorder (PDD) and autism

Table 18. Pesticide exposure and pervasive developmental disorder and autism

Grade	Exposure	Outcome
B	Any pesticide	ASD (102)
	Pesticide type (organophosphate)	Poorer social responsiveness in African-Americans and boys (103)
B -	Specific pesticide (dicofol and endosulfan, weeks 1 to 8 of pregnancy)	ASD (104)
	Specific application (living within 500m of high organochlorine application during pregnancy)	ASD (104)
	Specific application (residential proximity to carbamate application during pregnancy)	DD (105)
	Specific application (residential proximity to organophosphate application during pregnancy)	ASD (105)
	Specific application (residential proximity to chlorpyrifos application during second trimester of pregnancy)	ASD (105)
	Specific application (residential proximity to pyrethroids application just prior to conception)	ASD (105)
	Specific application (residential proximity to pyrethroids application during the third trimester of pregnancy)	ASD and DD (105)
D	Pesticide type (organophosphate)	Social responsiveness overall and in Whites, Hispanics or girls (103)

ASD: Autism Spectrum Disorder DD: Development Disorder

Three studies and one review examined the association between Autism Spectrum Disorder (ASD) and pesticide exposure. DeCock et al. (2012) examined 21 studies of ASD and pesticides and concluded that there was some increase in risk of ASD with exposure to pesticides.(102)

Roberts et al. (2007) studied 465 Californian cases of ASD and 6,975 controls for residential proximity to pesticide application during pregnancy. Children of mothers living within 500m of the highest poundage organochlorine application sites during pregnancy were 6 times more likely to be diagnosed with ASD but this estimate had a wide confidence interval (2.4-15.3). As well, the study reports an increased risk of ASD with exposure to dicofol and endosulfan in weeks 1 to 8 of pregnancy but does not report specific odds ratios.(104) A comment by McGovern (2007) pointed out that the conclusions of Roberts et al. (2007) are based on small sample size but that the significant findings warrant further study.(104,106)

Shelton et al. (2014) performed a retrospective case-control study of 486 ASD cases, 168 Developmental Delay (DD) cases and 316 controls in California and maternal residential proximity to sites of organophosphate, organochlorine, pyrethroid and carbamate application. For organophosphates, residential proximity within 1.25 kilometers (km) at any time in the pregnancy was associated with a 1.6-fold increase in risk of ASD and during the third trimester within 1.5 km with a 2-fold increase in risk of ASD. Second trimester residential proximity within 1.5km to a chlorpyrifos application site was associated with a 3-fold increase in risk of ASD. For carbamates, the risk of DD was increased 2.5-fold with residential proximity within

1.25 km of the application site. The application of pyrethroids just prior to conception increased the risk of ASD by 82% and during the third trimester increased the risk of ASD by 1.82-fold and DD by 2.34-fold at varying residential proximity cutoffs.(105)

Furlong et al. (2014) examined the Social Responsiveness Scales (SRS) and urinary biomarkers of prenatal organophosphate exposure in 136 children. They found no significant associations overall or for whites, Hispanics or girls. Poorer social responsiveness was significantly associated with each 10-fold increase in organophosphate metabolite in African-Americans and boys.(103)

7.2.5 Attention deficit disorders

Table 19. Pesticide exposure and ADHD

Grade	Exposure	Outcome
B	Pesticide type (pyrethroid)	High score on the SDQ (107)
	Pesticide type (organophosphate)	ADHD (108)
	Pesticide type (organophosphate, prenatal)	ADHD (109)
	Specific pesticide (hexachlorobenzene)	ADHD (96)
	Specific pesticide (2,4,6-TCP, urinary metabolite of hexachlorobenzene and hexachlorohexane)	ADHD (110)
B-	Pesticide type (organophosphate, prenatal)	ADHD in boys (109)
D	Pesticide type (pyrethroid)	LD or ADHD (111)
	Pesticide type (organophosphate)	Score on the SDQ (107)
	Pesticide type (organophosphate, prenatal)	ADHD in girls (109)
	Pesticide type (organophosphate, postnatal child levels)	ADHD (109)
	Specific pesticide (chlorpyrifos)	ADHD (112)
	Specific pesticide (2,4,5-TCP, urinary metabolite of hexachlorobenzene and hexachlorohexane)	ADHD (110)

ADHD: Attention Deficit/Hyperactivity Disorders LD: Learning Disorders

Seven studies examined the association between Attention Deficit/Hyperactivity Disorders (ADHD) and exposure to pyrethroid, organophosphate and organochlorine pesticides.

Pyrethroid pesticides and ADHD were examined by two studies. Quirós-Alcalá et al. (2014) examined a large cross-sectional sample of US children and found no associations between urinary pyrethroid biomarkers and parent reported Learning Disability (LD) or ADHD.(111) A second study, Oulhote and Bouchard (2014) examined 779 children in the Canadian Health Measures Survey found that a 10-fold increase in a urinary pyrethroid biomarker doubled the risk of high scores on the Strength and Difficulties Questionnaire (SDQ), a marker of increase risk for behavioural problems.(107)Oulhote and Bouchard (2014) also examined organophosphate metabolites and found no association with increased SDQ scores.(107) Bouchard et al. (2010) examined 1,139 children in a American survey and found that a 10-fold increase in urinary organophosphate metabolites increase the risk of ADHD by 55%.(108)

Marks et al. (2010) performed a complex diagnostic evaluation of ADHD outcomes and their association with urinary organophosphate metabolite levels. The composite ADHD measure used showed a 3.5-fold increased risk of ADHD with high prenatal urinary organophosphate levels. When stratified by sex, girls showed no association between prenatal urinary organophosphate levels and ADHD and boys showed and 11-fold increase in risk, although these estimate had wide confidence intervals. There were no associations between postnatal child urinary organophosphate levels and ADHD.(109) Fortenberry et al. (2014) examined 187 mother-child pairs and found no association between maternal chlorpyrifos metabolite levels and diagnosis of ADHD at ages 6 to 11 years.(112)

Xu et al. (2011) examined urinary metabolites of hexachlorobenzene (HCB) and hexachlorohexane (HCH) and parent-reported ADHD in 2,546 American children aged 6 to 15.

Children with high levels of one metabolite, 2,4,6-TCP had a 77% increase in parent reported ADHD. Levels of the other metabolite, 2,4,5-TCP were not associated with parent-reported ADHD.(110) Ribas-Fitó et al. (2007) examined HCB levels in cord blood and teacher measured ADHD and found that children with higher HCB levels at birth were 2.7 times more likely to meet the diagnostic criteria for ADHD.(96)

7.2.6 Child intelligence

Table 20. Pesticide exposure and child intelligence quotient

Grade	Exposure	Outcome
B	Pesticide type (organophosphate, prenatal)	Lower BMDI scores at 12 months in African-Americans and Hispanics (113)
	Pesticide type (organophosphate, prenatal)	Lower IQ and decreases in working memory, processing speed, verbal comprehension and perceptual reasoning (114)
B -	Pesticide type (organophosphate)	Poorer speed of attention, sequencing, mental flexibility, visual search, concept formation and conceptual flexibility (115)
D	Pesticide type (organophosphate, prenatal)	IQ at age 6 to 9 (113)
	Pesticide type (organophosphate, prenatal)	BMDI scores at 24 months (113)
	Pesticide type (organophosphate, prenatal)	Higher BMDI scores at 12 months in Whites (113)
	Pesticide type (organophosphate, childhood levels)	IQ (114)

BMDI: Bayley Mental Development Index IQ: Intelligence Quotient

Three studies examined associations between pesticide exposure and learning disorders, Intelligence Quotient (IQ) and cognitive development.

Three studies concentrated on organophosphate exposure and various outcomes. Engel et al. (2011) examined prenatal urinary biomarkers of organophosphate exposure and the Bayley Mental Development Index (BMDI) at 12 and 24 month and Intelligence Quotient (IQ) scores at age 6 to 9 years in 169 to 200 children. At 12-months higher prenatal organophosphate exposure was associated with lower BMDI scores in African-Americans and Hispanics and higher BMDI scores among whites. At 24 months, there were no associations between prenatal organophosphate exposure and BMDI. By 6 to 9 years of age, there was no association between IQ and prenatal organophosphate exposure.(113)

Sanchez-Lizardi et al. (2008) examined 48 children in Arizona for associations between urinary biomarker of organophosphate exposure and results of the Wisconsin Card Sorting Test (WCST) and other cognitive measures. Higher organophosphate concentrations were associated with poorer speed of attention, sequencing, mental flexibility, visual search, concept formation and conceptual flexibility. However, there were two outliers with very high levels of organophosphates in the study and the removal of these outliers made the study results non-significant.(115)

Bouchard et al. (2011) examined 329 children in California for associations between urinary organophosphate metabolite levels prenatally and at ages 6 months and 1, 2, 3.5 and 5 years and Intelligence Quotient (IQ) scores. A 10-fold increase in maternal urinary organophosphate levels was associated with significant decreases in working memory, processing speed, verbal comprehension, perceptual reasoning and overall IQ. Children in the highest quintile of maternal urinary organophosphate levels had an average IQ 7.0 points lower than those in the lowest quintile. The children's own urinary organophosphate levels were not consistently associated with cognitive measures.

8. Oncologic health outcomes and pesticides exposure

8.1 Adults

Research into associations between adult pesticide exposure and cancer is extensive. Most of the studies focus on occupational pesticide exposures. Although these provide some indication of the possible effects of a pesticide on the human body, they typically involve exposures at much higher level than those in the general population. These finding should be interpreted with this in mind.

Two approaches were taken to cancer research and pesticide exposure in adults. The first is the evaluation of multiple and specific pesticides and incident cancer overall. Studies that use this approach are presented in Sections 8.1.1 and 8.1.2. The second approach is the evaluation of multiple pesticides and their effect on one specific type of cancer. These studies are presented in Sections **Error! Reference source not found.** to 8.1.16.

8.1.1 General cancer and general pesticide exposure

Table 21. General pesticide exposure and general cancer

Grade	Exposure	Outcome
B	Any pesticide (occupational)	Testicular, non-melanoma skin cancer and MM (116)
	Specific pesticide (diazinon and EPTC)	All-cause cancer (117)
	Specific application (sometimes or always ate organic food)	NHL (118)
B -	Any pesticide	NHL, leukemia, brain breast, pancreatic, prostate and kidney cancer (119)
D	Any pesticide (occupational)	All-cause cancer (116,120)
	Any pesticide (occupational)	Cancers of the lip, oral cavity and pharynx, digestive organs and respiratory system (116)
	Specific application (sometimes or always ate organic food)	All-cause cancer, oral cavity and pharynx, esophageal, breast, stomach, colorectal, pancreatic, lung, endometrial, ovarian, kidney, bladder, brain cancer, malignant melanoma MM, STS or leukemia(118)

Three reviews covered the general association between cancer and pesticide use. Weichenthal et al. (2010) completed a reviewed 28 studies involving specific pesticides and cancer incidence in the Agricultural Health Study (AHS) cohort. The individual studies reviewed have all been included in this review so they will not be included here. Among the 32 pesticides studied, only the use of diazinon (1.6-fold) and EPTC (1.3-fold) were associated with all-cause cancer.(117) Alavanja et al. (2007) reviewed the epidemiological framework of studies examining the human health effects of cancer and the state of the literature in 2007.(121) Bassil et al. (2007) completed a systematic review of studies published between 1992 and 2003 on NHL, leukemia and eight solid tumors. Positive associations were found between pesticide use and cancer outcomes include NHL (4 of 12 studies), leukemia (14 of 16 studies), brain cancer (11 of 11 studies), breast cancer (5 of 6 studies), pancreatic cancer (all 3 studies), prostate cancer (all 8 studies) and

kidney cancer (all 6 studies). There was no association between ovarian cancer and pesticide exposure in the one study on the subject. It was not clear in this review whether positive association meant significant or just an outcome greater than the null value.(119)

Three cohort studies and one case-control study also considered the general relationship between cancer and pesticide exposure. Bradbury et al. (2014) examined the organic food consumption of 1.3 million British women and cancer incidence. They found a significant increase in the risk of breast cancer (1.1-fold) in women who sometime or always ate organic food and a significant 20% reduction in risk of NHL. There were no significant changes in the risk of overall cancer, STS, oral cavity and pharynx cancer, esophageal cancer, stomach cancer, colorectal cancer, pancreatic cancer, lung cancer, malignant melanoma, endometrial cancer, ovarian cancer, kidney cancer, bladder cancer, brain cancer, MM or leukemia.(118)

MacFarlane et al. (2010) completed an analysis of cancer incidence from 1983 onwards from a cohort of 12,050 men and 1,084 women from a cohort of occupationally exposed workers recruited 1960 to 1980. They found a significant 24% reduction in cancer risk among the cohort participants, probably the result of a healthy worker effect.(120)

Frost at al. (2011) examined cancer incidence and mortality among 65,910 British pesticide applicators from 1983 to 2004-2005. They found significant reductions in all-cause mortality, all-cause cancer and cancers of the lip, oral cavity and pharynx, digestive organs and respiratory system compared to the general British population. There was significantly higher incidence of testicular cancer (1.3-fold), non-melanoma skin cancer (1.1-fold) and MM (1.5-fold).(116)

8.1.2 General cancer and specific pesticide exposures

Research in the area of specific pesticide exposures and cancer incidence has focused primarily on studies involving the Agricultural Health Study (AHS) cohort in Iowa and North Carolina. Of the 30 studies reviewed here, only three do not specifically involve this cohort. These two studies are reviewed first. Second, the results from the AHS studies are presented in two tables (Table 23 and Table 24). The results have been grouped by pesticide type and class within these tables to improve interpretation.

Table 22. Specific pesticide exposures and general cancer

Grade	Exposure	Outcome
B	Pesticide type (organochlorines)	Leukemia (122)
	Specific pesticide (diazinon, EPTC, butylate)	Cancer (123–125)
	Specific pesticide (diazinon, butylate, alachlor)	All LHC (123,125,126)
	Specific pesticide (lindane, buylate)	NHL (122,125)
	Specific pesticide (imazethapyr)	Bladder cancer (127)
	Specific pesticide (methyl bromide)	Stomach cancer (128)
	Specific pesticide (acetochlor)	Colorectal cancer (129)
	Specific pesticide (trifluralin)	Colon cancer (130)
	Specific pesticide (imazethapyr)	Proximal colon cancer (127)
	Specific pesticide (chlordane)	Rectal cancer (122)
	Specific pesticide (carbaryl, toxaphene)	Melanoma (122,131)
	Specific pesticide (buylate)	Prostate cancer (125)
	Specific pesticide (coumaphos, fonofos, phorate)	Prostate cancer in men with a family history (132–134)
B -	Specific pesticide (diazinon, heptachlor/chlordane, metribuzin)	Leukemia (122,123,135)
	Specific pesticide (permethrin)	Multiple Myeloma (136)
	Specific pesticide (diazinon, chlorpyrifos, dieldrin, acetochlor, acetochlor/atrazine mix, dicambia)	Lung cancer (122,123,129,137,138)
D	Pesticide type (triazines)	Cancer (139)
	Specific pesticide (malathion, dichlorvos, carbofuran, captan, chlorothalonil, atrazine, cyanazine, pendimethalin, metoachlor, paraquat, glyphosphate)	Cancer (140–151)
	Specific application (chlordane and dieldrin in well water)	Cancer (152)

EPTC: (*S*-ethyl-*N*,*N*-dipropylthiocarbamate) NHL: Non-Hodgkin lymphoma

Sathiakumar et al. (2011) reviewed 36 studies in their examination of the association between triazine herbicide and cancer. They found that the most frequently investigated cancers were NHL, prostate and breast cancer and that the studies did not provide convincing evidence of a causal association between triazine herbicides and cancer. This review was sponsored by a triazine manufacturing company.(139) Lo et al. (2011) completed an ecological study of cancer incidence by comparing cancer incidence an area of high chlordane and dieldrin well water contamination with areas of low contamination in Connecticut. They found no significant difference between cancer incidence in the low and high contamination areas.(152)Finally, Ljunggren et al. (2014) completed a very small case-control study of eight cancer patients and

seven controls and their organochlorine levels in their serum lipoproteins. They found no significant difference between the cancer patients and the healthy controls.(153)

The AHS cohort is a study of 52,395 private pesticide applicators (mainly farmers) and 32,347 of their spouses recruited from 1993 to 1997 in North Carolina and Iowa. The applicators reported specific past pesticide exposures that are weighed based on either lifetime days of exposure or the intensity of exposure. Outcomes are either self-reported or ascertained from death certificates or cancer registries.{Citation}Table 23summarizes the significant findings of studies using the AHS cohort to examine the association between insecticides, fungicides and fumigants and cancer. Table 24provides the same summary for herbicides and cancer. Insecticides were significantly associated with increased risks of all cancer, all LHC, leukemia, MM, NHL, melanoma, and cancers of the lung, rectum and prostate cancer in men with a family history. Herbicides were significantly associated with increased risks of all cancer, all LHC, NHL, leukemia, and cancers of the prostate, colon, lung and bladder. Fungicides or fumigants were not associated with cancer in the AHS cohort.

Table 23. Agricultural Health Study cohort analyses of specific insecticides, fungicides and fumigants and incident cancer with enrollment 1993-1997.

Reference	Outcomes captured until	N	Pesticide	Significant outcomes*
Organophosphate insecticides				
Bonner 2007 (140)	2002	19,717	Malathion	None
Christensen 2010 (132)	2005	47,822	Coumaphos	Prostate cancer only in men with a family history (1.7-fold).
Freeman 2005 (123)	2005	23,206	Diazinon	LD highest tertile all cancer (1.1-fold), lung cancer (2.4-fold) and leukemia (3.4-fold). IW all LHC (2-fold).
Koutros 2008 (141)	2004	49,762	Dichlorvos	None
Mahajan 2006 (133)	2002	45,372	Fonofos	Prostate cancer only in men with a family history (1.7-fold).
Mahajan 2006 (134)	2002	21,016	Phorate	Prostate cancer only in men with a family history (1.5-fold).
Lee 2004 (137)	2001	54,383	Chlorpyrifos	Lung cancer (2.2-fold).
Carbamate insecticides				
Bonner 2005 (142)	2002	48,877	Carbofuran	None
Mahajan 2007 (131)	2003	21,416	Carbaryl	Melanoma with greater than 175 days of use (4.1-fold), 10 years of use (3.2-fold) or 10 days per year (5.5-fold).
Organochlorine and pyrethroid insecticides				
Purdue 2007 (122)	2002	22,409	Organochlorines	Leukemia (2.0-fold). Associations between high use of chlordane and rectal cancer (2.7-fold), lindane and NHL (2.6-fold), dieldrin and lung cancer (2.8-fold), toxaphene and melanoma (2.9-fold) and hepatachlor/chlordane and leukemia (2.6-fold).
Rusiecki 2009 (136)	2004	49,093	Permethrin and other pyrethroid products	MM (LD 5.7-fold, IW 5-fold) based on 15 cases.
Fungicides and fumigants				
Greenburg 2008 (143)	2004	48,986	Captan (F)	None
Mozzachio 2008 (144)	2004	47,625	Chlorothalonil (F)	None
Barry 2012 (128)	2007	53,588	Methyl bromide (Fu)	Stomach cancer

*Lower CI above 1.0 with dose-response association and consistent significance when low exposure or no exposure used as baseline where applicable

LHC: Lymphohematopoietic cancer MM: Multiple Myeloma, NHL: Non-Hodgkin lymphoma IW: Intensity weighed exposure LD: Lifetime days of exposure F: Fungicide Fu: Fumigant

Table 24. Agricultural Health Study cohort analyses of specific herbicides and incident cancer with enrollment 1993-1997.

Reference	Outcomes captured until	N	Pesticide	Significant outcomes*
Triazine and triazinone herbicides				
DeLancey 2009 (135)	2005	23,072	Metribuzin	Significant trend for leukemia but no individual significant increased risks.
Freeman 2011 (145)	2007	57,310	Atrazine	None
Rusiecki 2004 (146)	2001	53,943	Atrazine	None
Lynch 2006 (147)	2002	50,317	Cyanazine	None
Dinitroaniline herbicides				
Hou 2006 (148)	2002	24,374	Pendimethalin	None
Kang 2008 (130)	2002	50,127	Trifluralin	IW highest tertile colon cancer (1.8-fold)
Thiocarbamate herbicides				
Lynch 2009 (125)	2004	19,655	Butylate	LD highest exposure level all cancer (1.7-fold), prostate cancer (2.1-fold), all LHC (2.3-fold) and NHL (3.4-fold).
vanBemmel 2008 (124)	2002	48,378	EPTC	All cancer (1.2-fold).
Chloroacetanilide herbicides				
Rusiecki 2006 (149)	2002	50,194	Metolachlor	None
Lee 2004 (126)	2000	49,980	Alachlor	Significant trend for all LHC but no individual significant increased risks.
Lerro 2015 (129)	2010-2011	33,484	Acetochlor	Lung cancer (1.7-fold with ever use), lung cancer with use of acetochlor/atrazine mixtures (2.3-fold) and colorectal cancer (1.7-fold with highest use category).
Other herbicides				
Park 2009 (150)	2004	56,222	Paraquat (Dipyridyl)	None
DeRoos 2004 (151)	2001	57,311	Glyphosphate (OP)	None
Samanic 2006 (138)	2002	41,969	Dicamba (Benzoic acid)	Significant trend for lung cancer but no individual significant increased risks.
Kourtos 2009 (127)	2004	29,398	Imazethapyr (Aromatic amine)	LD top half highest tertile bladder cancer (2.4-fold) and proximal colon cancer (2.7-fold).

*Lower CI above 1.0 with dose-response association and consistent significance when low exposure or no exposure used as baseline where applicable

EPTC: (*S*-ethyl-*N*,*N*-dipropylthiocarbamate) OP: Organophosphate LHC: Lymphohematopoietic cancer IW:Intensity weighed exposure LD: Lifetime days of exposure

8.1.3 Brain

Seven case-control studies met our inclusion criteria for adult brain cancer and all of them examined occupational exposure to pesticides.(154–160) All of the studies relied heavily on the use of proxy respondents due to the progressive and high mortality nature of adult brain cancer. This may have introduced significant bias into the findings.

Table 25. Pesticide exposure and adult brain cancer

Grade	Exposure	Outcome
B	Any pesticide (occupational)	Brain tumor (156)
	Any pesticide (occupational)	Glioma (156)
	Pesticide class (insecticides, herbicides, nitrosatable)	Glioma in men (155)
	Pesticide class (herbicides, occupational)	Meningioma in women (159)
	Specific application (not immediately washing up or changing clothes after pesticide application)	Glioma (157)
	Specific application (home treatment of plants)	Brain tumor (156)
B -	Pesticide type (organochlorines, organophosphates, dinitroanilines, phenoxys and triazines)	Glioma (in proxy respondents only) (155)
	Specific pesticide (metribuzin, paraquat, bufencarb, chlorpyrifos, coumaphos)	Glioma (155)
	Specific pesticide (pentachlorophenol)	Glioma (157)
D	Any pesticide (occupational)	Meningiomas (156)
	Pesticide class (insecticide, occupational)	Glioma (159,161)
	Pesticide class (herbicide, occupational)	Glioma (159,161)
	Pesticide class (fungicide, occupational)	Glioma (161)
	Pesticide class (insecticide, occupational)	Meningioma (159)
	Pesticide class (insecticide, occupational)	Meningioma in men (159)
	Specific pesticides (multiple)	Glioma (160) in women (154) in men (157)
	Specific application (living on a farm)	Glioma (161)

Five case-control studies examined different subsets of the Upper Midwest Health Study and glioma outcomes.(154,157,158,160,161) These studies examined the health of adults aged 18 to 80 living in non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin from 1995 to 1997.

Carréon et al. (2005) found no significant association between multiple specific pesticide exposures and glioma when examining 342 female cases and 528 female controls.(154) Ruder et al. (2009) found a significantly increased risk of glioma in farmers who did not immediately wash up (3.1-fold) or change clothes (2.8-fold) after applying pesticides when the pesticide exposures of 288 cases and 474 controls were examined. A small number of farmers who used pentachlorophenol as a wood preservative also had an increased risk of glioma (4.5-fold) but only after excluding proxy respondents. (157) Ruder et al. (2004) found no significant positive associations between the use of 12 specific pesticides and primary intracranial glioma in 457 male cases and 648 controls.(158) Yiin et al. (2012) found no significant associations between glioma risk and cumulative years or estimated lifetime farm pesticide exposure among 798 cases

and 1,175 controls.(160) Finally, Ruder et al. (2006) found no significant associations between glioma and living on a farm or the ever use of pesticides, insecticides, herbicides or fungicides.(161)

Three other studies examined adult brain cancer and pesticide exposure. Lee et al. (2005) examined 251 cases of glioma and 498 controls for their self-reported pesticide use prior to 1985. There was a significant increase in glioma risk among adult male farmers who were exposed to insecticides (1.8-fold), herbicides (1.7-fold) or nitrosatable (1.9-fold) on the farm were they lived or worked. There were increased risks of glioma with exposure to organochlorines, organophosphates, dinitroaniline, phenoxy and triazine classes of pesticides but these were only significant for proxy respondents. There were significant associations, albeit imprecise ones based on small numbers, between glioma and metribuzin (3.4-fold), paraquat (11.1-fold), bufencarb (18.9-fold), chlorpyrifos (22.6-fold) and coumaphos (5.9-fold).(155)

Provost et al. (2007) examined 221 cases and 442 individually matched controls between 1999 and 2001 in Southwestern France. They created quartiles of cumulative occupational pesticide exposure and found significant associations between the highest quartile of exposure and brain tumors (2.2-fold) and gliomas (3.2-fold) but not meningiomas. There was also a significant association between brain tumors and home treatment of plants (2.2-fold).(156)

Samanic et al. (2008) examined 462 glioma cases, 195 meningioma cases and 765 hospital controls in the United States for occupational herbicide and insecticide exposure. There was no association between insecticide and herbicide exposures and the risk of glioma for men and women and the risk of meningioma in men. There was a significant increase in the risk of meningioma in women (2.4-fold) who had ever use herbicides, but not insecticides, with significant trends for years of use and cumulative exposure.(159)

8.1.4 Breast

There has been extensive research on the association between breast cancer and pesticide use. The research is presented in three categories based on the pesticides examined: 1) studies involving multiple pesticides 2) studies involving organochlorine pesticides and 3) studies concentrating on specific classes of pesticides other than organochlorines.

8.1.4.1 Multiple pesticides and breast cancer

Table 26. Pesticide exposure and breast cancer

Grade	Exposure	Outcome
B	Specific pesticide (diazinon)	Breast cancer in women with a family history of breast cancer (162)
	Specific application (husbands use of aldrin, carbaryl, chlordane, dieldrin, heptachlor, lindane, malathion, captan, 2,4,5-TP and 2,4,5-T)	Breast cancer (162)
	Specific application (proportion of county land used for agriculture)	ER+ breast cancer (163)
	Specific application (husbands use of parathion and paraquat)	Breast cancer in women with a family history of breast cancer (162)
B -	Any pesticide (residential, lawn and garden)	Breast cancer (164)
	Specific application (residential use of liquid or combined products)	Breast cancer (164)
	Specific application (professional residential pesticide application)	Breast cancer (164)
	Specific application (residential lawn and garden pesticide to control weeds, insects or diseases of lawns, trees and indoor or outdoor plants)	Breast cancer (164)
C	Any pesticide (residential)	Breast cancer (164–167)
	Specific pesticide (insect repellents)	Breast cancer (164,167)
D	Any pesticide (occupational)	Breast cancer (162,166,168)
	Specific application (nuisance pest products or products to control lice, fleas or ticks on pets)	Breast cancer (164)
	Specific application (residential proximity to pesticide application)	Breast cancer (169)
	Specific application (proportion of county land used for agriculture)	ER- breast cancer (163)
	Specific application (washing clothes worn during pesticide application)	Breast cancer (162)

ER: Estrogen Receptor Positive (+) or Negative (-)

One cohort study and two case-control studies examined occupational pesticide exposure and breast cancer. Engel et al. (2005) followed 30,454 women from enrollment (1993-1997) to 2000 for incident breast cancer cases in the Agricultural Health Study cohort. They found no association between breast cancer and ever applying pesticides or washing clothes worn during pesticide application. There was a 1.4 to 2.7-fold significant increase in breast cancer risk when the husbands applied aldrin, carbaryl, chlordane, dieldrin, heptachlor, lindane, malathion and captan. Higher cumulative use of dieldrin, 2,4,5-TP and 2,4,5-T showed significant trends of increasing risk of breast cancer with increasing use of husbands. When women had a family

history of breast cancer, their own use of diazinon and their husbands use of parathion and paraquat significantly increased their risk of breast cancer.(162) Mills et al. (2005) completed a case-control study of 128 cases and 640 Hispanic controls in California from 1998 to 2001.(168) El-Zaemey et al. (2014) also completed a case-controls study of 1,205 cases and 1,789 controls in Western Australia.(166) Both studies examined occupational pesticide exposure and failed to find an association between overall occupational pesticide use and breast cancer risk.(166,168)

Two ecological studies examined residential proximity to agricultural pesticide application and breast cancer. Reynolds et al. (2005) examined residential proximity to agricultural pesticide use and breast cancer rates in their ecological study comprising 70 million person years of follow-up and 176,302 invasive breast cancer cases. They found no association between high agricultural overall pesticide use, carcinogenicity category or specific pesticides and breast cancer rates.(169) A second ecological study by St-Hilaire et al. (2011) examined county level Estrogen Receptor (ER) negative (-) and positive (+) breast cancer rates and proportion of agricultural land in 439 counties and 11 states in the United States between 2000 and 2003. They found that ER+ breast cancer rates were significantly positively associated with an increasing proportion of agricultural land in a county and that this association strengthened as the annual precipitation decreased. There was no association with ER- breast cancer cases.(163)

Finally, four case-control studies examined the residential use of pesticides and breast cancer. Farooq et al. (2010) examined residential pesticide application by 447 cases and 758 controls in New York City. They found no significant increase in the odds of breast cancer with either professional or personal application of residential pesticides.(165)

A second case-control study by Teitelbaum et al. (2006) in New York examined residential pesticide use by 1,508 cases and 1,556 controls. They found 1.3 to 1.4-fold increases in risk of breast cancer with ever lifetime residential pesticide use and ever lawn and garden pesticide use but these relationships lacked a dose-response association. Use of lawn and garden pesticides to specifically control weeds, insects or diseases of lawns, trees and indoor or outdoor plants were all associated a 1.5-fold increase in breast cancer risk. Slightly higher associations were reported for professional pest control applications and for the use of liquid or combined products. There was no association with breast cancer risk for nuisance pest products, insect repellents or products to control lice, fleas or ticks on pets.(164)

Conversely, a case-controls study by Zota et al. (2010) of 787 cases and 721 controls in Massachusetts failed to find an association between residential pesticide use and breast cancer risk, except for a 1.5-fold increase in risk for women who reported often or very often insect repellent use compared to never use.(167) El-Zaemey et al. (2014) also found no association between breast cancer risk and residential pesticide use.(166)

8.1.4.2 Organochlorines and breast cancer

Table 27. Organochlorine exposure and breast cancer

Grade	Exposure	Outcome
A	Specific pesticide (heptachlor)	Breast cancer (170)
B	Specific pesticide (hexachlorocyclohexane)	Breast cancer (171,172)
	Specific application (combination of aldrin, DDE and DDD)	Breast cancer (173)
B -	Pesticide type (organochlorine)	Breast cancer relapse (174)
	Pesticide type (organochlorine)	Breast cancer in Artic populations(175)
	Specific pesticide (methoxychlor and toxaphene)	Breast cancer (168)
C	Pesticide type (organochlorine)	Breast cancer (176–181)
	Specific pesticide (hexachlorobenzene)	Breast cancer (171,172)
D	Specific application (combination of lindane and endrin)	Breast cancer (173)
E	Pesticide type (cyclodienes organochlorines)	Breast cancer (170)

Organochlorines have been the most frequently studied pesticides in research studies of breast cancer and pesticide use. Given their propensity for bioaccumulation and the easy availability of serum biomarkers, it is possible to quantitatively assess exposure.

Khanjani et al. (2007) completed a meta-analysis of 21 case-control studies completed from 1966 to 2006 of breast cancer and cyclodienes organochlorines (aldrin, dieldrin, oxychlordane, chlordane, heptachlor and heptachlor epoxide). They found no association between cyclodienes organochlorines and breast cancer except for heptachlor.(170)

Boada et al. (2012) examined serum organochlorine levels in 121 cases and 103 controls in Gran Canaria Island, Spain and found that cases more frequently had a combination of aldrin, DDE and DDD than controls. Controls presented more frequently with a combination of lindane and endrin.(173)

Charlier et al. (2007) examined serum organochlorine levels in a cohort of 125 women with breast cancer and found that those who relapsed had higher mean organochlorine concentrations. No information was provided as to the year the study was initiated or the length of follow-up.(174)

Fredslund et al. (2012) reviewed articles pertaining to serum organochlorine levels and postulated that high organochlorine levels in Artic populations may be related to high breast cancer rates in these populations.(175)

Khanjani et al. (2006) examined breast cancer rates in 11 statistical zones in Victoria, Australia comprising 47,250 breast cancer cases among over 2 million women. They found that three region with high organochlorine contamination had significantly higher incidence of breast cancer compared to the region with the lowest level of contamination.(176) A second ecological study by Mills et al. (2006) examined county level organochlorine use and breast cancer incidence rates in Hispanic women from 1988 to 1999 for a total of 23,513 cases. There were

significant1.2-fold increases in the incidence of breast cancer in county in the highest quartile of methoxychlor and toxaphene use.(168)

Waliszewski et al. (2005) examined 127 cases of malignant breast cancer, 127 benign breast tumors and 127 controls in Mexico. They found a 1.6 to 2-fold increase in risk of benign and malignant breast tumors with high hexachlorobenzene and hexachlorocyclohexane levels.(171) Ociepa-Zawal et al. (2010) also found significantly higher level of ß-hexachlorocyclohexane in the adipose tissue of 54 cases compared to 23 controls. There was no significant increase in the adipose tissue levels of γ-hexachlorocyclohexane or hexachlorobenzene levels.(172)

One case-control, one cross-sectional study and 3 reviews found no associations between serum organochlorine levels and breast cancer. Rubin et al. (2006) examined serum organochlorine levels 63 cases and 63 controls and Xu et al. (2010) examined serum organochlorine levels in 4,753 participants in the US National Health and Nutrition Examination Survey.(177,178) All three comprehensive reviews of published studies failed to find an association between serum organochlorine levels and breast cancer.(179–181)

8.1.4.3 Other specific pesticides and breast cancer

Table 28. Other specific pesticides and breast cancer

Grade	Exposure	Outcome
B-	Specific pesticide (simazine)	Breast cancer (168)
D	Pesticide class (fungicide)	Breast cancer (182)
	Pesticide type (organophosphate)	Breast cancer (179)
	Pesticide type (triazine herbicides)	Breast cancer (168)
	Specific pesticide (atrazine)	Breast cancer (183)
	Specific application (nitrate levels in well water)	Breast cancer (184)
	Specific application (fraction of agricultural land in well recharge zones)	Breast cancer (184)

This section presents studies focusing on specific types of non-organochlorine pesticides including fungicides, nitrates in well water, organophosphates and triazine herbicides.

Ashley-Martin et al. (2012) examined the residential proximity to agricultural fungicide exposure in 207 cases and 621 controls in Prince Edward Island and found no significant association between fungicide exposure and breast cancer.(182)

Brody et al. (2006) examined the association between nitrate well water contamination and fraction of land use in recharge zones as an indicator of wastewater contamination in 824 cases and 745 controls from 1988-1995 in Cape Cod, Massachusets. No association was found between well water nitrate levels or fraction of land use in recharge zones and breast cancer.(184)

Shakeel et al. (2010) reviewed relevant articles on the association between organophosphates and breast cancer published 1990 to 2009. They found no consistent association between breast cancer and organophosphate use.(179)

Two studies examined triazine herbicide use and breast cancer rates. Mills et al. (2006) found no association between triazine herbicide use and breast cancer, except for a 1.4-fold increase in breast cancer rate in the second quarter of simazine use.(168) McElroy et al. (2007) examined atrazine well water levels and breast cancer in 3,275 cases and 3,669 controls in rural Wisconsin from 1987 to 2000. They found no association between atrazine in well water and breast cancer rates, although there were very few participants in the highest exposure level.(183)

8.1.5 Gastrointestinal cancers

Table 29. Pesticide exposure and gastrointestinal cancer

Grade	Exposure	Outcome
B	Any pesticide	Cardia adenocarcinoma (185)
	Any pesticide	Diffuse adenocarcinoma (186)
	Specific pesticides (chlorpyrifos, carbaryl, toxaphene and aldicarb)	Colorectal cancer (187)
	Specific pesticides (propargite and trifluralin)	Gastric cancer (188)
	Specific application (work with citrus crops)	Gastric cancer (188)
	Specific application (work in agriculture)	Diffuse adenocarcinoma in men (186)
B -	Pesticide class (insecticide, residential)	Colorectal cancer (189)
	Specific pesticides (2,4-D and chlordane)	Gastric cancer (188)
D	Any pesticide	Esophageal and esophageal squamous cell carcinoma (185)
	Any pesticide	Intestinal gastric cancer (186)

Five studies were identified that considered gastrointestinal cancers and pesticide exposure. Jansson et al. (2006) examined 189 cases of esophageal carcinoma, 262 cases of cardia adenocarcinoma and 167 cases of esophageal squamous cell carcinoma and 820 frequency matched controls for self-reported and occupational airborne pesticide exposure. They found a 2-fold increase in cardia adenocarcinoma with high exposure to pesticides. There was no association between esophageal or esophageal squamous cell carcinoma and pesticide exposure.(185)

Lee et al. (2007) examined the association between colorectal cancer and self-reported occupational pesticide exposure to 50 pesticides in 305 cases and 56,813 controls participating in the Agricultural Health Study from 1993-1997 to 2002. There were approximately 2-fold increases in risk of colorectal cancer with high exposure to chlorpyrifos, carbaryl and toxaphene and a 4-fold increase in risk with high exposure to aldicarb. There were also several pesticides inversely related to colorectal cancer. (187) Sritharan et al. (2014) completed a cross-sectional examination of colorectal cancer rates and home insecticide use in 114 participants from Timiskamig and Peel, two health regions in Ontario. They found significantly more insecticide use in homes of participants from Timiskamig, an area with a high colorectal cancer incidence rate.(189)

Mills et al. (2007) completed a nested case-control study of 100 gastric cancer cases and 210 Hispanic controls followed from 1988 to 2003 as members of the United Farm Workers in the United States. There was a 1.8 to 2.9-fold increase in the risk of gastric cancer with the use of 2,4-D, chlordane and propargite and with work in citrus crop operations. When divided into exposure tertiles, results were similar to ever use and also showed a significant association with trifluralin.(188) Santibañez et al. (2012) considered 399 cases (241 intestinal and 109 diffuse adenocarcinoma) and 355 controls in Spain and their risk of stomach cancer and occupational pesticide exposure. They found that there was a 10.4-fold increase in risk of diffuse adenocarcinoma with the highest level of pesticide exposure. Men working in agriculture had a

significant 6.2-fold increase in risk of diffuse adenocarcinoma. There were significant findings for the intestinal gastric cancer.(186)

Despite the limited research in this area, there appears to be a pattern of significant findings for gastric adenocarcinomas and not for intestinal gastric cancers, perhaps due to different causal pathways.

8.1.6 Kidney

Table 30. Pesticide exposure and kidney cancer

Grade	Exposure	Outcome
I	Any pesticide (occupational)	Renal cell carcinoma (190)

Only one study was identified that considered kidney cancer and the risk of renal cell carcinoma (RCC). Karami et al. (2008) completed a case-control study of 1097 cases and 1476 controls using self-reported and job matrix occupational exposures to any pesticide. They found that there was a significant 1.6-fold increase in RCC with any pesticides exposure with significant trends for increasing cumulative exposure.(190)

8.1.7 Leukemia

The research body exploring associations between adult leukemia and pesticide use is extensive. Fortunately, several relevant meta-analyses were retrieved and this simplified the presentation of the research considerably. The results of the two meta-analyses and five observational studies that met the inclusion criteria for adult leukemia are presented below.(191–197)

Table 31. Pesticide exposure and adult leukemia

Grade	Exposure	Outcome
A	Any pesticide (occupational)	AML (191)
	Any pesticide (occupational)	CML in men (191)
	Specific application (agricultural worker)	Leukemia (191)
B	Any pesticide (occupational)	MDS (192)
	Specific pesticide (mancozeb and toxaphene)	Leukemia (197)
	Specific pesticide (malathion, chlorothalonil and trifluralin)	Leukemia in women (197)
	Specific application (smoking during pesticide application)	Leukemia, MDS (196)
	Specific application (eating during pesticide application)	Leukemia (196)
	Specific application (living on a farm)	Leukemia in women (194)
D	Any pesticide	Leukemia or CLL (195)
	Any pesticide (occupational)	CLL (197)
	Pesticide class (herbicides, fungicides, fumigants, insecticides)	Leukemia (197)
	Pesticides type (phenoxy herbicides)	Leukemia (197)
	Specific pesticides (MCPA and 2,4-D)	Leukemia (197)
	Specific application (living in rural areas and crop acreage within 750m of the residence)	Leukemia in women (194)
E	Any pesticide (occupational)	Leukemia (191,192,197)

AML: Acute Myeloid Leukemia MDS: Myelodysplastic syndrome CLL: Chronic Lymphocytic Leukemia LHC: Lymphohematopoietic Cancers (LHC) CML: Chronic Myeloid Leukemia

Merhi et al. (2007) found no significant association between occupational pesticide exposure and adult leukemia in their meta-analysis of 13 case-control studies published between 1990 and 2005. They did find a significant 3-fold increase in risk of myelodysplastic syndromes with occupational pesticide exposure.(192)

Van Maele-Fabry et al. (2007) also found no association between myeloid leukemia and occupational pesticide exposure in a meta-analysis of 17 cohort and 16 case-control studies published between 1979 and 2005. They did find significant increased risks of Acute Myeloid Leukemia (AML) (1.5-fold) and Chronic Myeloid Leukemia (CML) (1.4-fold) in men with occupational pesticide exposure. As well, farmers or agricultural workers had a 1.4-fold higher risk of developing leukemia than the general population.(191)

Mills et al. (2005) completed a nested case-control study of 131 cases of lymphohematopoietic cancers (LHC) and 5 age-matched controls per case from a cohort of 139,000 Hispanic farm workers. They found a significant increase in risk of leukemia with exposure to mancozeb (2.3-

fold) and toxaphene (2.2-fold). They also found almost a 5-fold increase in risk of leukemia in women with occupational exposure to either malathion, chlorothalonil and trifluralin.(197) They found no significant associations between leukemia or Chronic Lymphocytic Leukemia (CLL) and any pesticide use, including herbicides, fungicides, fumigants, insecticides, phenoxy herbicides, MCPA, and 2,4-D with protective equipment.(197) Hoffman et al. (2008) completed a case-control study of LHC cancers but failed to report outcomes by case or control status.(193)

Miligi et al. (2006) examined 1925 cases of incident leukemia and 1232 random controls for self-reported pesticide exposure. There was no significant association between self-reported pesticide exposure and overall leukemia or CLL risk.(195)

Jones et al. (2014) completed a cohort study of 37,099 Iowa women aged 55-65 and enrolled in 1986 and used GIS residential address to determine crop acreage or pasture land within 750m (i.e. farm or rural residence location) and leukemia outcome by cancer registry. There was a 2.2-fold increased risk of leukemia among women living on farms but not in rural areas when compared to towns with populations of more than 10,000. There were no significant associations between crop acreage within 750m of the residence and overall leukemia risk.(194)

Kokouva et al. (2011) examined 354 cases and 455 age and sex matched hospital controls for an association between self-reported farm pesticide exposure and leukemia and myelodysplastic syndrome. They found a 1.4-fold increase in risk of LHC and a 2-fold increase in leukemia risk after controlling for age, smoking and family history. Smoking during pesticide application significantly increased the risk of myelodysplastic syndrome and leukemia and eating during pesticide application significantly increase the risk of leukemia. There were no significant association between leukemia and myelodysplastic syndrome and specific classes of pesticides.(196)

8.1.8 Liver

Table 32. Pesticide exposure and liver cancer

Grade	Exposure	Outcome
B	Any pesticide (occupational)	Extrahepatic biliary tract carcinoma (198)
I	Any pesticide (residential)	Liver cancer

One relevant study was identified of the association between occupational pesticide exposure and liver cancer. Schmeisser et al. (2010) completed a case-control study of 104 male cases age 35 to 70 and 1,401 population controls in a multi-center European study. There was no association between occupational pesticide exposure and extrahepatic biliary tract carcinoma.(198)

No studies were identified that examined liver cancer and residential pesticide exposure.

8.1.9 Lymphoma

There has been extensive research in the area of pesticide exposure and lymphoma. The results of the 27 studies included in this review are grouped into four general categories by study outcome: Lymphohematopoietic Cancers (LHC) in general, Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and other lymphomas (Multiple Myeloma (MM), Soft Tissue Sarcoma (STS) and other). The studies that examined multiple study outcomes are described in the LHC section and the results pertaining to the NHL, HL and other lymphoma sections are listed in the appropriate section.

8.1.9.1 Lymphohematopoietic cancers

Table 33. Pesticide exposure and lymphohematopoietic cancers (LHC)

Grade	Exposure	Outcome
A	Any pesticide (occupational)	LHC (192,196)
B	Specific application (smoking or eating during pesticide application)	LHC (196)
	Specific application (workers cultivating vegetables)	LHC (197)
D	Pesticide class (insecticides, fungicides and herbicides)	LHC (196)
	Specific application (farm or rural residence)	LHC in women (194)

Merhi et al. (2007) completed a meta-analysis of 13 case-control studies from 1990 to 2005 of occupational pesticide exposure and LHC cancer risk. They found a 1.3-fold significant increase in the odds of combined LHC with occupational pesticide exposure.(192) Mills et al. (2005) completed a nested case-control study of 131 cases of LHC and 5 age-matched controls per case from a cohort of 139,000 Hispanic farm workers. They found a significant 1.7-fold increase in risk of LHCs in workers cultivating vegetables.(197) Jones et al. (2014) completed a cohort study of 37,099 Iowa women aged 55-65 and enrolled in 1986 and used GIS residential address to determine crop acreage or pasture land within 750m (i.e. farm or rural residence location) and LHC outcome by cancer registry. They found no association between LHC and farm or rural residence.(194) Kokouva et al. (2011) examined 354 cases and 455 age and sex matched hospital controls for an association between self-reported farm pesticide exposure and LHC. They found a 1.4-fold increase in risk of LHC after controlling for age, smoking and family history. Smoking during pesticide application significantly increased the risk of LHC and eating during pesticide application significantly increase the risk of LHC. There were no significant association between LHC and specific classes of pesticides.(196)

The following four studies had results for multiple outcomes (NHL, HL and other lymphoma). Orsi et al. (2009) examined occupational and non-occupational self-reported pesticide exposure in their study of 491 LHC male cases (244 NHL, 87 HL, 104 Lymphoproliferative syndromes (LPS) and 56 MM) and 256 controls from 2000 to 2004.(199) Hoffman et al. (2008) completed a case-control study of LHC cancers but failed to report outcomes by case or control status.(193) Cooper at al. (2008) completed a review of 15 case-control and 2 cohort studies on the health effects of pentachlorophenol and chlorophenol exposure.(200) Miligi et al. (2006) examined 1925 cases of incident LHC and 1232 random controls for self-reported pesticide exposure.(195)

McDuffie et al. (2009) examined self-reported pesticide exposure over 10 hours per year in 1528 male cases (316 HL, 342 MM, 513 NHL and 357 STS) and 1506 male controls in 6 Canadian province using data from the Cross-Canada Study of Pesticides and Health.(201) This same dataset was used by Pahwa et al. (2006), Navaranjan et al. (2013), Kachuri et al. (2013), Karunanayake et al. (2012), Hohenadel et al. (2011), Pahwa et al. (2009), Hossain et al. (2007), Pahwa et al. (2011), Pahwa et al. (2012) and McDuffie et al. (2005) in their analyses.(202–211)

8.1.9.2 Non-Hodgkin lymphoma

NHL has attracted the most research effort because it is the most common type of lymphoma. The research presented here will be divided in four categories by pesticide class investigated: pesticides in general, multiple specific pesticides, organochlorines and herbicides and insecticides.

8.1.9.2.1 General pesticide exposure

Table 34. General pesticide exposure and Non-Hodgkin lymphoma

Grade	Exposure	Outcome
A	Any pesticide (occupational)	NHL (192)
B	Specific application (more than 10 hours per year of pesticide use and a positive family history of cancer)	NHL in men (201)
D	Any pesticide	NHL(195,199)
	Specific application (crop acreage within 750m of residence)	NHL (194)

NHL: Non-Hodgkin Lymphoma

One meta-analysis and five studies examined pesticide exposure in general and the risk of NHL. Merhi et al. (2007) found a significant 1.3-fold increase in the risk of NHL with occupational pesticide exposure in their meta-analysis. There was a 1.6-fold increased in NHL risk if there were long periods of occupational pesticide exposure.(192) Jones et al. (2014) found no significant association between nearby crops within 750m of the residence and NHL risk in women.(194) Orsi et al. (2014) found no significant association between occupational or non-occupational pesticide exposure and NHL.(199) McDuffie et al. (2009) found that a positive family history of cancer combined with more than 10 hours a year of pesticide exposure produced a significant 1.7-fold increase in NHL risk.(201)Miligi et al. (2006) found no significant associations between NHL and general pesticide use.(195)

8.1.9.2.2 Multiple specific pesticides

Table 35. Exposure to specific pesticides and Non-Hodgkin Lymphoma (NHL)

Grade	Exposure	Outcome
A	Pesticide type (phenoxy herbicides, carbamate/thiocarbamates herbicides, organophosphorus insecticides, triazine herbicides, carbamate insecticides and organochlorine insecticides)	NHL (212)
	Specific pesticides (lindane, dicamba, 2,4-D, carbaryl, carbofuran, glyphosphate, diazinon and malathion)	NHL (212)
B	Pesticide class (impregnating agents)	NHL (213)
	Carcinogenicity category (use of 5 or more potentially carcinogenic pesticides)	NHL in men (206)
	Specific pesticide (phenoxyacetic acids and glyphosate)	NHL (213)
	Specific pesticide (2,4-D)	NHL (197)
	Specific pesticide (methyl bromide)	NHL in women (197)
	Specific pesticide (mecoprop)	NHL in men (206)
	Specific pesticide (malathion in combination with either 2,4-D, carbaryl, glyphosphate or mecoprop)	NHL in men (206)
	Specific application (2,4-D without protective equipment)	NHL (195)
	Specific application (exposure to increasing number of pesticides)	NHL in men (206)
	Specific application (exposure to increasing number of herbicides, insecticides and fungicides)	NHL in men (206)
	Specific application (exposure to increasing number of organophosphates or phenoxy herbicides)	NHL in men (206)
D	Pesticide class (herbicides, fungicides, fumigants and insecticides)	NHL (195)
	Pesticide type (phenoxy herbicides)	NHL (195)
	Specific pesticides (MCPA)	NHL (195)
	Specific application (2,4-D with protective equipment)	NHL (195)

2,4-D: 2,4-Dichlorophenoxyacetic acid MCPA: 2-methyl-4-chlorophenoxyacetic acid

One meta-analysis and three studies examined the association between NHL and exposure to multiple specific pesticides.

Schinasi and Leon (2014) completed a meta-analysis of 44 studies examining occupational pesticide exposure and NHL. For classes of pesticides, they found a 1.3 to 1.7-fold increase in risk of NHL with exposure to phenoxy herbicides, carbamate/thiocarbamates herbicides, organophosphorus insecticides, triazine herbicides, carbamate insecticides and organochlorine insecticides. Several specific pesticides were also associated with a 1.4 to 1.8-fold increase in risk of NHL including lindane, dicamba, 2,4-Dichlorophenoxyacetic acid (2,4-D), carbaryl, carbofuran, glyphosphate, diazinon and malathion.(212)

Hohenadel et al. (2011) found an increased risk of NHL when increasing numbers of pesticides in general, and specifically increasing numbers herbicides, insecticides, fungicides, phenoxy herbicides or organophosphates were used. The risk of NHL increased to 2-fold when five or more potentially carcinogenic pesticides were considered in the analysis. Finally, there was a 2-fold increase in risk of NHL with the use of mecoprop alone or the use of malathion in combination with either 2,4-D, carbaryl, glyphosphate or mecoprop.(206)

Eriksson et al. (2008) completed a case-control study of 910 cases and 1016 controls and the risk of NHL with self-reported pesticide exposure. Exposure to herbicides was associated with a 1.7-fold increase in risk of NHL, although this risk was rendered non-significant when phenoxyacetic acids and glyphosate were removed from the herbicide analysis, as these were each independently associated with a 2-fold increased risk of NHL. Impregnating agents (chlorophenols, arsenic, creosote, tar and others) were also associated with a 1.6-fold increase in NHL risk.(213)

Mills et al. (2005) found significant 3.8-fold increases in risk of NHL with 2,4-D exposure and with methyl bromide exposure specifically in women.(197)

Miligi et al. (2006) found no significant associations between NHL and the use of herbicides, fungicides, fumigants, insecticides, phenoxy herbicides, 2-methyl-4-chlorophenoxyacetic acid (MCPA), and 2,4-D with protective equipment. The use of 2,4-D without protective equipment was associated with a 4.4-fold increased risk of NHL but this estimate lacked precision with a high upper confidence interval.(195)

8.1.9.2.3 Organochlorines

Table 36. Organochlorine exposure and Non-Hodgkin Lymphoma (NHL)

Grade	Exposure	Outcome
B	Specific application (chlorophenol exposure during fencing work)	NHL (200)
	Specific application (high exposure to pentachlorophenol)	NHL (200)
	Specific application (high Epstein-Barr antibody levels and high levels of hexachlorobenzene or sum of chlordanes)	NHL (214)
C	Specific pesticide (ß-hexachlorocyclohexane, dieldrin, trans-nonachlor, hexachlorobenzene, cis-nonachlor and sum of the chlordanes)	NHL (214–218)
	Specific pesticide (occupational pentachlorophenol use)	NHL (200)
D	Pesticide type (organochlorine)	NHL (219)
	Specific pesticide (pentachlorophenol)	NHL (200,218)

The association between NHL and exposure to organochlorine pesticides was examined in 7 studies. Cooper at al. (2008) included several studies of NHL risk in their review of the health effects of pentachlorophenol and chlorophenol exposure. Exposure to pentachlorophenol was found to not increase risk of NHL in one study but was associated with a significant 8.8-fold increased risk of NHL with high levels of exposure. Exposure to chlorophenol was found to increase the risk of NHL in one study only when the exposure occurred doing fencing work (2-fold). One of the two cohort studies reviewed showed a significant association between occupational pentachlorophenol exposure and NHL with 2 to 5 years of exposure and a 20-year latency.(200)

Bräuner et al. (2012) completed a case-control study of 256 NHL cases and 256 controls within a cohort of 57,053 Danish controls examining organochlorine concentrations in pre-diagnostic adipose tissue. They found a significant dose-response trend for cis-nonachlor. There was no association between the risk of NHL and tissue levels of ß-hexachlorocyclohexane, dieldrin, trans-nonachlor, hexachlorobenzene or the sum of the chlordanes.(216)

Viel et al. (2011) examined 34 newly diagnosed NHL cases and 34 controls for serum organochlorine levels and found that increased ß-hexachlorocyclohexane levels were associated with a very small but significant 1.05-fold increased in NHL risk. No association between other organochlorines and increased NHL risk was found.(215)

Hardell et al. (2009) examined 99 cases of NHL and 99 population controls in Sweden for serum levels of organochlorines. They found approximately a 2-fold increase in NHL risk with high sum of chlordanes, oxychlordane, and trans-nonachlordane. Having a combination of high Epstein-Barr IgE antibody levels and high level of hexachlorobenzene or sum of chlordanes was associated with a respective 5.3-fold and 6.8-fold increase in NHL risk.(214)

Cocco et al. (2008) found no association between NHL and serum organochlorine levels in their study of 174 NHL cases and 203 controls.(219) Colt et al. (2005) also found no association between NHL and chlordane or pentachlorophenol residential carpet dust levels in the home of 603 cases and 443 controls.(218) Finally, DeRoos et al. (2005) found no significant association between NHL and serum levels of dieldrin, ß-hexachlorocyclohexane, heptachlor epoxide, oxychlordane, and trans-nonachlor in 100 cases and 100 controls.(217)

8.1.9.2.4 Herbicides and insecticides

Table 37. Herbicide and insecticide exposure and Non-Hodgkin Lymphoma (NHL)

Grade	Exposure	Outcome
B	Specific pesticide (chlordane)	NHL (220)
	Specific application (use of DEET insect repellents and mecoprop or dicambia)	NHL in men (208)
	Specific application (use of DEET insect repellents, rubber gloves and any phenoxy herbicide by farmers)	NHL in men (208)
	Specific application (use of DEET insect repellents, rubber gloves and mecoprop or dicambia by farmers)	NHL in men (208)
C	Specific application (herbicide percolation)	NHL (221)
D	Pesticide class (insecticide except chlordane, residential exposure)	NHL (218)
	Specific pesticide (2,4-dichlorophenoxy-acetic acid and dicamba, residential)	NHL (222)
	Specific pesticide (mecoprop or dicambia)	NHL in men (208)
	Specific application (use of DEET insect repellents)	NHL in men (208)

NHL risk and exposure to herbicides or insecticides was examined in one ecological and two case-control studies. Fazzi et al. (2010) conducted an ecological study of two samples of 370 and 281 deaths from NHL in Pisa, Italy and herbicide percolation constructed from land use data. In the first sample of 370 deaths, there was no significant correlation. In the second sample of 281 deaths, there was a significant correlation between high herbicide percolation and NHL deaths.(221)

Hartge et al. (2005) examined self-reported home herbicide use and vacuum bag dust samples in a subset of participants for 2,4-dichlorophenoxy-acetic acid and dicamba exposure in 1,321 cases and 1,057 controls and found no association with NHL occurrence.(222)

McDuffie et al. (2005) examined the Cross-Canada Study of Pesticides and Health dataset NHL cases and a farmer subset analysis of 235 NHL cases and 673 controls. They found a significant increase in NHL risk with the simultaneous use of DEET insect repellent and mecoprop (2-fold) or dicamba (1.8-fold). In the farmer subset, they found that there was an increased risk of NHL with the simultaneous use of rubber gloves, DEET and any phenoxy herbicide (2-fold) or specifically mecoprop (3.9-fold) or dicamba (2-fold).(208)

Colt et al. (2006) examined NHL risk and both self-reported residential insecticide exposure and a subset of vacuum dust samples in 1,321 cases and 1,057 controls. Homes treated for termites before the 1988 chlordane ban and those with increasing levels of chlordane had a significantly increased risk of NHL.(220)

8.1.9.3 Hodgkin lymphoma

Table 38. Pesticide exposure and Hodgkin Lymphoma (HL)

Grade	Exposure	Outcome
B	Any pesticide (occupational)	HL in men under 40 years (203)
	Cacinogenicity category (use of 3 or more probably carcinogenic pesticides)	HL (203)
	Pesticide type (triazole fungicides)	HL (199)
	Specific pesticide (dichlorprop, more than 10 hours of lifetime use)	HL (207)
	Specific application (use of 2 acetylcholinesterase inhibitors or occupational use of 2 to 4 fungicides or 2 to 4 insecticides)	HL in men under 40 years (203)
B-	Specific pesticide (chloropyrifos)	HL (205)
C	Pesticide type (urea herbicides)	HL (199,203)
D	Any pesticides (non-occupational)	HL (199,201,202)
	Pesticide type (herbicides, fungicides, fumigants or insecticides)	HL (205)
	Pesticide type (phenoxy herbicide)	HL (202)

Orsi et al. (2014) found a significant increase in HL risk with occupational exposure to triazole fungicides (8.4-fold) and urea herbicides (10.8-fold) but these associations had wide confidence intervals. There were no significant associations between non-occupational pesticide exposure and HL.(199)

McDuffie et al. (2009) found that there were no significant associations between pesticide exposure of more than 10 hours per year and HL.(201)

Pahwa et al. (2006) found no significant association between HL and any or specific phenoxy herbicide exposures.(202)

Navaranjan et al. (2013) found a 2.5-fold increase in HL risk with the use of 3 or more probably carcinogenic pesticides. In those aged less than 40 years, there was a significantly increased HL risk with use of 2 acetylcholinesterase inhibitors (3.2-fold), work-related use only (11-fold), occupational use of 2 to 4 fungicides (4.7-fold) or 2 to 4 insecticides (2.3-fold). There was no association between HL and the use of herbicides or phenoxy or urea herbicides.(203)

Karunanayake et al. (2012) reported that there was no significant increase in HL risk with exposure to herbicides, fungicides, fumigants or insecticides except for chlorpyrifos (1.2-fold).(205) Pahwa et al. (2009) reported that only the herbicide dichlorprop increased the risk of HL 6.3-fold in an analysis of multiple pesticides.(207)

8.1.9.4 Other lymphomas

Table 39. Pesticide exposure and other lymphomas

Grade	Exposure	Outcome
A	Specific pesticide (pentachlorophenol, occupational)	STS (200)
B	Any pesticide (with a family history of cancer and more than 10 hours/year of exposure)	MM (201)
	Pesticide class (insecticides, fungicides or herbicides, occupational)	MM (199)
	Pesticide class (fungicide)	MM in men (204)
	Pesticide type (carbamate, phenoxy, organochlorine)	MM in men (204)
	Pesticide type (carbamate)	MM in men (211)
	Cacinogenicity category (probably carcinogenic or higher)	MM in men (204)
	Specific pesticide (chlorophenol)	STS (200)
	Specific pesticide (captan, carbaryl, mecoprop)	MM in men (211)
	Specific pesticide (aldrin, diazinon)	STS in men (210)
	Specific pesticide (carbaryl, lindane, captan, mecoprop)	MM in men (204)
	Specific pesticide (MCPA)	MM (202)
	Specific application (working in agriculture)	MM in men (223)
	Specific application (chicken farming)	STS in men (209)
C	Specific pesticide (pentachlorophenol)	MM (200)
D	Any pesticide	MM (195,197)
	Any pesticide (non-occupational)	MM (199)
	Any pesticide (with a family history of cancer and more than 10 hours/year of exposure)	STS (201)
	Pesticide class (phenoxys)	STS (202)
	Specific pesticide NOS	MM in men (211)
	Specific pesticide NOS	STS in men (210)
	Specific application (working in agriculture)	MM in women (223)
	Specific application (crops within 750m of residence)	MM in women (194)
	Specific application (Farming of grain, mixed, beef, hogs, sheep, small animal, market garden, orchards, dairy, egg production, seed cleaning plant, nurseryman, gardener, greenhouse operator or landscaper)	STS in men (209)
E	Any pesticide (occupational)	MM (192)

MM: Multiple myeloma STS: Soft Tissue Sarcoma MCPA: 2-methyl-4-chlorophenoxyacetic acid NOS: Not herwise Specified

Merhi et al. (2007) found no significant association between MM and occupational pesticide exposure in their meta-analysis.(192)

Mills et al. (2005) found no significant associations between MM and pesticide exposure, although this subgroup contained only 20 cases.(197) Jones et al. (2014) found no significant association between nearby crops within 750m of the residence and MM risk in women.(194)

Orsi et al. (2014) found a significant 3-fold increase in MM risk with occupational exposures to insecticides, fungicides or herbicides but these associations had wide confidence intervals. There were no significant associations between non-occupational pesticide exposure and MM. For LPS, there were only significant associations with subtypes and these are not reported here.(199)

McDuffie et al. (2009) found that a positive family history of cancer combined with more than 10 hours a year of pesticide exposure produced a significant 1.7-fold increase in MM risk but no significant increase in STS risk.(201)

Cooper at al. (2008) performed a meta-analysis of 4 studies of pentachlorophenol exposure and STS risk. They found a 2.8-fold increased risk of STS with occupational pentachlorophenol exposure. Occupational chlorophenol exposure was associated with an increased risk of STS in three studies. One case-control of the association between occupational pentachlorophenol exposure and MM found no association however a cohort study found a significant 3.8-fold increased risk of MM with more than 5 years exposure and a 20-year latency.(200)

Pahwa et al. (2006) found no significant association between STS and any or specific phenoxy herbicide exposures. They did find a significant 1.7-fold increase in risk of MM with exposure to MCPA.(202)

Kachuri et al. (2013) found significantly increased risk of MM for fungicides and pesticides classified as probably carcinogenic or higher.There were excess risks of MM in men who reported using at least one carbamate pesticide (1.9-fold), one phenoxy herbicide (1.6-fold) and 3 or more organochlorines (2.2-fold). There were also significantly higher odds of MM were seen for specific exposures to carbaryl (2.7-fold) lindane (2.4-fold) and captan (3-fold). Using mecoprop and carbaryl for more than 2 days per year increased the risk of MM 3-fold.(204)

Lope et al. (2008) completed a job matrix analysis of a cohort of 2,992,166 workers in Sweden where 3,127 men and 1,282 women were diagnosed with MM from 1971 to 1989. Working in agriculture, in occupations associated with pesticide use, primarily farming and probable pesticide exposure were associated with a 1.2-fold increase in MM risk among men but not among women, possibly due to small numbers of exposed women.(223)

Miligi et al. (2006) found no significant association between MM and self-reported pesticide exposure.(195)

Hossain et al. (2007) found a significant association between chicken farming and the development of STS. Other type of farming including grain, mixed farms, beef, hogs, sheep, small animal, market garden, orchards, dairy, egg production, seed cleaning plant, nurseryman, gardener, greenhouse operator or landscaper were not significantly associated with STS.(209)

Pahwa et al. (2012) noted an increased risk of MM with exposure to carbamate insecticides (1.9-fold), and specifically the fungicide captan (2.3-fold), herbicide mecoprop (1.9-fold) and the insecticide carbaryl (2.4-fold). No other pesticides examined were significantly associated with MM.(211)

Pahwa et al. (2011) noted an increased risk of STS with exposure to the organochlorine aldrin (3.7-fold) and the organophosphate diazinon (3.3-fold). No other significant associations with STS were seen with the other pesticides examined.(210)

8.1.10 Ovarian

Table 40. Pesticide exposure and ovarian cancer

Grade	Exposure	Outcome
D	Pesticide type (triazine herbicides)	Epithelial ovarian cancer (224,225)
I	Any pesticides	Ovarian cancer (225)

Only two studies met the inclusion criteria and considered ovarian cancer and triazine pesticide exposure. Young et al. (2005) completed a case-control study of 256 cases and 1,122 controls that examined the association between triazine herbicides and ovarian epithelial cancer. They found no association between triazine herbicide exposure and ovarian epithelial cancer.(224) Salehi et al. (2008) reviewed 4 studies, including Young et al. (2005) on the association between triazine herbicides and ovarian cancer. They found only weak evidence of an association and suggested further study.(224,225)

8.1.11 Pancreas

Table 41. Pesticide exposure and pancreatic cancer

Grade	Exposure	Outcome
B	Specific pesticide (pendimethalin and EPTC)	Pancreatic cancer (226)
B -	Specific pesticide (hexachlorobenzene and sum of chlordane)	Exocrine pancreatic cancer (214)
C	Specific pesticide (organochlorine NOS)	Exocrine pancreatic cancer (214,227)
D	Any pesticide (occupational)	Exocrine pancreatic cancer (228)
E	Pesticide type (occupational, insecticide and fungicides)	Pancreatic cancer in farmers (229)
I	Specific pesticides NOS	Pancreatic cancer (227)

NOS: Not Otherwise Specified

Research into the association between pancreatic cancer and pesticide use is the subject of eight papers reviewed here. The research can be divided into papers that consider pesticide use in general and papers considering organochlorine use specifically.

Four studies examined the occupational use of pesticides and pancreatic cancer. Ojajärvi et al. (2007) completed a meta-analysis of 77 studies published from 1969 to 1998 of occupational exposure to pesticides based on job title and pancreatic cancer. There was no excess risk of pancreatic can for farmers exposed to insecticides or fungicides.(229) Andreotti and Silverman (2012) completed a review of studies published from 1998 to 2010 on pesticide exposure and pancreatic cancer. They concluded that there might be an association between pancreatic cancer and non-organochlorine pesticides but that further research is needed to determine the specifc pesticides or pesticide classes that contribute to the increased risk.(227) Andreotti et al. (2009) completed a case-control study of 93 cases and 82,503 cancer-free controls nested within the Agricultural Health Study cohort. Of the 24 pesticides considered, they found a 2.6 to 3-fold increase in incident pancreatic cancer risk with the highest 50% of those exposed to pendimethalin and EPTC compared to never users.(226) Santibañez et al. (2010) completed a case-control study of 161 cases and 455 controls and their occupational job exposures and incident exocrine pancreatic cancer risk. They found no significant increase in pancreatic cancer risk for agricultural workers.(228)

Five studies considered organochlorine pesticide exposure and pancreatic cancer. Andreotti and Silverman's 2012 review found that there was some evidence for an association between pancreatic cancer and organochlorine exposure but that it required further research.(227) Hardell et al. (2007) examined serum organochlorine levels in 21 exocrine pancreatic cancer cases and 59 controls in Sweden. They found significantly higher concentrations of hexachlorobenzene and sum of chlordane in cases, although the small sample size created large confidence intervals. As well, there was significantly longer survival time in cases with sum of chlordane levels below the median.(214) Three additional cross-sectional studies or serum organochlorine levels and exocrine pancreatic cancer were reviewed. They focused on the association between organochlorine serum level and occupational history, occupational social class and risk factors for pancreatic cancer, respectively.(230–232) Given the lack of a control group, they do not contribute to the body of knowledge of the effect of organochlorine pesticide exposure on pancreatic cancer risk and the results are not presented here.

8.1.12 Prostate

8.1.12.1 General pesticide exposures and prostate cancer

Table 42. General pesticide exposure and prostate cancer

Grade	Exposure	Outcome
B	Pesticide type (organochlorines)	Prostate cancer (233)
	Specific pesticide (high levels of captan)	Prostate cancer (233)
C	Any pesticide	Prostate cancer (234)
	Specific pesticides (β-hexachlorocyclohexane, *trans*-nonachlor and dieldrin)	Prostate cancer (178,235,236)
D	Specific pesticides (organochlorines NOS)	Prostate cancer (178,235,236)
	Specific pesticides (simazine, maneb and paraquat)	Prostate cancer (233)
E	Specific pesticide (methyl bromide)	Prostate cancer (233,237)

NOS: Not Otherwise Specified in the table

Nine studies covered general pesticide exposure and the association with prostate cancer. Budnik et al. (2012) completed a meta-analysis of 5 epidemiological studies published 1990 to 2011 of the association between methyl bromide exposure and prostate cancer. They found no significant association between methyl bromide exposure and prostate cancer.(237)

Three studies examined the association between organochlorine exposure and prostate cancer. Xu et al. (2010) completed a cross-sectional study of 4,753 participants in 3 cycles of the National Health and Nutrition Examination Survey. Serum concentrations of three specific chemicals (β-hexachlorocyclohexane, *trans*-nonachlor and dieldrin) were significantly associated with prevalent prostate cancer.(178) Aronson et al. (2010) examined 79 cases and 329 controls in Kingston, Ontario and found no association between the serum levels of 13 organochlorine pesticides and prostate cancer.(235) Sawada et al. (2010) examined 201 cases and 402 controls within a cohort of 14,203 Japanese men followed from 1990 to 2005 and also found no association between serum levels of seven organochlorine pesticides and prostate cancer.(236)

Barranco et al. (2007) examined prostate cancer incidence and mortality from the Texas Cancer Registry and groundwater boron concentrations in their ecological study. They found that areas with higher boron concentration had significantly lower prostate cancer incidence and mortality.(238)

Three papers examined pesticide exposure in general and the risk of prostate cancer. A review by Mullins et al. (2012) concluded that there were conflicting results in the literature on the association between prostate cancer and overall pesticide exposure.(234)

Prins et al. (2008) did not provide a specific quantitative description of the risks associated with pesticides exposure and prostate cancer. They did provide an in-depth discussion of possible biological mechanisms of the potential endocrine disruption of pesticides and the effect of this endocrine disruption as a contributing factor to prostate cancer.(239) Cockburn et al. (2011) examined 173 cases and 162 controls in California for ambient past pesticide exposure based on land use data and residential history. They found a 1.6 to 1.7-fold increase in prostate cancer risk

with exposure to methyl bromide, organochlorines and high levels of captan. No association was found with other chemicals examined, including simazine, maneb or paraquat.(233) The methyl bromide results from this study are included in the meta-analysis by Budnik et al. (2012).(233,237)

8.1.12.2 Occupational pesticide exposures and prostate cancer

Table 43. Occupational pesticide exposure and prostate cancer

Grade	Exposure	Outcome
B	Specific pesticides (fonofos, malathion, terbufos and aldrin)	Aggressive prostate cancer (240)
	Specific pesticides (azinphis-methyl, endosulfan, malathion and mercury, copper sulfate, dichlone, ferbam, maneb, sulfur, ziram, 2,4-DB, MCPA, simazine, 3,5-Dinitro-cresol, diazinon and lindane)	Prostate cancer (241)
	Specific application (farming)	Prostate cancer (242)
	Specific application (farming)	Prostate cancer in Caucasian farmers (243)
B -	Specific pesticides (captan and hydrogen sulfide)	Prostate cancer (241)
C	Specific pesticides (carbaryl)	Prostate cancer (241,244)
D	Pesticide types (organophosphates, organochlorines, phenoxy herbicides, other herbicides and other pesticides)	Prostate cancer (245)
	Specific pesticides (cyanazine, 2,4,5-T, metolachlor and Imazethapyr)	Prostate cancer (244)
	Specific application (farming)	Prostate cancer in African-American farmers (243)
E	Any pesticide (occupational)	Prostate cancer (240,242,243,245–247)

Nine papers examined the risks of occupational pesticide exposure and prostate cancer. Ragin et al. (2013) completed a meta-analysis of 12 case-controls studies including 3,978 cases and 7,393 controls and exposures to pesticides or farming and prostate cancer. They found that when controls with Benign Prostatic Hyperplasia (BPH) were used, farming was associated with a 3.8-fold increase in risk of prostate cancer. When non-BPH controls were used, farmers were at a 1.4-fold increased risk of prostate cancer. Pesticide exposure was significantly inversely associated with prostate cancer.(242) Doolan et al. (2014) reviewed research on occupational pesticide exposure and concluded that there was no association between overall pesticide exposure and prostate cancer and that more research was needed for risks associated with specific pesticides.(248) A second review by Mink et al. (2008) of 8 cohort studies and 5 case-control studies concluded that there were no consistently increased risks of prostate cancer to support a casual association with agricultural pesticide exposure.(247)

Band et al. (2011) examined 1,153 prostate cancer cases and 3,999 controls with other cancers using self-reported and job matrix lifetime pesticide exposures. They found 1.3 to 2.4-fold significant increase in risk of prostate cancer with ever exposure to azinphis-methyl, carbaryl, endosulfan, malathion and mercury. They also found a 1.5 to 2-fold increase in risk of prostate cancer with high exposure to copper sulfate, dichlone, ferbam, maneb, sulfur, ziram, 2,4-DB, MCPA, simazine, 3,5-Dinitro-cresol, azinphos-methyl, carbaryl, diazinon, lindane and

malathion. Finally, low but not high exposure to captan and hydrogen sulfide was associated with a 1.7 to 1.8-fold increase in risk of prostate cancer.(241)

Barry et al. (2011) examined 776 cases and 1,444 controls in a subset of Caucasian Agricultural Health Study participants for self-reported occupational pesticide use and prostate cancer. They found significant inverse associations between prostate cancer and carbaryl, cyanazine, 2,4,5-T, metolachlor and imazethapyr.(244) Koutros et al. (2013) completed a study of 1,962 cases of prostate cancer, of which 919 were aggressive cases, among 54,412 participants in the Agricultural Health Study cohort. There were no associations between incident prostate cancer and pesticide exposure. For aggressive prostate cancer, there was a 1.3 to 1.6-fold increased risk with high exposure to the organophosphates fonofos, malathion and terbufos and the organochlorine aldrin.(240)

Boers et al. (2005) examined the occupational history of 1,386 cases and 2,335 controls within a cohort of 58,279 men from the Netherlands followed from 1986 to 1995. They found a significant negative association between the highest tertile of pesticide exposure and prostate cancer.(246)

Fritschi et al. (2007) examined 606 cases and 471 controls in Western Australia for self-reported occupational pesticide exposure. They found no significant associations between pesticide exposure and prostate cancer, including exposure to organophosphates, organochlorines, phenoxy herbicides, other herbicides and other pesticides.(245)

Meyer et al. (2007) completed a case-control study of farming or applying pesticides in 405 cases and 392 controls in South Carolina from 1999 to 2001. There was a 1.8-fold increased risk of prostate cancer in Caucasian farmers but not African-American farmers. As well, among farmers who applied pesticides, there was a 1.6-fold increased risk of prostate cancer.(243) This study was included in the meta-analysis completed by Ragin et al. (2013).(242,243)

8.1.13 Respiratory tract (including lung)

Table 44. Pesticide exposure and respiratory tract cancer

Grade	Exposure	Outcome
B	Any pesticide	NK/T-cell lymphoma (249)
	Pesticide class (insecticide, residential)	Nasal cancer in men (250)
	Pesticide class (herbicide, insecticide, fungicide, risk reduced with protective measures)	NK/T-cell lymphoma (249)
	Specific pesticides (metolachlor, pendimethalin, chlorpyrifos and diazinon)	Lung cancer (251)
B -	Any pesticide	Lung cancer (252)

Four studies were identified that examined respiratory tract cancers. McHugh et al. (2010) completed a case-control study of 212 Mexican-American lung cancer cases and 328 practice-based controls from 1991 to 2005 in Texas. They examined environmental and occupational job exposures and found that the use of conventional pesticides was associated with a 2-fold increase in the risk of lung cancer.(252) Alavanja et al. (2004) completed an analysis of 57,284 pesticide applicators from the Agricultural Health Study with follow-up from 1993-1997 to 2001 and incident lung cancer. The study did not present any overall measures of associations between pesticides and lung cancer. Instead, they focused on the analysis of specific pesticide exposure and found significant associations with high exposure to two herbicides; metolachlor and pendimenthalin and two insecticides; chlorpyrifos and diazinon.(251)

Greiser et al. (2012) conducted a case-control study of 427 cases and 2,401 controls in Germany examining the association between insecticide use in residences and nasal cancer. They found a 1.5-fold increase in risk of nasal cancer with home insecticide use.(250)

Finally, a review of nasal NK/T-cell lymphoma by Aozasa and Zaki (2011) reported results of a case-control study of 88 cases and 305 controls from Japan, Korea and China. They reported significant increases in risk of nasal NK/T-cell lymphoma with ever pesticide use (2-fold), herbicide (3.2-fold), insecticide (3.4-fold) or fungicide (6-fold), although these risks were slightly attenuated with the use of protective measures.(249)

8.1.14 Skin

Table 45. Pesticide exposure and skin cancer

Grade	Exposure	Outcome
A	Any pesticide (occupational)	Cutaneous melanoma (253,254)
B	Any pesticide	Cutaneous melanoma (255)
	Specific pesticide (cis-nonachlor, hexachlorobenzene, mirex and trans-nonachlor)	Cutaneous malignant melanoma (256)
	Specific pesticide (maneb/mancozeb, parathion and carbaryl)	Cutaneous melanoma (257)
	Specific application (lead arsenate and either benomyl or maneb/mancozeb)	Cutaneous melanoma (257)
	Specific application (indoor pesticide use more than 4 times annually)	Cutaneous melanoma (255)
	Specific application (use of pesticides for more than 10 years)	Cutaneous melanoma (255)
	Specific application (occupational use of pesticides for more than 10 years)	Mycosis fungoides in men (258)
I	Any pesticide (occupational)	Mycosis fungoides in women (258)

Four studies and two reviews considered the subject of skin cancer and pesticide exposure. Fortes et al. (2008) examined 10 studies of cutaneous melanoma and pesticide exposure. Eight of the ten studies considered found a significant increase in risk of cutaneous melanoma with occupational pesticide exposure.(253) MacKie et al. (2009) agreed with this conclusion and stated that pesticide use appears to be a contributor to cutaneous melanoma.(254)

Dennis et al. (2010) completed a cohort analysis of 150 cases and 24,554 controls among the Agricultural Health Study participants for their exposure to 50 pesticides. They found significant increases in cutaneous melanoma cases with high number of exposures to maneb/mancozeb (2.4-fold), parathion (2.4-fold) and carbaryl (1.7-fold). Simultaneous exposure to lead arsenate and benomyl (6.7-fold) or maneb/mancozeb (10.8-fold) increased the risk of cutaneous melanoma further.(257)

Fortes et al. (2007) examined 287 cases and 299 hospital controls for their occupational and residential pesticide exposure history. They found a 2.2 to 2.5-fold increases in risk of cutaneous melanoma with indoor pesticide use more than four times annually versus less than once annually and for pesticide use for greater than 10 years compared to less than 10 years. There was a significant trend of increasing risk of cutaneous melanoma with increasing overall intensity of pesticide use.(255)

Gallagher et al. (2011) measured the serum organochlorine levels in 80 cases and 310 controls in British Columbia. They found significantly increased risks and positive trends for cutaneous malignant melanoma and exposure to cis-nonachlor (2.3-fold), hexachlorobenzene (3.1-fold), mirex (2.7-fold) and trans-nonachlor (4.3-fold).(256)

Finally, Morales-Suárez et al. (2005) completed a case-control study of 118 cases of mycosis fungoides, a rare type of cutaneous lymphoma, and 833 controls with colon cancer and 2,071 population controls across Europe. They found that men with greater than 10 years of occupational pesticide exposure were at a 6.8-fold increased risk of mycosis fungoides. The findings for women involved only 5 exposed cases and were not significant.(258)

8.1.15 Testicular

Table 46. Pesticide exposure and testicular cancer

Grade	Exposure	Outcome
B	Pesticide class (insecticide, household)	TGCC (259)
	Pesticide class (insecticide, occupational with a 20 year lag)	Testicular cancer (260)
	Pesticide type (organochlorine)	Testicular cancer (261)
	Specific pesticides (*cis*-nonachlor and *trans*-nonachlor)	TGCC (262)
	Specific pesticides (*cis*-nonachlor, *trans*-nonachlor and oxychlordane)	Seminoma (262)
C	Any pesticide (occupational)	TGCC (260,263)
	Pesticide type (organochlorine)	TGCC (259,264,265)
	Specific application (exposures associated with work in agriculture)	TGCC and testicular cancer(261,263)
D	Pesticide class (herbicide or fungicide)	TGCC (260)
	Specific pesticide (oxychlordane, ß-hexachlorohexane or mirex)	TGCC (262)

TGCC: Testicular Germ Cell Carcinoma

Five papers specifically examined organochlorine pesticides and testicular cancer. McGlynn and Traberts' 2012 review of the literature suggested that organochlorines are likely associated with the development of testicular cancer but that agriculture exposure to pesticides in general had not been linked to testicular cancer.(261) Biggs et al. (2008) examined the association between serum organochlorine levels and Testicular Germ Cell Carcinoma (TGCC) in 246 cases and 630 controls in Washington States. They found no association between testicular germ cell tumors and serum organochlorine levels.(264) Giannandrea et al. (2011) examined 50 cases and 48 hospital based controls in Italy for serum hexachlorobenzene and DDE levels and self-reported pesticide use. They found that household insecticide use and total organochlorine levels were significantly associated with a 3-fold increase in risk of testicular cancer.(259) McGlynn et al. (2008) examined 754 cases and 928 controls in the United States military for serum organochlorine levels. Having serum levels in the fourth quartile for *cis*-nonachlor and *trans*-nonachlor was associated with a significant 1.5 to 1.6-fold increase in TGCC. Serum levels of *cis*-nonachlor, *trans*-nonachlor and oxychlordane in the fourth quartile were associated with a 1.6 to 1.9-fold increase in risk of seminoma. There were no associations found between serum oxychlordane, ß-hexachlorohexane or mirex levels and TGCC.(262) Finally, Purdue et al. (2009) examined Norwegian 49 cases and 51 controls and found no association between serum organochlorine levels and TGCC.(265)

Béranger et al. (2013) completed a systematic review of 72 articles from 1990 to 2012 on occupational and environmental pesticide exposures and TGCC. They found significant associations between occupational exposures associated with agricultural workers, construction workers, firemen, policemen, military personnel, as well as workers in paper, plastic or metal industries and TGCC. They also found evidence suggestive of an association between TGCC and pesticide exposure but it was more limited and of poorer quality.(263) Guo et al. (2005) completed a cohort study of all economically active Finnish men born 1906 to 1907 with 387

cases of testicular cancer identified. They found that exposure to insecticide was associated with a significant 4.3-fold increase in risk of testicular cancer with a lag of 20 years from exposure to outcome. The were no associations between TGCC and overall pesticide, herbicide or fungicide exposure.(260)

8.1.16 Other cancers

Table 47. Pesticide exposure and other cancers

Grade	Exposure	Outcome
B	Specific application (pesticide application in forestry)	Uveal melanoma of the eye (266)
B -	Any pesticide (occupational)	Mouth and pharynx cancer (267)
	Any pesticide (occupational, risk reduced with use of protective equipment)	Bone cancer (268)
	Pesticide class (herbicide or insecticide)	Bone cancer (268)
	Pesticide class (fungicide)	Mouth and pharynx cancer (267)
D	Pesticide class (herbicide and insecticide)	Mouth and pharynx cancer (267)
	Specific pesticide (mancozeb)	Thyroid cancer (36)
	Specific application (pesticide mixing or application in farming)	Uveal melanoma of the eye (266)

Three articles are included in this section. Norby et al. (2005) completed a retrospective cohort study of 105,403 female and 131,243 male farmers born 1925-1971 and their 300,805 children born 1952-199. They examined mancozeb exposure using fungal forecasts as an exposure proxy and thyroid cancer. No association between thyroid cancer and mancozeb exposure was found.(36)

Behrens et al. (2012) examined 293 cases of uveal melanoma of the eye and 3,198 controls for self-reported pesticide exposure. They found no significant association with pesticide mixing or application in farming. Application of chemical in the forestry industry was associated with a 8.9-fold increase in risk of uveal melanoma of the eye.(266)

Tarvainen et al. (2008) followed 46.8 million person-years of a cohort of Finns born 1906-1945 and used a job exposure matrix to estimate occupational pesticide exposure and incidence of mouth and pharynx cancer. They found no association between occupational pesticide exposure and mouth and pharynx cancer except at the highest tertile of cumulative exposure (1.9-fold). There was also a 1.5-fold increase in mouth and pharynx cancer in the lowest tertile of fungicide exposure, but not in the middle and highest tertiles. No associations were seen between insecticide or herbicide exposure and mouth and pharynx cancer.(267)

One study examined the association between bone cancers and occupational or residential pesticide exposure. Merletti et al. (2006) examined 96 cases of chondrosarcoma (n=68) and osteosarcoma (n=28) and 2,632 population controls in 7 European countries from 1995 to 1997 for occupational pesticide exposure. There were approximately 2.5-fold increases in the risk of overall bone cancer with the ever use of pesticides, herbicides and insecticides. The tertiles of pesticide use did not, however, demonstrate a dose-response relationship with only the middle tertile having a significant increase in odds of bone cancer. The increased risk of bone cancer associated with ever use of pesticides was reduced from 2.5-fold to 2-fold with the use of protective equipment (i.e. mask, gloves, glasses, overalls or handkerchief).(268)

8.2 Children

Research into associations between childhood cancers and pesticide use is also extensive. The main challenge with these studies is the enormous variety of critical exposure periods that can be applied for each pesticide exposure. Studies need to consider pesticide exposure in the mother, father and child during the pre-conceptual, prenatal and childhood risk periods. In addition, studies often consider occupational and residential pesticide use separately. Exposure assessment is a significant challenge in these studies because outcomes are so rare even among exposed subjects in cohort studies. In case-control studies, exposure recall bias is a major problem because of the grave nature of childhood cancer and parental perception of the effect of pre-illness exposures.

8.2.1 General cancer

Table 48. Pesticide exposure and general childhood cancer

Grade	Exposure	Outcome
A	Any pesticide (childhood exposure)	Lymphoma, leukemia, brain cancer, Ewing's sarcoma and neuroblastoma (269)
	Any pesticide (maternal, prenatal)	Lymphoma and leukemia (269)
	Any pesticide (maternal, after birth)	Leukemia (269)
	Any pesticide (paternal, before birth)	Brain cancer (269)
	Any pesticide (paternal, after birth)	Brain cancer and leukemia (269)
	Any pesticide (combined parental, prenatal)	Leukemia (269)
	Any pesticide (paternal, occupational)	Brain cancer, leukemia and Ewing's sarcoma (269)
	Any pesticide (paternal, residential)	Brain cancer (269)
	Any pesticide (maternal, residential use)	Lymphoma and leukemia (269)
	Pesticide class (herbicide and insecticide)	Lymphoma, leukemia and brain cancer (269)
	Pesticide class (fungicide)	Lymphoma and brain cancer (269)
B	Any pesticide	Leukemia, brain cancer, Hodgkin lymphoma and neuroblastoma (270)
	Any pesticide (paternal, occupational)	Cancer, lymphoma and HL (271)
	Specific pesticide (aldrin, paternal prenatal application)	Cancer (271)
	Specific application (Residence in counties of high agricultural activity)	Leukemia, lymphoma, NHL, HL brain tumors (astrocytoma and PNET), sympathetic nervous system tumors (neuroblastoma and retinoblastoma), renal tumors, hepatic tumors, malignant bone tumors (oseteosarcoma and Ewing's sarcoma), STS, rhabdomyosarcoma, germ cell trophoblastic and other gonadal neoplasms, thyroid cancer and malignant melanoma and other and unspecified cancers (272)
	Specific application (paternal failure to use chemically resistant gloves during pesticide application)	Cancer (271)
B -	Any pesticide (occupational, paternal)	Neuroblastoma and gaglineuroblastoma and fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasm in male children (273)
	Pesticide class (herbicide)	Neuroblastoma and gaglineuroblastoma and fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasm in male children (273)
C	Any pesticide (childhood)	Cancer (269,274–276)
D	Any pesticide (frequency of prenatal application)	Cancer (271)
	Any pesticide (maternal application or mixing of pesticides)	Cancer (271)
	Specific application (Residence in counties of high agricultural activity)	Cancer (272)
	Specific application (County level agricultural pesticide application)	Cancer (277)
	Specific application (Maternal residence within 800 to 1,000m of crop fields at birth)	Cancer (278,279)
	Specific application (Maternal residence within 800 of crop fields at birth)	Leukemia and brain cancer (279)
E	Any pesticide (childhood)	Germ cell or renal tumors (269)

HL: Hodgkin lymphoma NHL: Non-Hodgkin lymphoma STS: soft tissue sarcoma PNET: primitive neneuroectodermal tumors

One meta-analysis and five reviews met the inclusion criteria and covered the area of childhood cancer and pesticide exposure. Vinson et al. (2011) completed a meta-analysis of two cohort studies and 38 case-control studies published from 1985 to 2008. They found no association between parental pesticide exposure and childhood cancer, including leukemia, lymphoma and brain cancer, when only the cohort studies were considered. There was no association between any childhood pesticide exposure and germ cell tumors or renal tumors. As well, living in an agricultural area was not association with an increased risk of childhood cancers. When they considered all 40 studies, they found significant association between:

- Any childhood pesticide exposure and lymphoma (1.4-fold), leukemia (1.2-fold), brain cancer (1.2-fold), Ewing's sarcoma (2.0-fold) and neuroblastoma (1.7-fold)
- Maternal prenatal pesticide exposure and lymphoma (1.5-fold) and leukemia (1.5-fold)
- Paternal pesticide exposure before (BB) or after birth (AB) and brain cancer (BB 1.5-fold, AB 1.7-fold) and leukemia (AB 1.3-fold)
- Maternal pesticide exposure after birth and leukemia (AB 2.1-fold)
- Combined maternal and paternal prenatal pesticide exposure and leukemia (BB 1.8-fold)
- Paternal occupational (O) and residential (R) pesticide exposure and brain cancer (O 1.4-fold, R 1.5-fold)
- Paternal occupational exposure and leukemia (O 1.4-fold) and Ewing's sarcoma (O 2.3-fold)
- Maternal use of residential pesticides and lymphoma (R 1.5-fold) and leukemia (R 1.6-fold)
- Herbicide (H), fungicide (F) and insecticide (I) exposure and lymphoma (H 1.3-fold, I 1.5-fold, F 1.4-fold), leukemia (H 1.3-fold, I 1.2-fold) and brain cancer (H 1.3-fold, I 1.2-fold, F 1.3-fold)(269)

Infante-Rivard and Weichenthal (2007) reviewed 15 case-control studies, four cohort studies and two ecological published from 1999 to 2004. They found that 15 of 21 studies reported significant increases in the risk of childhood cancer with either childhood pesticide exposure or parental occupational exposure. However, they could not define definitive unambiguous causal relationships based on the Bradford-Hill criteria and found gaps in the research regarding critical windows for exposure and the role of genetic susceptibility in the relationship between pesticide exposure and cancer.(274)

Jurewicz and Hanke (2006) reviewed studies on childhood cancer published from 1998 to 2005 and found potential associations between pesticide exposure and leukemia, brain cancer, HL and neuroblastoma. They also identified limitations in the epidemiological evidence including problems with exposure assessment, small numbers of exposed subjects, difficulties defining critical exposure windows and the limited number of studies focusing on each type of cancer.(270)

Nasterlack (2006) and (2007) published two reviews of pesticide exposure and childhood cancer encompassing 18 studies from 1998 to 2004 and 36 studies from 1998 to 2006 respectively. They found that the studies suggested an increase in many different types of childhood cancer but that many of the estimates were not significant.(275,276)

Six other studies considered childhood cancer and pesticide exposure, including four case-control designs, and one each with ecological and cohort designs. Carozza et al. (2008) completed an ecological study of all children aged 0 to 14 years in 25 states in the United States and all incident childhood cancers. They used the percent of the land in each county used as cropland in 1,078 counties to classify the exposure to agricultural activity as low, medium or high. They did not find an increased risk of overall childhood cancer for living in an area of high agricultural activity. They did find that residence in an area of high agricultural activity was associated with an increased risk of:

- Leukemia (1.2-fold), lymphoid leukemia (1.3-fold) and acute myeloid leukemia (1.8-fold)
- Lymphoma (1.4-fold), HL (2.1-fold) and NHL (2.1-fold)
- Brain tumors (1.3-fold), astrocytomas (1.5-fold) and PNET (1.9-fold)
- Sympathetic nervous system tumors (1.7-fold), neuroblastoma (1.8-fold) and retinoblastoma (2.6-fold)
- Renal tumors (2.1-fold), Wilms' tumor (2.1-fold) and renal carcinoma (3.3-fold)
- Hepatic tumor (3.3-fold) and hepatoblastoma (4.0-fold)
- Malignant bone tumor (2.3-fold), osteosarcoma (2.7-fold) and Ewing's sarcoma (4.3-fold)
- STS (1.7-fold, rhabdomyosarcoma (2.5-fold), germ cell trophoblastic and other gonadal neoplasms (2.3-fold)
- Carcinoma and other (2.2-fold), including thyroid cancer (3-fold) and malignant melanoma (4.6-fold)
- Other and unspecified cancers (11.2-fold)

The estimates for medium agricultural activity countries were generally between 1.0 and the OR for the specific cancer in the high agricultural activity counties.(272)

Flower et al. (2004) examined the children of 17,357 Iowa farmers participating in the Agricultural Health Study for self-reported parental occupational use of 50 specific pesticides and childhood cancer. They examined incident childhood cancers that occurred 1975 to 1998. There was an increased risk of all childhood cancers (1.4-fold), all lymphomas (2.2-fold) and HL (2.6-fold) compared to the expected number based on cancer incidence in the population of Iowa children. There was no association with frequency of prenatal pesticide application or maternal application or mixing of pesticides. Among specific pesticides, only paternal prenatal use of aldrin was associated with cancer incidence (2.7-fold). Encouragingly, children of fathers who used chemically resistant gloves during pesticides application did not have an increased risk of childhood cancer when compared to children of fathers who did not use gloves.(271)

Reynolds et al. (2005) completed a case-control study of 2,189 cases and 4,335 controls and examined the association between the mother's residential proximity to agricultural application of pesticides at the child's birth and early childhood cancer and leukemia risk. They found no association between all cancer, leukemia or brain cancer risk and the proximity to agricultural pesticide application. There was a considerable lack of exposed cases and controls in this study.(279)

Walker et al. (2007) examined 6,974 cases and 6,974 controls identified through Texas State Registries and found no association between childhood cancer and the percent cropland and

pesticide carcinogenicity county-level exposure.(277) Carozza et al. (2009) also completed a Texas-based study of 1,778 cases and 1,802 controls and their probable agricultural pesticide exposure based on proximity of birth residence within 1,000m of crop fields. They found no association between having agricultural land within 1,000m of the birth residence and all cancers or any specific cancer examined.(278)

Pearce et al. (2006) examined 4,723 cases and all cancer registry patients with a different cancer and 100 cancer-free controls in Northern England for parental occupational pesticide exposure. They found no significant positive association between paternal occupational pesticide or herbicide exposure except for male neuroblastoma and ganglioneuroblastoma (2.4-fold) and male fibrosarcoma, neurofibroscarcoma and other fibromatous neoplasm (3.9-fold). These associations were present when the cancer registry patients were used as controls but not when using the cancer-free controls. There were multiple negative associations found when using the cancer-free participants as controls.(273)

8.2.2 Brain

Research on childhood brain divided into three subsections based on paternal, maternal or childhood pesticide exposure. Research into associations between pesticide exposure and childhood brain cancer is limited, particularly for maternal and childhood pesticide exposure. One meta-analysis and four studies were identified that met inclusion criteria.(279–283) The studies considered associations between childhood brain tumors (CBT) and paternal and maternal preconception and prenatal exposure and childhood exposure, in both an occupational and residential context.

8.2.2.1 Paternal prenatal pesticide exposure

Table 49. Paternal pre-conceptual and prenatal pesticide exposure and childhood brain tumor

Grade	Exposure	Outcome
B	Pesticide class (herbicide, residential)	Astrocytoma(283)
	Pesticide class (insecticide, residential)	Non-astrocytoma, non-PNET brain tumors (283)
B -	Specific application (lawn care during pregnancy)	Medulloblastoma and PNET (282)
D	Any pesticide (residential)	PNET (283)
	Pesticide class (NOS, residential)	CBT(283)
	Pesticide class (herbicide, residential)	Non-astrocytoma, non-PNET brain tumors (283)
	Pesticide class (insecticide, residential)	Astrocytoma (283)
	Specific application (use of protective measures with residential pesticide application)	Astrocytoma (283)
E	Any pesticide (occupational)	Neuroblastoma, CBT (280,281)

PNET: Primitive Neuroectodermal Tumors CBT: Childhood Brain Tumors NOS: Not otherwise specified

Regarding paternal occupational pesticide exposure, Moore et al. (2011) completed a meta-analysis of 7 case-control and 2 cohort studies comprising 1,426 cases of neuroblastoma. They concluded that there was no association between paternal occupational pesticide exposure and neuroblastoma.(280) Greenop et al. (2013) supported this finding of no effect of paternal occupational pesticide exposure in the year prior to conception in their case-control study of 374 CBT cases and 1,497 matched controls.(281)

Paternal residential pesticide exposure prior to conception and during pregnancy showed increased risk of some forms of CBT in two studies. In their case-control study of 526 one-to-one matched controls, Shim et al. (2009) found a 1.9-fold increased risk of astrocytoma with paternal residential application of herbicides in the 2 years prior to birth. The increased risk of astrocytoma was rendered null when the father washed immediately afterwards or wore protective clothing. Paternal application of or occupational exposure to insecticides was associated with a 2.9-fold increased risk of non-astrocytoma, non-primitive neuroectodermal tumors (non-PNET). There were no associations between paternal insecticide application and PNET or astrocytoma. No associations between PNET and other pesticide classes were found.(283)

Rosso et al. (2008) studied 318 cases and 318 matched controls diagnosed with CBT before age 6 and self-reported paternal hobbies. They found a 1.6-fold increase in medulloblastoma (MB) and PNET when the father engaged in lawn care during pregnancy, with the estimated increase

in risk increasing to 1.9-fold for children over 23 months at diagnosis and rendered non-significant in the younger age group. There was evidence of recall bias for lawn care.(282)

8.2.2.2 Maternal prenatal pesticide exposure

Table 50. Maternal pre-conceptual and prenatal pesticide exposure and childhood brain tumor

Grade	Exposure	Outcome
B	Any pesticide (residential)	High-grade gliomas (281)
	Specific application (professional pest control treatment in the home in the year before pregnancy)	CBT (281)
	Specific application (professional pest control treatment in the home once in the year before pregnancy)	CBT (281)
	Specific application (professional pest control treatment in the bedroom)	CBT (281)
	Specific application (termite treatment)	CBT (281)
D	Any pesticide (residential)	CBT (279)
	Specific application (professional pest control treatment in the home during pregnancy)	CBT (281)
I	Any pesticide (occupational)	CBT (283)

PNET: Primitive Neuroectodermal Tumors CBT: Childhood Brain Tumors

Maternal occupational pre-conceptual and prenatal pesticide exposure has historically been difficult to study due to small number of exposed individuals and will not be considered further here.(283)

Maternal residential pre-conceptual and prenatal pesticide exposure was considered in two studies. Reynolds et al. (2005) examined 2,189 cases of early childhood cancers and 4,335 controls and the mother's residential proximity to agricultural pesticide application around the time of birth and found no association with central nervous system tumors.(279)

Greenop et al. (2013) also considered maternal exposures and found a significant increase in risk of CBT with professional pest control treatment in the home in the year before the pregnancy (1.5-fold), if the only treatment happened in the year before pregnancy (1.9-fold), with bedroom treatment (1.6-fold) and with any termite treatment (2.2-fold). Risks for low-grade gliomas were similar to CBT overall, but risk of high-grade glioma were increased with exposure to pesticides before (3-fold) and during (4.6-fold) pregnancy. There was no association between CBT and professional pest control treatments during pregnancy.(281)

8.2.2.3 Childhood pesticide exposure

Table 51. Childhood pesticide exposure and childhood brain tumor

Grade	Exposure	Outcome
B	Specific application (professional pest control treatment while the child is in the home)	CBT (281)
	Specific application (paternal lawn care during childhood)	Medulloblastoma and PNET (282)
D	Specific application (professional pest control treatment)	CBT (281)
I	Any pesticide (Residential)	CBT

PNET: Primitive Neuroectodermal Tumors CBT: Childhood Brain Tumors

Greenop et al. (2013) also considered childhood residential exposures. They found a 1.6-fold increase in risk of CBT with the child being home for professional pest control treatment. There was no association between CBT and professional pest control treatments in childhood.(281)

Rosso et al. (2008) found a 1.8-fold increase in MB and PNET when the father engaged in lawn care in childhood, with the estimated increase in risk increasing to 2-fold for children over 23 months at diagnosis and rendered non-significant in the younger age group. There was some evidence of recall bias for lawn care.(282) Neither prenatal nor childhood exposures to residential pesticides and its association with CBT have been extensively studied in terms of specific risk periods and implicated pesticides.

8.2.3 Leukemia

The association between childhood leukemia and pesticide exposure has been extensively studied. There were 3 meta-analyses and ten studies that met our inclusion criteria.(200,279,284–294) Given the complexity of the topic, the study results are divided into functional areas based on pesticide use context (occupational or residential), time frame (pre-conceptual and prenatal or childhood) and relationship to the child (maternal, paternal or self). In addition, the beginning of each section presents a table detailing the grade of evidence for each exposure and outcome relationship and the relevant reference. Following the table is a description of the study and results used to assign the grade.

8.2.3.1 Occupational pesticide exposure

Table 52. Occupational pesticide exposure reviews and childhood leukemia

Grade	Exposure	Outcome
B	Specific pesticides (metam sodium and diocofol)	Childhood leukemia (289)
	Specific application (living on a farm)	Childhood leukemia (289)
C	Specific pesticides (pentachlorophenol and chlorophenol)	Childhood leukemia (200)

Agricultural and occupational pesticide exposures were the subject of two meta-analyses, two reviews and one study. McNally et al. (2006) reviewed one ecological study and four case-control studies of agricultural pesticide use. Three of the four case-control studies reported an increased risk of leukemia with residence near and parental exposure to pesticides, specifically pesticide use on farms (1.5-fold) and the agricultural use of metam sodium (2-fold) and diocofol (1.8-fold).(289)

Cooper at al. (2008) included 2 childhood leukemia studies in their review of the health effects of pentachlorophenol and chlorophenol exposure. One cohort study found no significant increase in leukemia risk and one case-control study found significantly increased risks of leukemia with pre-conceptual and perinatal exposure but these were based on less than 7 cases each.(200)

8.2.3.1.1 Paternal occupational pesticide exposure

Table 53. Paternal occupational pesticide exposure and childhood leukemia

Grade	Exposure	Outcome
B	Pesticide classes (insecticides, herbicides and fungicides)	Childhood leukemia (285)
C	Any pesticide (around conception)	ALL (286,294)
E	Any pesticide	Childhood leukemia (285)
	Any pesticide (around conception)	AML (286)

ALL: Acute Lymphocytic Leukemia AML: Acute Myeloid Leukemia

Paternal occupational pesticide exposure was considered in two meta-analyses and one study. Wigle et al. (2009) completed a meta-analysis of 26 case-control and 5 cohort studies and found no significant overall association between childhood leukemia and paternal occupational pesticide exposure. There was an elevated risk of childhood leukemia with paternal occupational exposure to insecticides (1.4-fold), herbicides (1.2-fold) and fungicides (1.7-fold).(285)

Bailey et al. (2014) completed a meta-analysis of 13 case-control studies. They found an increased risk of ALL (1.2-fold) but not AML with paternal occupational pesticide exposure around conception.(286)

Glass et al. (2012) conducted a case-control study of occupational exposures in 378 mothers and 327 fathers of ALL cases and 854 mothers and 748 fathers of controls and found no association between paternal occupational pesticide exposure and ALL risk.(294)

8.2.3.1.2 Maternal occupational pesticide exposure

Table 54. Maternal occupational pesticide exposure and childhood leukemia

Grade	Exposure	Outcome
A	Any pesticide (prenatal)	Childhood leukemia (285)
	Any pesticide (prenatal)	AML (286)
E	Any pesticide (prenatal)	ALL (286)

ALL: Acute Lymphocytic Leukemia AML: Acute Myeloid Leukemia

Maternal occupational pesticide exposure was considered in two meta-analyses and one study. Wigle et al. (2009) found a significantly increased risk of childhood leukemia with prenatal maternal pesticide exposure (2.1-fold) and specifically with prenatal insecticide (2.7-fold) and herbicide (3.6-fold) exposure.(285)

Bailey et al. (2014) found an increased risk of AML (1.9-fold) but not ALL with maternal occupational pesticide exposure during pregnancy.(286)

Glass et al. (2012) concluded they had insufficient sample size to make conclusions about maternal occupational pesticide exposure and ALL risk.(294)

8.2.3.2 Maternal residential pesticide exposure

Table 55. Maternal residential pesticide exposure and childhood leukemia

Grade	Exposure	Outcome
A	Any pesticide	Childhood leukemia (284)
	Pesticide class (insecticides and herbicides)	Childhood leukemia (284)
B	Any pesticide	ALL in children with Down's Syndrome (288)
	Specific pesticides (metam sodium and dicofol)	Childhood leukemia (279)
	Specific pesticides (metam sodium)	ALL (279)
D	Any pesticide	AML in children with Down's Syndrome (288)

ALL: Acute Lymphocytic Leukemia AML: Acute Myeloid Leukemia

Maternal pre-conceptual and prenatal residential pesticide exposure was the subject of one meta-analysis and three studies. Turner et al. (2010) conducted a meta-analysis of 15 case-control studies from 1950 to 2009. They concluded that there was a significantly increased risk of leukemia with maternal prenatal residential exposure to pesticides overall (1.5-fold), insecticides (2-fold) and herbicides (1.6-fold).(284)

Alderton et al. (2006) examined the association between leukemia and maternal pesticide exposure in 158 cases and 173 controls with Down's syndrome. They found a significant 2.2-fold increase in risk of ALL in children with Down's syndrome with maternal exposure to professional pest extermination or any pesticide. No significant associations were found for AML.(288)

Menegaux et al. (2006) examined 280 incident cases of acute leukemia and 288 controls and parental home and garden pesticide use. They found a significant 1.8-fold increase in risk of acute leukemia with maternal home insecticide use during pregnancy. There was no increase in risk with use of garden herbicide during pregnancy.(290) This study is not included in the grading table as it was used in the meta-analysis by Turner et al. (2010).(284)

Reynolds et al. (2005) examined maternal residential proximity to low, high and very high (when sample size allowed) agricultural pesticide application at the time of the child's birth in 2189 cases and 4335 age and sex matched controls. They found a significantly increased risk of ALL with high use of metam sodium (3.3-fold). There was a significantly increased risk of leukemia with high use of metam sodium (2-fold), and dicofol (1.8-fold).(279)

8.2.3.3 Childhood residential exposure to agricultural pesticides

Table 56. Childhood exposure to agricultural pesticides and childhood leukemia

Grade	Exposure	Outcome
B	Pesticide type (fumigants, chlorinated phenols, organophosphates, triazines, azoles and urea pesticides)	ALL (291)
	Specific pesticide (chlorthal)	ALL (287)
B -	Carcinogenicity category (probable carcinogens, possible carcinogens, probable or possible carcinogens, cholinesterase inhibitors and suspected genotoxins)	ALL (291)
D	Pesticide classes NOS	ALL (291)
	Carcinogenicity category NOS	ALL (291)
	Specific pesticides NOS	ALL (287,291)
I	Any pesticide	AML

NOS: Not Otherwise Specified ALL: Acute Lymphocytic Leukemia AML: Acute Myeloid Leukemia

Residential exposure to agricultural pesticides in childhood was considered in two studies. Metayer et al. (2013) sampled carpet dust in the homes of 269 ALL cases and 333 controls under age 8 and living in the same residence since diagnosis or study entry. They found a significant association and dose-response relationship for ALL and chlorthal home carpet dust levels. Despite testing many other individual pesticide levels, no other significant associations were found.(287)

Rull et al. (2009) examined 213 ALL cases and 268 matched controls for their residential proximity to agricultural pesticide application within 0.5 miles of the maternal residence during the first year of life and to the date of diagnosis. The exposed sample sizes, particularly in the high exposure groups, were small and this resulted in a loss of precision in the estimates and may explain the lack of significant findings in the high exposure groups. When they examine the risk of exposure to individual pesticides, they found a significant 1.6 to 2-fold increase in risk of ALL with exposure to moderate but not high levels of lifetime fumigants, chlorinated phenols, organophosphates, triazines and urea pesticides. A significant 1.5 to 1.6-fold increase in risk of ALL was also seen with moderate but not high levels of lifetime exposure to pesticides classifieds as probable carcinogens, possible carcinogens, probable or possible carcinogens, cholinesterase inhibitors and suspected genotoxins. Exposure to probable carcinogens in the first year of life was associated with a 1.9-fold increase in risk of ALL. The authors then adjusted for simultaneous chemical exposures and, after this adjustment, found that there were approximately 4-fold significant increases in ALL risk with moderate triazine and high azole exposures.(291)

8.2.3.4 Childhood exposure to residential pesticides

Table 57. Childhood residential pesticide exposure and childhood leukemia

Grade	Exposure	Outcome
A	Any pesticide	Childhood leukemia (284,289,290)
B	Pesticide class (Garden insecticide and fungicide)	Childhood leukemia (290)
	Pesticide class (Insecticides)	Childhood leukemia (284,289,290)
	Pesticide type (Organophosphate)	ALL (292)
	Specific application (Repeated insecticidal treatments of pediculosis)	Childhood leukemia (290)
D	Any pesticide	AML or ALL in children with Down's Syndrome (288)
	Pesticide class (Garden herbicide)	Childhood leukemia (290)
	Pesticide type (Organochlorine)	ALL (293)

ALL: Acute Lymphocytic Leukemia AML: Acute Myeloid Leukemia

Exposure to residential pesticides was the subject of one meta-analysis and four studies. In their meta-analysis, Turner et al. (2010) concluded that there was a significantly increased risk of childhood leukemia with childhood residential pesticide exposure overall (1.4-fold) and to insecticides (1.6-fold). Once they excluded lower quality studies from the analysis, the association between childhood residential insecticide exposure and leukemia was no longer significant.(284)

McNally et al. (2006) reviewed 4 case-control studies. Three of the four case-control studies reported an increased risk of leukemia with childhood exposure to pesticides, specifically residential exposure to insecticides (2.6-fold).(289)

Alderton et al. (2006) found no association between childhood pesticide exposure and AML or ALL in children with Down's syndrome.(288)

Menegaux et al. (2006) found a significant 1.7-fold increased risk of acute leukemia with any pesticide use during childhood. Specifically, there was an increased risk of acute leukemia with childhood exposure to garden insecticides (2.4-fold) and fungicides (2.5-fold) and insecticidal treatment of more than one episode of pediculosis (1.9-fold). There was no increase in risk with use of garden herbicide during childhood.(290)

Soldin et al. (2009) completed a small case-control study of 41 ALL cases and 77 age, sex and residence matched controls for self-reported and urine biomarkers of organophosphate use. They found that ALL cases were significantly more likely to report maternal insecticide use at home and had significantly higher levels of two urinary organophosphate biomarkers than the controls.(292)

Finally, Ward et al. (2009) examined home carpet dust organochlorine levels in 184 ALL cases and 212 age, sex and race matched controls. They found no significant association between chlordane, methoxychlor or pentachlorophenol levels and ALL risk.(293)

8.2.4 Wilms' tumor

Table 58. Pesticide exposure and Wilms' tumor

Grade	Exposure	Outcome
B-	Any pesticide (residential use, prenatal to diagnosis)	Wilms' tumor (295)
	Pesticide class (insecticide, prenatal to diagnosis)	Wilms' tumor (295)
D	Any pesticide (parental occupational exposure, prenatal)	Wilms' tumor (296,297)

Three studies met the inclusion criteria and considered the association between Wilms' tumor and pesticide exposure.(295–297)

Both Tsai (2006) and Fear (2009) considered the association between parental occupational pesticide exposure and Wilms' tumor.(296,297) Tsai (2006) examined 303 cases and 575 frequency match controls in 6 US states for self-reported parental occupational exposures in the 2 years prior to birth.(296) Fear (2009) examined the parental occupation and probable associated occupational exposures at birth in Great Britain of 2,568 cases and 2,568 controls from 1962 to 1999.(297) Both studies found no association between occupational pesticide exposure and Wilms' tumor, although Fear (2009) relied solely on job title for exposure measurement.(296,297)

Cooney et al. (2007) conducted the only study of Wilms' tumor and residential pesticide exposure. They examined 523 cases and 517 frequency matched controls from the US and Canada for exposure to residential pesticides from the month before pregnancy through the diagnosis date. There was a small increase in risk of Wilms' tumor in children exposed to pesticides (1.3-fold) or insecticides (1.4-fold) in the home. This increase may have been due to recall bias. As well, this study grouped all exposures, pre-conceptual, prenatal and childhood until diagnosis together, making risk period assessment difficult.(295)

8.2.5 Other cancers

Table 59. Pesticide exposure and other childhood cancers

Grade	Exposure	Outcome
B	Any pesticide (paternal pre-conceptual occupational)	Retinoblastoma(298)
	Any pesticide (residential, maternal)	Germ cell tumors in girls (299)
B -	Any pesticide (residential, household extermination)	Ewing's sarcoma in boys less than 15 years of age (300)
D	Any pesticide (occupational)	Germ cell tumors (301)
	Any pesticide (residential, childhood)	Germ cell tumors (299)
	Any pesticide (residential, paternal)	Germ cell tumors (299)
	Any pesticide (residential, maternal)	Germ cell tumors in boys (299)
	Any pesticides (occupational, parental exposure)	Ewing's sarcoma (300)
	Any pesticide (residential, household extermination)	Ewing's sarcoma in girls and boys older than 15 years of age (300)

Four articles are included in this section. Abdolahi et al. (2013) examined 198 retinoblastoma cases and 245 controls from paternal occupational pesticide exposures. There was a significant exposure-response trend for pesticides and the risk of retinoblastoma. Paternal pesticide exposure in both the ten years and one year prior to conception was associated with a 1.6 to 2.1-fold significant increase in the risk of retinoblastoma.(298)

Moore et al. (2005) examined 196 cases aged 1.6 to 22.8 years and 196 population controls for parental occupational and residential pesticide exposure. There was no association between parental occupational pesticide exposure and Ewing's sarcoma. In boys less than 15 years of age, a household extermination during childhood was associated with a 3-fold increase in Ewing sarcoma risk. No association was found between having a household extermination during childhood and Ewing's sarcoma in girls or in boys older than 15 years of age.(300)

Chen et al. (2005) and Chen et al. (2006) examined the association between parental and childhood pesticide exposures and childhood germ cell tumors in 253 cases and 294 controls in the Untied States.(299,301) Chen et al. (2005) examined parental occupational exposures and found no association between parental occupational exposure and childhood germ cell tumors.(301) Chen et al. (2006) examined residential parental and childhood pesticide exposures. They found no association between residential parental or childhood pesticide exposures and germ cell tumors except for maternal herbicide exposure in girls, which was associated with a 1.4-fold increase in risk.(299)

9. Respiratory health outcomes and pesticide exposure

9.1.1 Asthma

9.1.1.1 Pediatric asthma

Table 60. Pesticide exposure and pediatric asthma

Grade	Exposure	Outcome
B	Specific application (children living with agricultural workers)	Higher levers of Th2 (302)
	Specific application (children of mothers who worked in the fields)	Higher levers of Th2 (302)
B-	Any pesticide (maternal prenatal and postnatal)	Wheeze at 81 months and asthma diagnosis in first 81 months (303)
	Any pesticide (exposure in first year of life)	Asthma and early persistent asthma (304)
	Any pesticide (residential, use in kitchen or dining room)	Wheeze or dry cough (305)
	Pesticide type (herbicide in first year of life)	Asthma and early persistent asthma (304)
C	Any pesticide	Asthma (306–308)
D	Any pesticide (residential, except kitchen or dining room use)	Wheeze or dry cough (305)

Six studies met the inclusion criteria and focused on children under the age of 18 and the association between asthma and pesticide exposure. The evidence for an association between pediatric asthma and pesticide exposure is mixed. A 2014 comprehensive review of relevant studies found that four of five studies reviewed found a positive association between pediatric asthma and general pesticide exposure but listed significant methodological challenges with the studies.(308) While some results support a significant association between asthma or wheezing and pesticide exposure, others find no or mixed evidence to support this association(306,307). Many of the studies lacked appropriate precision and variability in their exposure measurements and this could be part of the reason for the lack of a consistent direction of findings.(303–305)

9.1.1.1.1 General pesticide exposure

Three of these studies used exposure to pesticides in general. Xu et al. (2012) examined home pesticide application location and the associations with wheeze and dry cough in a cross-sectional sample of 14,065 children. They found that residential pesticide application was not associated with wheezing or chronic cough, except when the pesticide was applied in the kitchen or dining room.(305) Salam et al. (2004) used a case-control approach to examine pesticides or herbicide exposure and the development of asthma in 4,244 school aged children in Southern California. They found that the odds of both asthma diagnosis in the first 5 years of life and the odds of early persistent asthma significantly increased with exposure to pesticides and herbicides in the first year of life.(304) Tagiyeva et al. (2010) examined a large birth cohort for maternal and paternal antenatal and postnatal fungicide/biocide exposure. Medium/high maternal biocide/fungicide exposure both antenatally and postnatally was associated with parent-reported wheeze at 81 months. Postnatal medium/high maternal biocide/fungicide exposure was associated with asthma diagnosis in the first 81 months.(303) All three of these studies lack a specific exposure index and there is potential for significant exposure misclassification. Failing

to measure exposure to specific pesticides would make it very difficult to determine if a specific pesticide exposure was associated with the development of asthma in children.

9.1.1.1.2 Specific pesticide exposures

The next three studies examined the association between the development of asthma in children and exposure to specific pesticides. Reardon et al. (2009) used air monitors to measure pesticide exposure for 2 days in the last trimester of pregnancy in 72 women of African American and Dominican descent. They found that diazinon exposure was significantly inversely related to cough, wheeze or specific IgE markers and that *cis*-permethrin exposure was positively associated with cough by 5 years of age. No significant asthma associations were reported.(306)The exposure measurement window was very short in this study and it was difficult to be certain of the number of participants included in the final analysis. Duramad et al. (2006) examined T-helper 1 (Th1) and T-helper 2 (Th2) cytokines, biomarkers of allergic asthma, in blood samples collected from 36 12-month olds and 239 24-month olds in Salinas Valley, California. The study found that children who lived with agricultural workers had higher levels of Th2 than children who did not. Specifically, children of women who worked in the fields had a significant 25.9% increase in Th2 compared to children of mothers who did not work in agriculture.(302) Unfortunately, pesticide exposure was determined only by parental work status. Weselak et al. (2007) examined asthma and chronic cough/bronchitis in a retrospective cohort of 3,405 children and found no association between asthma or chronic cough/bronchitis and specific pesticide exposures in utero or after birth.(307)

9.1.1.2 Adult asthma

Table 61. Pesticide exposure and adult asthma

Grade	Exposure	Outcome
B	Any pesticide (occupational)	Asthma (309)
	Any pesticide (occupational)	Atopic asthma in women (309)
	Pesticide class (insecticide and herbicide)	Atopic asthma in women (309)
	Pesticide type (organophosphate)	Wheeze (310)
	Pesticide type (carbamate, organophosphate, organochlorine)	Atopic asthma in women (309)
	Specific pesticides (alachlor, atrazine, EPTC, petroleum oil, trifluralin, malathion and permethrin on animals)	Wheeze (310)
	Specific pesticides (clorimuron-ethyl and chlorpyrifos)	Days of wheeze (310)
	Specific pesticides (carbaryl, coumaphos, malathion, parathion, phorate, permethrin, 2,4-D, glyphosphate, metalaxyl)	Atopic asthma in women (309)
	Specific pesticides (permethrin on crops)	Non-atopic asthma in women (309)
	Specific pesticides (2,4,5-TP, EPTC, paraquat, chlordane, heptachlor, lindane, diazinon, parathion, coumaphos, captan, ethylene dibromide and 80/20 mix)	Allergic asthma in men (311)
	Specific pesticides (petroleum oil, phorate and malathion)	Non-allergic asthma in men (311)
	Specific pesticides (pendimethalin and aldicarb)	Asthma exacerbation in participants with asthma and hay fever (312)
	Specific application (use of captan and metalaxyl treated seed)	Allergic asthma in men (311)
	Specific application (pesticide use on grasslands, vineyards and fruit-growing crops)	Allergic asthma (313)
	Specific application (pesticide use on beets)	Non-allergic asthma (313)
B-	Any pesticide	Asthma (308)
D	Any pesticide (occupational, grape farmers)	Asthma (314)
	Specific pesticides (malathion and resmethrin, aerial spraying)	Rate or severity of asthma emergency department presentations (315)
	Specific pesticides (glyphosphate and paraquat)	Asthma exacerbation (312)

Six relevant studies examined the association between adult asthma and pesticide exposure. The literature on adult asthma presents mixed evidence for an association between pesticide exposure and adult asthma. A 2014 comprehensive review of relevant studies found that seven of 12 studies reviewed found a positive association between adult asthma and general pesticide exposure but listed significant methodological challenges with the studies.(308)All of the occupational Agricultural Health Study (AHS) analyses found significant associations between a number of pesticides and adult asthma in farmers and farm woman, a group with higher than average exposure to pesticides for occupational reasons.(309–311) Other studies in the area have failed to find a significant association between adult asthma and pesticides use, but they were limited in the number of pesticides considered (315,316) sample size (314) and consideration for non-occupational pesticide exposure(315). Given the limited and conflicting evidence available,

it is not possible to draw a definite conclusion on the effect of pesticides on adult asthma in the general population.

9.1.1.2.1 Occupational pesticide exposure

Three of these studies were conducted on the AHS cohort of approximately 89,000 pesticide applicators (i.e. farmers) and their spouses in Iowa and North Carolina. Hoppin et al. (2006) examined 17,820 AHS participants for the association between self-reported wheeze and never use, former use (not in the past year) and current use in the past year of 40 individual pesticides. Current use of organophosphates in general and the specific use of six pesticides were significantly associated with a 5 to 37% increase in the odds of experiencing wheeze. There was a significant increase in the odds of wheeze with increasing days of chlorimuron-ethyl and chlorpyrifos use.(310)

A second analysis by Hoppin et al. (2009) of 19,704 male AHS participants examined the association between lifetime use of 48 pesticides and adult onset allergic asthma (asthma with eczema or hay fever) and non-allergic asthma. Three herbicides, six insecticides, one fungicide and two fumigants were positively associated with a significant 1.5- to 2.6-fold increase in the odds of reporting allergic asthma. The use of captan-and metalaxyl-treated seed was associated with a 2.5- and 5-fold increase, respectively, in the odds of allergic asthma. One herbicide and three insecticides were associated with a significant 1.3- to 1.4-fold increase in the odds of non-allergic asthma.(311)

A third analysis by Hoppin et al. (2008) examined 25,814 AHS farmwomen and their personal use of 50 specific pesticides and self reported atopic asthma (defined as asthma with eczema or hay fever) and non-atopic asthma (defined as asthma without eczema or hay fever). Atopic asthma increased a significant 1.3 to 2.8-fold with the use of any pesticide and the specific use of: any insecticide, any herbicide, any carbamate, any organophosphate, any organochlorine and 10 specific pesticides. Only permethrin use on crops was associated with a 2.2-fold increase in the odds of non-atopic asthma. Interestingly, all analyses performed for this study were confounded by growing up on a farm.(309)

Only two other relevant studies of asthma and occupational pesticide exposure in adults that met our inclusion criteria have been conducted. Chatzi et al. (2007) studied 120 grape farmers and 100 controls in Northern Crete and found no association between the use of 50 common pesticides and current asthma diagnosis.(314) Baldi et al. (2014) examined 15,494 French farmers for associations between any occupational pesticide use on specific crops and allergic (with hay fever or eczema) or non-allergic (without hay fever or eczema) asthma. Allergic asthma was associated with the use of pesticides on grassland, vineyards and fruit-growing crops. Non-allergic asthma was associated with the use of pesticides on beets.(313)

Henneberger et al. (2014) completed a cross-sectional analysis of a subset of the AHS cohort with asthma (n=926) for exacerbations in the last 12 months (n=202). They found that asthma exacerbations were inversely associated with the use of glyphosphate and paraquat, perhaps due to selective avoidance by participants with asthma. Among individual with asthma and hay fever or eczema, the use of pendimethalin and aldicarb was associated with increased odds of asthma exacerbations.(312)

9.1.1.2.2 Non-occupational exposure

Only one study examined associations between asthma and non-occupational pesticide exposure. O'Sullivan et al. (2005) examined hospital asthma presentations to Lincoln Hospital in New York in relation to a 4-day aerial spraying of malathion and resmethrin in September of 1999. They found that the city-wide spraying of these insecticides did not increase the rate or severity of asthma presentations.(315)

9.1.2 Chronic obstructive pulmonary diseases

Table 62. Pesticide exposure and COPD

Grade	Exposure	Outcome
B	Any pesticide	COPD (308)
	Specific pesticides (dichlorvos, cyanazine, paraquat and methyl bromide)	Chronic bronchitis (317)
	Specific pesticides (heptachlor, chlordane, lindane, toxaphene, coumaphos, diazinon, dichlorvos, malathion, parathion, carbaryl, carbofuran, permethrin, 2,4,5-T, 2,4,5-TP, chlorimuron-ethyl and petroleum oil)	Chronic bronchitis (318)
	Specific application (any pesticide in potato farmers)	Chronic bronchitis (319)
	Specific application (agricultural pesticides applied more than 20 lifetime days)	Chronic bronchitis in women (317)
	Specific application (use of three or more pesticides in addition to the most common pesticides (glyphosphate, 2,4-D, malathion, diazinon and carbaryl)	Chronic bronchitis in women (317)
D	Any pesticide	Chronic bronchitis (317)
	Pesticide types (fungicides and fumigants)	Chronic bronchitis (318)

Three relevant studies examined the association between Chronic Obstructive Pulmonary Disease (COPD) and pesticide use. A 2014 comprehensive review of relevant studies found that a weak possible association between COPD and pesticide exposure in general.(308)All studies focused on occupational exposure to pesticides. Two of these studies drew participants from the AHS cohort. Overall, there appears to be an association between occupational exposure to pesticides and COPD.

Valcin et al. (2007) analyzed 21,541 non-smoking women in the AHS cohort for their lifetime reported use of 50 pesticides and self-report of doctor-diagnosed chronic bronchitis. Five pesticides were associated with chronic bronchitis after multivariate adjustment and sensitivity analyses. Several other pesticides were significantly associated with chronic bronchitis in the base models but not in the final adjusted models. The odds of chronic bronchitis was increased 1.5 times among women who applied pesticides 120 days or more in their lifetime. Women who used three or more agricultural pesticides in addition to the most commonly used pesticides (glyphosate, 2,4-D, malathion, diazinon, carbaryl) had a 1.5 times increased odds of chronic bronchitis; however, those who used fewer agricultural pesticides showed no elevated risk. There was no association between overall use of pesticides and chronic bronchitis.(317)

Hoppin et al. (2007) analyzed 20,908 pesticide applicators (mostly farmers) in the AHS for an association between lifetime use of 50 specific pesticides and doctor-diagnosed chronic bronchitis after age 20. After adjustment for correlated pesticides as well as confounders, eleven pesticides were significantly associated with chronic bronchitis.(318)

Finally, Tual et al. (2013) examined a 10% sample for the French AGRIculture and CANcer cohort of farmers (n=14,441) for an association between any pesticide use and self-reported

chronic bronchitis diagnosed after age 20. They found a 1.6-fold significant increase in odds of chronic bronchitis with exposure to pesticides in potatoes farmers specifically.(319)

9.1.3 Lung function

Table 63. Pesticide exposure and lung function

Grade	Exposure	Outcome
B -	Any pesticide (occupational)	Lower FEV1 (320)
	Pesticide type (herbicide)	Lower FEV 1, lower ratio of FEV 1 to FVC (320)
	Pesticide type (herbicide)	Mild and moderate/severe airway obstructions (320)
	Pesticide type (herbicide)	Lower ratio of FEV 1 to FVC in men (320)

FEV1: Forced Expiratory Volume in 1 second FVC: Forced Vital Capacity

One study examined lung function and exposure to pesticides. DE Jong et al. (2014) demonstrated reductions in lung function, measured by FEV1 with occupational exposure to pesticides.(320)

De Jong et al. (2014) examined occupational pesticide, herbicide and insecticides exposure in 11,851 participants aged 18 to 89 in the Netherlands and 2,364 participants from a second general population cohort. They found that occupational exposure to both low and high levels of pesticides and high levels of herbicides was associated with a lower Forced Expiratory Volume in 1 second (FEV1) with smoker experiencing an even larger decrease in FEV1 with exposure to high levels of pesticides and herbicides. The ratio of FEV1 to Forced Vital Capacity (FVC) was reduced with high exposure to herbicides overall and in men specifically. The odds of mild and moderate/severe airway obstructions were increased between 1.5 and 3.5-fold with high herbicide exposure in the two population cohorts. Unfortunately, exposure to pesticides was based solely on job title, leading to significant possible exposure misclassification.(320)

9.1.4 Respiratory symptoms

Table 64. Pesticide exposure and respiratory symptoms

Grade	Exposure	Outcome
B	Any pesticide (prenatal)	Hay fever in children (307)
	Any pesticide (prenatal)	Allergies and hay fever in male children (307)
	Any pesticide (prenatal)	Allergies and hay fever in children over age 12 (307)
	Any pesticide (occupational)	Allergic rhinitis with or without atopy (314)
	Pesticide class (herbicide, fungicide, insecticides)	Allergic rhinitis with or without atopy (314)
	Pesticide class (herbicide, fungicide, insecticides, prenatal)	Hay fever in children (307)
	Pesticide class (herbicide, fungicide, insecticides, prenatal)	Allergies and hay fever in male children (307)
	Pesticide class (herbicide, fungicide, insecticides, prenatal)	Allergies and hay fever in children over age 12 (307)
	Pesticide type (bipyridyls, dithiocarbamates, triazoles and carbamates)	Allergic rhinitis with or without atopy (314)
	Pesticide type (phenoxys and organophosphates, prenatal)	Hay fever in children (307)
	Pesticide type (phenoxys)	Allergies and hay fever in male children (307)
	Specific pesticide (thiophthalimide,glyphosphate and paraquat)	Allergic rhinitis with or without atopy (314)
	Specific pesticide (2,4-D, prenatal)	Hay fever in children (307)
	Specific pesticide (2,4-D, prenatal)	Allergies and hay fever in male children (307)
B-	Any pesticide	Wheeze in children and adults (308)

A 2014 comprehensive review of relevant studies found an association between general pesticide exposure and adult wheezing in 4 of 12 studies and pediatric wheezing in 3 of 4 studies but listed significant methodological challenges with the studies.(308)Two studies examined respiratory symptoms and pesticide exposure. Both studies demonstrate possible associations between exposures to various pesticides and allergic rhinitis with and without atopy, allergies and hay fever although further study is required.(307,314)

Chatzi et al. (2007) studied 120 grape farmers and 100 controls in Northern Crete for the presence of Allergic Rhinitis (AR) with or without atopy (defined as a positive skin prick or enzyme immunoassay test). Grape farmers who used pesticides had higher prevalence rates of allergic rhinitis symptoms compared with grape farmers who reported no current use of pesticides, and control subjects. Logistic regression models controlling for age, sex and smoking status showed that the highest risks of a 2.2 to 4.8-fold increase in AR were observed for paraquat and other bipyridyl herbicides, dithiocarbamate fungicides and carbamate insecticides. Other significant associations with AR included any herbicide, glyphosate herbicides, any fungicide, thiophthalimide, triazole and any insecticides.(314)

Weselak et al. (2007) examined allergies and hay fever in a retrospective cohort of 3,405 children of farmers and found several significant associations. Any pesticide use and reported use of all three major pesticide classes (herbicides, insecticides and fungicides, phenoxy herbicides) and organophosphates, and the active ingredient 2,4-D during pregnancy showed a significant 1.5-fold increases in the odds of the children developing allergies or hay fever. Male

children exhibited significant 1.5 to 2.1 fold increases in the odds of allergies and hay fever in relation to reported farm use of any pesticide, fungicides insecticides, herbicides, phenoxy herbicides and 2,4-D during the pregnancy period. The odds of developing allergies or hay fever were significantly higher in children over age 12 at the time of the survey when they had been exposed to herbicides, insecticides or any pesticide in utero.(307)

9.1.5 Respiratory tract infections

No articles were found that considered respiratory tract infections and met our inclusion criteria.

9.1.6 Interstitial lung disease

Table 65. Pesticide exposure and interstitial lung disease

Grade	Exposure	Outcome
B	Pesticide class (insecticides)	Sarcoidosis (321)
	Pesticide type (organochlorine and carbamate)	Farmer's lung (322)
	Specific pesticide (aldicarb)	Farmer's lung (322)
	Specific application (work in agriculture)	Sarcoidosis (321)
D	Pesticide type (organophosphate, phenoxy and triazine)	Farmer's lung (322)
	Specific pesticide (permethrin)	Farmer's lung (322)

Studies on interstitial lung disease and pesticide exposure are limited. An AHS cohort study suggests a relationship between pesticide exposure and farmer's lung and a case-control study provides limited evidence of a potential association with sarcoidosis.(321,322)

Hoppin et al. (2007) examined 21,393 farmers and 30,242 spouses using the AHS cohort for their lifetime use of 50 pesticides and a self-reported diagnosis of farmer's lung. They found that the ever use of organochlorine and carbamate pesticides were associated with a 1.3-fold increase farmer's lung. The insecticide aldicarb was positively associated with a 1.6-fold increase in farmer's lung among farmers. No association was observed for other chemical classes of pesticides, organophosphate insecticides, permethrin insecticides, phenoxy herbicides and triazine herbicides. A dose response relationship was apparent for farmers and spouses based on lifetime days of pesticide application.(322)

Newman et al. (2004) examined agricultural employment and insecticide exposure at work in 706 adults with sarcoidosis and 706 controls. They found a significant 1.5-fold increase in odds of sarcoidosis with agricultural employment and exposure to insecticides at work.(321)

11. Endocrine health outcomes and pesticide exposure

11.1.1 Diabetes

Table 66. Pesticide exposure and diabetes

Grade	Exposure	Outcome
A	Specific pesticides (*trans*-nonachlor and oxychlordane)	Incident and prevalent diabetes and prevalent Type II diabetes (323–328)
B	Any pesticide (agricultural, first trimester)	Gestational diabetes (329)
	Pesticide type (organochlorines and other persistant organic pollutants)	Incident diabetes in obese participants (BMI over 30 kg/m^2)(325)
	Pesticide type (organochlorines)	Peripheral neuropathy in individuals with diabetes (330)
	Specific pesticide (chlordane, heptachlor, trichlorfon, alachlor, cyanazine and atrazine)	Incident diabetes (331)
	Specific pesticides (heptachlor epoxide)	Prevalent diabetes and prevalent Type II diabetes (328)(332)
	Specific pesticides (heptachlor epoxide)	Pre-diabetes (328)
	Specific pesticides (hexachlorobenzene)	Prevalent diabetes and Prevalent Type II diabetes (333,334)
	Specific pesticides (hexachlorobenzene)	Increased fasting glucose and insulin levels (57)
	Specific pesticides (ß-hexachlorocyclohexane)	Prevalent diabetes (327,328)
	Specific pesticides (*trans*-nonachlor and sum of p,p'-DDE, *trans*-nonachlor and hexachlorobenzene)	Incident diabetes (335)
	Specific pesticide (aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor and cyanazine)	Incident diabetes in participants less than 60 years of age (331)
	Specific pesticide (trichlorfon)	Incident diabetes in overweight participants (BMI 25 to 30 kg/m^2)(331)
	Specific pesticide (aldrin, heptachlor, alachlor and cyanazine)	Incident diabetes in obese participants (BMI over 30 kg/m^2)(331)
	Specific pesticides (oxychlordane and *trans*-nonachlor)	Insulin resistance in participants with a high waist circumference (336)
	Specific pesticides (dieldrin, fonofos, parathion, phorate and 2,4,5-T/2,4,5-TP)	Incident diabetes and gestational diabetes (337)
B -	Specific pesticides (2,4,5-T, 2,4,5-TP, atrazine, butylate, diazinon, phorate and carbofuran, first trimester)	Gestational diabetes (329)
C	Pesticide type (organochlorine)	Insulin resistance (324,336)
	Specific pesticides (oxychlordane and *trans*-nonachlor)	Insulin resistance (335,336,338)
D	Any pesticide (residential, first trimester)	Gestational diabetes (329)
	Specific pesticides (hexachlorobenzene)	Insulin resistance (335,338)
	Specific pesticide (mirex)	Prevalent diabetes (328,334)
	Specific pesticide (dieldrin)	Prevalent diabetes (328)
	Specific pesticides (mirex and dieldrin)	Pre-diabetes (328)
	Specific pesticides (mirex and DDE)	Prevalent diabetes (333)
	Specific application (indirect crop work)	Gestational diabetes (329)

11.1.1.1 Diabetes and pesticide exposure

One study examined agricultural exposure to 50 individual pesticides and incident diabetes in 1,176 participants with diabetes and 30,611 participants without diabetes in the Agricultural Health Study cohort. Six pesticides were associated with significant trends of increasing incident diabetes with higher cumulative use, including chlordane, heptachlor, trichlorfon, alachlor, cyanazine and atrazine. All of these pesticides are organochlorine or organophosphate pesticides. The significant effects of aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor and cyanazine were limited to participants under 60 years of age. The significant effect of trichlorfon was limited to those who were overweight (BMI 25 to 30 kg/m^2) and the significant effects of aldrin, heptachlor, alachlor and cyanazine were limited to participants who were obese (over 30 kg/m^2).(331)

11.1.1.2 Diabetes, insulin resistance and organochlorine pesticide exposure

Studies performed in the last 10 years on the association between pesticide exposure and diabetes are primarily concerned with exposures to Organochlorine Pesticides (OCs) and Persistent Organic Pollutants (POPs).(57,323–328,330,332–335) Since DDE and DDT were excluded from the literature review, results pertaining to these chemicals are excluded from this summary unless they are presented as part of an aggregate result. OC pesticides are not well metabolized and tend to accumulate in the body over time. Studies in this section primarily use serum levels of specific OCs as a proxy for overall lifetime exposure through a variety of sources. In general, increasing lifetime exposure to OCs was associated with incident and prevalent diabetes, insulin resistance and peripheral neuropathy.

11.1.1.2.1 Incident diabetes

Three studies examined serum levels OCs and incident diabetes and demonstrated the temporal association between some OCs and the development of diabetes.(325,335) In their nested case-control study of 90 cases and 90 controls of African American decent over 20 years, Lee et al. (2010) found a 4-fold increased risk of incident diabetes with low serum levels (second quartile) of *trans*-nonachlor. They also found a 2-fold increased risk of incident diabetes with the highest quartile of serum oxychlordane levels. The overall association between diabetes and POPs increased when only obese adults (BMI over 30 kg/m^2) were considered and showed a U-shape with greater effects seen at low serum levels.(325)

In a 5-year prospective cohort study of 725 adults over age 70 in Uppsala, Sweden, Lee et al. (2011) demonstrated a significant trend in increasing incidence of diabetes with increasing serum concentrations of *trans*-nonachlor, although only the 4^{th} quintile odds ratio was significant. The odds of incident diabetes also saw an increasing trend with increasing serum concentrations of the sum of p,p'-DDE, *trans*-nonachlor and hexachlorobenzene, although most individual odds ratios were also not significant.(335)

Starling et al. (2014) completed an analysis of 13,637 women spouses of Agricultural Halthe Study participants followed for a mean of 10 years from 1993-1997. They found a significantly

increased risk of incident diabetes with more than 30 years of pesticides exposure (1.6-fold) and with specific exposure to dieldrin, fonofos, parathion, phorate and 2,4,5-T/2,4,5-TP.(337)

11.1.1.2.2 Prevalent Type II diabetes

Four studies specifically focused on prevalent Type II diabetes and serum levels of OC exposure.(323,324,332,334) A longitudinal birth cohort in Helsinki (n=1,988 born 1934-1944) found significant linear trends between increasing serum concentrations of oxychlordane and *trans*-nonachlor and type II diabetes at a 2003 examination. The odds ratios of having diabetes were twice as high in the highest serum category compared to the lowest serum category for oxychlordane and *trans*-nonachlor.(323)

A hospital based cross-sectional study of 386 Spanish adults showed 3-fold and 5-fold increased risk of Type II diabetes with the second and third tertiles, respectively, of adipose tissue ß-hexachlorobenzene concentration.(334)

Patel et al. (2010) combined 3 cohorts of the National Health and Nutrition Examination Survey (n=291 with diabetes, n=3811 without diabetes) to demonstrate a significant 1.7-fold increase in the odds of having Type II diabetes with each standard deviation increase in log serum levels of hepatachlor epoxide.(332)

Pal et al. (2013) found that individuals with Type II diabetes among the 72 adults surveyed in two northern Ontario reserves were found to have significantly higher levels of serum oxychlordane and *trans*-nonachlor than those without diabetes.(324)

11.1.1.2.3 Prevalent diabetes

Prevalent diabetes and organochlorine exposure was the focus of the next four studies.(326–328,333) Lee et al. (2006) examined serum organochlorine levels in their cross-sectional study of 2,016 adults and found a significant dose-response relationship with diabetes prevalence. The odds of having diabetes were 4.3 times higher for oxychlordane and 11.8 times higher for *trans*-nonachlor at the 90^{th} percentile of serum levels compared to no detectable serum levels.(326)

A second cross-sectional study of 352 Native American adults found that having serum levels in the highest tertile increased the odds of having diabetes risk by 6.2 times for hexachlorobenzene. No association between serum mirex concentration and diabetes prevalence was noted.(333)

A third cross-sectional study of 1,303 Mexican Americans found increased prevalence of diabetes with increased serum concentrations of *trans*-nonachlor, oxychlordane and β-hexachlorocyclohexane.(327)

Finally, Everett and Matheson (2010)'s cross-sectional study of National Health and Nutrition Survey participants found a strong significant association between serum concentrations of heptachlor epoxide and oxychlordane and increased odds of self-reported diabetes. A slightly weaker but still significant association was found between ß-hexachlorocyclohexane and *trans*-nonachlor and increased odds of self-reported diabetes. Mirex and dieldrin were not associated with total diabetes.(328)

11.1.1.2.4 Gestational diabetes and pesticide exposure

Two studies covered gestational pesticide exposure and diabetes. In an analysis of 11,273 female Agricultural Health Study (AHS) participants, Saldana et al. (2007) reported increased odds of gestational diabetes with first trimester agricultural exposure in general and with agricultural exposure to four herbicides and three insecticides. Residential pesticide application and indirect crop work (planting, pruning, weeding, picking or harvesting) was not associated with gestational diabetes.(329)

In their analysis of the same AHS data with longer follow-up, Starling et al. (2014) also found a significantly increased risk of gestational diabetes with exposure to dieldrin, fonofos, parathion, phorate and 2,4,5-T/2,4,5-TP.(337)

11.1.1.2.5 Peripheral neuropathy

Lee et al (2008) examined the association between serum organochlorine levels and peripheral neuropathy in 246 adults with diabetes. They found a significant dose-response trend of increasing odds of peripheral neuropathy with increasing serum organochlorine levels.(330)

11.1.1.2.6 Insulin resistance and organochlorine exposure

Several studies examined insulin resistance and organochlorine serum levels. In line with the evidence surrounding diabetes, the evidence is suggestive that increasing organochlorine serum levels (except mirex and dieldrin) are associated with increasing odds of insulin resistance. Pal et al. (2013) found no association between the odds of insulin resistance and organochlorine levels but the study had a small sample size (n=72).(324) Conversely, Langer et al. (2014) found significantly increased fasting glucose and insulin levels with increasing serum levels of hexachlorobenzene for males aged 41 to 75 years and for women aged 21 to 75 years.(57)

Everett and Matheson (2010) reported increased odds of pre-diabetes with increasing serum levels of heptachlor epoxide but not mirex or dieldrin.(328) Lee et al (2011) found no association between insulin resistance and serum levels of oxychlordane, *trans*-nonachlor and hexachlorobenzene in their nested case-control study of the 90 diabetes-free controls.(338)

Lee et al. (2007) found a strong association between increased serum organochlorine levels, specifically oxychlordane and *trans*-nonachlor, and increased odds of insulin resistance. High measurements of waist circumference were associated with a stronger association between serum oxychlordane and *trans*-nonachlor and odds of insulin resistance among the 749 diabetes-free participants.(336)

11.1.2 Other endocrine outcomes

Table 67. Pesticide exposure and other endocrine outcomes

Grade	Exposure	Outcome
B	Pesticide class (fungicides)	Hypothyroidism in women (339)
	Pesticide type (organochlorines insecticides)	Hypothyroidism in women (339)
	Specific pesticides (chlordane, aldrin, benomyl, maneb/mancozeb and paraquat)	Hypothyroidism in women (339)
	Specific pesticides (maneb/mancozeb)	Hyperthyroidism and hypothyroidism in women (339)
	Specific pesticide (oxychlordane *trans*-nonachlor and hexachlorobenzene)	Increased triglyceride levels (335)
	Specific pesticide (hexachlorobenzene)	Higher body weight and BMI at age 6.5 (340)
D	Any pesticide	Thyroid disease (339)
	Pesticide type (organochlorine)	Thyroid disease (339)
	Pesticide type (organochlorines)	Free T4, total T3 and TSH at age 4 (341)
	Specific pesticide (hexachlorobenzene)	Height at age 6.5 (340)

11.1.2.1 Thyroid conditions and pesticide exposure

Two studies examined thyroid conditions and pesticides exposure. The limited evidence suggests a potential association between adult thyroid disorders and organochlorine pesticide and fungicide exposure in adults but not in children, although further study would be required.

Goldner at al. (2010) examined the 16,529 female spouses enrolled in the Agricultural Health Study in a prospective 5-year cohort study. There was a significant increase in the odds of hypothyroidism with ever use of organochlorine insecticides and fungicides. Specifically, the use of the organochlorines chlordane, aldrin, and the fungicides benomyl, maneb/mancozeb, and the herbicide paraquat was significantly associated with increased odds of hypothyroidism. Maneb/mancozeb use was also significantly associated with increased odds of hyperthyroidism.(339)

Alvarez-Pedrerol et al. (2008) found no association between serum organochlorine concentrations and serum concentrations of free T4, total T3 and TSH at age 4 in 259 children from a general Spanish birth cohort.(341)

Obesity, elevated lipid levels and organochlorine exposure

Two studies examined associations between BMI and lipid levels and organochlorine exposure. The limited available evidence suggests a potential association between increased BMI and lipid levels and organochlorine exposure among adults and children, although further study would be required.

A prospective birth cohort of 482 children in Spain found that children with HCB levels higher than 1.03 ng/mL in cord blood were 1.14 kg heavier and had a higher BMI than children with HCB levels lower than 0.46 ng/mL at 6.5 years of age. No significant associations were found

between height and HCB levels. This significant association between BMI and HCB serum levels persisted even when the analysis was restricted to children of normal weight mothers.(340)

Lee et al. (2011) reported increased triglyceride levels in a 20-year follow-up of 90 diabetes-free controls with exposure to increasing levels of oxychlordane,*trans*-nonachlor and hexachlorobenzene.(338)

13. Other health outcomes and pesticide exposure

13.1.1 Dermatitis

Table 68. Pesticide exposure and dermatitis

Grade	Exposure	Outcome
B -	Any pesticide (occupational)	Pesticide-induced dermatitis (342)
D	Pesticide type (organochlorine)	Atopic dermatitis in infants (343)
	Specific pesticide (methyl bromide)	Pesticide-induced dermatitis (342)

Only two studies were conducted on dermatitis and pesticide exposure that met the inclusion criteria for the review. Horiuchi et al. (2007) conducted a descriptive study of 394 cases of pesticide-induced dermatitis in Japan. They found that the heaviest distribution of cases was during the farming season, with exposures occurring during spraying (63%) or other non-spraying farm work (35%). All pesticides except methyl bromide were implicated in pesticide-induced dermatitis.(342)

Ochiai et al. (2014) conducted a birth cohort study of 81 infants and the relationship between atopic dermatitis and umbilical cord blood pesticide levels. No association was found between organochlorine pesticide umbilical cord blood levels and atopic dermatitis.(343)

13.1.2 Other health outcomes

Table 69. Pesticide exposure and other health outcomes

Grade	Exposure	Outcome
B	Pesticide class (herbicide, insecticide and fungicide)	Wheeze (8)
	Pesticide class (insecticide)	RA/SLE in women (344)
	Pesticide class (insecticide)	Hearing loss (345)
	Pesticide class (fungicide)	Retinal degeneration in women (346)
	Pesticide type (organophosphate)	Hearing loss (345)
	Specific pesticides (atrazine, heptachlor, chlorpyrifos, malathion, fonofos, diazinon, phorate, terbufos and parathion)	Hearing loss (345)
	Specific pesticide (ethylene dibromide, maneb/mancozeb, and ziram)	Fatal myocardial infarction (347)
	Specific pesticide (Aldrin and 2,4,5-trichlorophenoxyacetic acid)	Non-fatal myocardial infarction (347)
	Specific pesticide (alachlor, atrazine, cyanazine, EPTC, chlorpyrifos, malathion, parathion, permethrin and metalaxyl)	Wheeze (8)
	Specific pesticide (chlorpyrifos)	Mortality from external causes, non-motor vehicle accidents and blood and immune disorders (348)
	Specific application (orchard farming and fungicide, carbamate and fumigant exposure)	Retinal degeneration (8)
	Specific application (farming and raising crops)	Mortality from RA or any autoimmune disease (349)
	Pesticide class (insecticide on a farm)	RA/SLE in women (344)
B -	Any pesticide (occupational, mixing)	SLE (350)
	Specific pesticide (trans-nonachlor levels in the Low Density Lipoprotein/ Very Low Density Lipoproteins)	Cardiovascular disease (153)
C	Any pesticide (occupational)	Rheumatoid arthritis (349,351)
D	Any pesticide	All-cause mortality (352)
	Any pesticide	Myocardial infarction (347)
	Any pesticide	BPH (245)
	Any pesticide (occupational, applying)	SLE (350)
	Pesticide class (fumigants, herbicides, insecticides	Retinal degeneration in women (346)
	Pesticide type (organochlorines, carbamates and organophosphates)	Retinal degeneration in women (346)
	Pesticide type (carbamates, organochlorines and pyrethroids)	Hearing loss (345)
	Specific pesticide (chlorpyrifos)	Mortality from all causes, malignant neoplasm, endocrine, nutritional and metabolic disease, cardiovascular disease, lower respiratory diseases(348)
	Specific application (farming)	Mortality from SS or SAD(349)

The other outcomes examined by studiesof the human health effects of pesticides are diverse and include studies of overall mortality, myocardial infarction and cardiovascular disease, hearing loss, benign prostatic hyperplasia, retinal degeneration, and autoimmune disease.

Three studies examined overall mortality related to pesticide use. Blair et al. (2005) examined mortality in 52,393 pesticide applicators and 32,345 spouses enrolled in the Agricultural Health Study (AHS) from 1993-1997 to 2000. They found that those who handled pesticides had a significantly lower mortality than the general state population due to a healthy worker effect. Handling pesticides for less than 10 years was associated with significantly lower mortality from all causes, all cancers, pancreatic cancer, lung cancer, COPD and cardiovascular disease. Handling pesticides for more than 11 years was associated with significantly lower mortality from all causes, all cancers, colon cancer, lung cancer, prostate cancer, COPD and cardiovascular disease.(352)

Lee et al. (2007) focused on chlorpyrifos exposure and mortality among 55,071 AHS participants followed from 1993-1997 to 2001. There were no significant associations between chlorpyrifos exposure and mortality from all causes, malignant neoplasm, endocrine, nutritional and metabolic disease, cardiovascular disease, lower respiratory diseases.There were significant trends for and significantly increased risk of mortality in the highest tertile of chlorpyrifos exposure for external causes (1.7-fold), non-motor vehicles accidents (2.1-fold) and blood and immune disorders (12.7-fold).(348) A second analysis of disease and injury to 2005 among 89,658 AHS participants showed significantly increased risks of retinal degeneration with orchards farming and exposure to fungicides (1.7 to 2-fold) in Iowa and North Carolina and carbamate (1.9-fold) and fumigant (1.7-fold) exposure in Iowa. There was also a significant increase in risk of wheeze with exposure to increasing days of pesticide use and use of herbicides (alachlor, atrazine, cyanazine, EPTC), insecticides (chlorpyrifos, malathion, parathion and permethrin) and fungicides (metalaxyl).(8)

Four studies examined autoimmune outcomes and pesticide exposure. DeRoos et al. (2005) performed a case-control study nested within the AHS cohort of 135 female cases and 675 female controls of Rheumatoid Arthritis (RA) and pesticide exposure. They found no association between applying or mixing any pesticide, pesticide type or specific pesticide and RA.(351)

Gold et al. (2007) performed a case-control study of deaths where autoimmune disease was a contributor and occupational pesticide exposure. They examined 36,178 RA cases, 7,241 Systemic Lupus Erythematous (SLE) cases, 5,642 Systematic Sclerosis (SS) cases and 4,270 other Systemic Autoimmune Disease (SAD) cases in 26 United States states from 1984 to 1998 and 5 population controls per case. They found a significant increase in risk of death from any autoimmune disease (1.3-fold) and from RA in farmers, particularly those engaged in raising crops from RA (1.4-fold) and SLE (1.3-fold). There were no significant associations between farming and SS or SAD.(349)

Parks et al. (2011) examined 178 cases of RA, 27 cases of SLE and 8 cases with both in a cohort of 76,861 women aged 50 to 79 years enrolled 1993-1998 for residential and workplace insecticide exposure. They found that personal use of insecticides increased the risk of RA/SLE (1.5-fold), particularly when used more than 6 times annually (2-fold) or for more than 20 years (2-fold). There was also an increased risk of RA/SLE with application of insecticide by others for more than 20 years (1.9-fold) or with application more than 6 times annually in women who had lived on a farm (3-fold).(344)

Cooper et al. (2004) examined 265 cases and 355 controls for occupational pesticide exposure and SLE. They found a significant association between SLE mixing pesticides for agricultural work (7.4-fold) but not for applying pesticides, although this estimate is based on only nine exposed cases.(350)

Two studies examined pesticides as risk factors for cardiovascular disease. Mills et al. (2009) examined 476 deaths from myocardial infarction and 836 non-fatal myocardial infarctions among participants in the AHS. There was no association with overall pesticide use or by pesticide class with fatal or non-fatal myocardial infarction. Ethylene dibromide (1.5-fold), maneb/mancozeb (1.3-fold), and ziram (2.4-fold) were associated with myocardial infarction mortality.Aldrin (1.2-fold), and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (1.2-fold) were associated with nonfatal myocardial infarction incidence.(347) Ljunggren et al. (2014) conducted a very small case-control study of serum lipoprotein organochlorine levels in 13 cases of cardiovascular disease and 7 controls. They found elevated trans-nonachlor levels in the Low Density Lipoprotein (LDL)/ Very Low Density Lipoproteins (VLDLs) of individuals with cardiovascular disease compared to the controls.(153)

Fritschi et al. (2007) examined 400 cases of Benign Prostatic Hyperplasia (BPH) and 471 controls in Western Australia for occupational pesticide exposure. They found no significant association between pesticide exposure, including organophosphate, organochlorine, phenoxy herbicides, other herbicides and other pesticides, and BPH.(245)

Crawford et al. (2008) examined 4,926 cases of hearing loss among 14,229 Caucasian Male participants in the AHS from 1993-1997 to 1999-2003. They found an increased risk of hearing loss with exposure to insecticides (1.2-fold) and organophosphates (1.2-fold). There was no association with carbamates, organochlorines or pyrethroids. Individual pesticides significantly associated with hearing loss included atrazine, heptachlor, chlorpyrifos, malathion, fonofos, diazinon, phorate, terbufos and parathion.(345)

Kirrane et al. (2005) examined retinal degeneration in 31,173 wives of farmers in the AHS. They found that the wives' own use of fungicides was associated with a 1.9-fold increase in risk of retinal degeneration. There was no association with fumigants, herbicides, insecticides, carbamates, organochlorines or organophosphates.(346)

14. Conclusion

The relationship between pesticide exposure and human effects is complex, with multiple exposures and outcomes to consider. Much of the evidence is based on research on occupational pesticide exposures. Although these studies provide some indication of the possible health effects of a specific pesticide exposure, we cannot be certain that they transfer to a general population level of exposure to a specific pesticide. All results presented must be interpreted with this in mind and we have not presented occupational and other exposures separately in this summary. The reader should refer to the subject area of interest for the specific nature of the exposure associated with the outcome.

Many areas of pesticide exposure research comprise only one or a few studies. Given this limited evidence, it is difficult to conclude that there does not exist a significant relationship between a pesticide exposure and a health outcome.

Grade A findings are listed for quick reference in Table 70. Grade B findings are similarly listed in Tables 71-73.

14.1.1 Reproductive outcomes

Pesticide exposure is associated with a number of reproductive outcomes. There is good evidence to suggest that cleft palate is associated with any pesticide exposure.

There is moderate evidence that any pesticide exposure is associated with any congenital defect, neural tube defect and gastroschisis in children of women over the age of 20. Any pesticide exposure is also associated with a reduced fetal length and placental weight, reduced semen quality, sperm motility and concentration and increased time-to-pregnancy. Insecticides and herbicides are associated with esophageal atresia. Dinitroanilines and thiocarbamates are associated with cleft palate. Petroleum derivatives are associated with anencephaly and hydroxybenzonitriles are associated with spina bifida.

Table 70. Grade A research findings for any pesticide, pesticide class or pesticide type.

Exposure		Outcome	
Any pesticide	Any	Cleft palate (22) PD (74–78) ALS (81) ML in adults (191) CML in adult men (191) LHC in adults (192,196) NHL in adults (192)	Lymphoma, brain cancer, Ewing's sarcoma & neuroblastoma in children (269) AML in children (286) Childhood leukemia (269,284,285,289,290) Cutaneous melanoma (253,254)
Pesticide class	Insecticide Herbicide Fungicide Solvents	Lymphoma & brain cancer(269) Childhood leukemia (284) Lymphoma & brain cancer (269) PD (74)	Childhood leukemia (269,284)
Pesticide type	Organophosphates	Increased number of abnormal reflexes in newborns (89–91)	NHL (212)
	Organochlorines	NHL (212)	
	Carbamates	NHL (212)	
	Triazines and triazonines	NHL (212)	
	Thiocarbamates	NHL (212)	
	Phenoxys	NHL (212)	
Specific pesticides or applications	Paraquat	PD (74,78)	
	Maneb/mancozeb	PD (74,78)	
	Heptachlor	Breast cancer (170)	
	Lindane	NHL (212)	
	Dicambia	NHL (212)	
	2,4-D	NHL (212)	
	Carbaryl	NHL (212)	
	Carbofuran	NHL (212)	
	Glyphosphate	NHL (212)	
	Diazinon	NHL (212)	
	Malathion	NHL (212)	
	Pentachlorophenol	STS (200)	
	Trans-nonachlor	Diabetes (323–328)	
	Oxychlordane	Diabetes(323–328)	
	Specific application (agricultural worker)	Leukemia (191)	

PD: Parkinson's Disease ALS: Amyotrophic Lateral Sclerosis ASD: Autism Spectrum Disorder ML: Myeloid leukemia CML: Chronic Myeloid Leukemia LHC: Lymphohematopoietic Cancer NHL: Non-Hodgkin Lymphoma AML: Acute Myeloid Leukemia STS: Soft Tissue Sarcoma

14.1.2 Neurological outcomes

Significant neurological outcome were also prominent in the research evidence. There was good evidence for an association between any pesticide exposure and Parkinson's disease and ALS. There was also good evidence that solvents, paraquat and maneb/mancozeb were associated with Parkinson's disease. Organophosphates were implicated in an increased number of abnormal reflexes in newborns.

There was moderate evidence that any pesticide exposure was associated with a number of neurological outcomes (seeTable 71), autism spectrum disorder, incident Parkinson's disease, ALS, depression, suicide, all-cause dementia and Alzheimer's disease. Herbicide exposure was associated with an increased risk of ALS. Insecticide, fungicide, fumigant, organophosphate, organochlorine, carbamate and pyrethroid exposure was associated with increased risk of experiencing more than 10 of 23 neurological symptoms. Insecticide, herbicide, fungicide, fumigant, organophosphate and organochlorine exposure was associated with an increased risk of depression. An increased risk of Alzheimer's disease was seen with organophosphate and carbamate exposure. Organophosphate exposure was also associated with increased mental and emotional problems in adolescents, decreased short-term memory, increased reaction time and increased risk of impaired mental development or pervasive developmental problems in children. Pyrethroid exposure was associated with a higher Social Difficulties Questionnaire Score.

There was also moderate evidence that organophosphate exposure was associated with a number of further outcomes. These included neurological testing outcomes (Table 73), pervasive development disorder and attention deficit/hyperactivity disorder.

Table 71. Grade B research findings for any pesticide.

Exposure	Outcome	
Any pesticide	Fetal length &placental weight(10)	Diffuse adenocarcinoma (186)
	Congenital defects (23)	MDS (192)
	NTD (25)	Lung cancer (252)
	Gastroschisis in children of women over age 20 (24)	Extrahepatic biliary tract carcinoma (198)
	Semen quality, sperm motility and concentration (50,58)	NK/T-cell lymphoma (249)
	Time-to-pregnancy (10,48)	HL in adult men under 40 years (203)
	Reduced attention, visuomotor integration, verbal abstraction and perception in adults (67)	MM (201)
	Drop in MMSE score in adults (68)	Cutaneous melanoma (255)
	Reduced Stroop bad answer score in adults (68)	Leukemia, brain cancer, Hodgkin lymphoma and neuroblastoma in children (270)
	Decreased visual memory, attention and memory in adults(70)	Cancer, lymphoma and HL in children(271)
	Headache, tension, insomnia, irritability, dizziness, numbness in hands or feet, depression, difficulty concentrating, twitches in arms or legs, fast heart rate, poor balance, poor night vision, tremor in hands, blurred double vision, changes in smell or taste, difficulty speaking and loss of consciousness (69)	High-grade gliomas in children (281)
		ALL in children with Down's Syndrome
		Retinoblastoma in children (298)
		Germ cell tumors in girls in children (299)
		Wheeze or dry cough in children (305)
		Wheeze at 81 months and asthma diagnosis in first 81 months in children (303)
		Asthma and early persistent asthma in children (304)
	Incident PD (79)	Asthma in adults (308)
	ALS (82)	Asthma 2)(309–311)
	All-cause dementia and AD (83)	Atopic asthma in adult women (309)
	Depression (85)	COPD (308)
	Suicide (80,84)	Wheeze in children & adults (308)
	ASD (102)	Hay fever in children (307)
	Testicular, non-melanoma skin cancer and MM (116)	Allergies & hay fever in male children (307)
	Brain tumor in adults (156)	Allergies & hay fever in children over age 12 (307)
	Glioma in adults (156)	Allergic rhinitis with or without atopy in adults (314)
	Cardia adenocarcinoma (185)	Gestational diabetes (329)

NTD: Neural Tube Defect MMSE: Mini Mental State Examination PD: Parkinson's Disease ALS: Amyotrophic Lateral Sclerosis AD: Alzheimer's Dementia MM: Multiple Myeloma MDS: Myelodysplastic Syndrome HL: Hodgkin Lymphoma MM: Multiple Myeloma ALL: Acute Lymphoblastic Leukemia

14.1.3 Cancer outcomes

Cancer was the largest outcome area with a large volume of research into multiple different outcomes. There was good evidence for significant associations between NHL and any pesticide, organophosphates, organochlorines, carbamates, triazine and triazonines, thiocarbamates, phenoxys and a number of specific pesticides (Table 70). In adults, any pesticide use was associated with any LHC, some types of leukemia and cutaneous melanoma. In children, any pesticide use was associated with lymphoma, brain cancer, Ewing's sarcoma, neuroblastoma and leukemia. Insecticides and fungicide exposure was associated with lymphoma and brain cancer in children. Insecticide and herbicide exposure was associated with leukemia in children. Hepatachlor was associated with breast cancer. Employment as an agricultural worker was also associated with leukemia.

There were numerous associations with moderate evidence for pesticide exposure and cancer. These associations with any pesticide included cancers of the brain, gastrointestinal tract, lung, liver, reproductive tract, lymphohematopoietic system and others (Table 71-Table 73). Insecticide exposure was associated with brain cancer, nasal cancer, testicular cancer, multiple myeloma and leukemia in children. Herbicide exposure was associated with brain cancer, nasal cancer, multiple myeloma and leukemia in children. The use of fungicides was associated with multiple myeloma and childhood leukemia. Fumigant use was associated with nasal cancer and leukemia in children. Nitrosatable pesticides were associated with brain cancer and impregnating agents with Non-Hodgkin Leukemia. Organophosphates, triazines and triazonines, chlorinated phenols, azoles and urea pesticides were all associated with Acute Lymphocytic Leukemia in children. Organochlorines were associated with leukemia, multiple myeloma, prostate and testicular cancer. Carbamates were associated with multiple myeloma and triazines and triazonines were associated with Hodgkin Lymphoma.

Table 72. Grade B research findings by pesticide class.

Exposure	Outcome	
Insecticide	Esophageal atresia (26)	Hay fever in children (307)
	Experiencing more than 10 of 23 neurological symptoms (69,71)	Atopic asthma in adult women (309)
	Depression (85)	Allergic rhinitis with or without atopy in adults (314)
	Glioma in adult men (155)	Allergies and hay fever in male children (307)
	Nasal cancer (250)	Allergies and hay fever in children over age 12 (307)
	NK/T-cell lymphoma (249)	Sarcoidosis (321)
	MM (199)	Wheeze (8)
	TGCC (259)	RA/SLE in women (344)
	Testicular cancer (260)	Hearing loss (345)
	Non-astrocytoma, non-PNET brain tumors in children (283)	
	Childhood leukemia (284,285,289,290)	
Herbicide	Esophageal atresia (26)	Asthma and early persistent asthma in children(304)
	ALS (82)	Atopic asthma in adult women (309)
	Depression (87)	Allergic rhinitis with or without atopy in adults (314)
	Glioma in adult men (155)	Allergies & hay fever in male children (307)
	Meningioma in adult women (159)	Allergies & hay fever in children over age 12 (307)
	NK/T-cell lymphoma (249)	Wheeze (8)
	MM (199)	
	Astrocytoma in children (283)	
	Childhood leukemia (285)	
	Hay fever in children (307)	
Fungicide	Experiencing more than 10 of 23 neurological symptoms (69,71)	Hay fever in children (307)
	Depression (85)	Allergies and hay fever in male children (307)
	MM (199)	Allergies and hay fever in children over age 12 (307)
	MM in men (204)	Hypothyroidism in women (339)
	Childhood leukemia (285,290)	Wheeze (8)
	Allergic rhinitis with or without atopy in adults (314)	Retinal degeneration in women (346)
Fumigants	Experiencing more than 10 of 23 neurological symptoms (69,71)	NK/T-cell lymphoma (249)
	Depression (85)	ALL in children (291)
Nitrosatable Impregnating agents	Glioma in adult men (155)	
	NHL (213)	

MM: Multiple Myeloma TGCC: Testicular Germ Cell Cancer ALS: Amyotrophic Sclerosis NHL: Non-Hodgkin Lymphoma RA: Rheumatoid Arthritis SLE: Systemic Lupus Erythematosus ALL: Acute Lymphoblastic Leukemia

Table 73. Grade B research findings for pesticide type.

Exposure	Outcome	
Organophosphates	Decreased GA at birth (18) Sperm quality and count (51) Experiencing more than 10 of 23 neurological symptoms (69,71) Decreased memory, response speed, fine motor control, mental flexibility and strategy making (72) AD (83) Depression (72,85) Reduced BMDI score (92) PDD (92) Decreased short-term memory, increased reaction time and increased risk of impaired mental development or pervasive developmental problems in children (91)	ADHD (108)(109) Lower BMDI scores at 12 months in African-Americans and Hispanics (113) Lower IQ and decreases in working memory, processing speed, verbal comprehension and perceptual reasoning in children (114) Increased mental and emotional problems in adolescents (91) Poorer social responsiveness in African-Americans and boys in children (103) ALL in children (291,292) Wheeze in adults (310) Atopic asthma in adult women (309) Hay fever in children (307) Hearing loss (345)
Organochlorines	Experiencing more than 10 of 23 neurological symptoms (69,71) Depression (85) Leukemia (122) MM in men (204) Prostate cancer (233) Testicular cancer (261) Atopic asthma in adult women (309) Farmer's lung (322)	Incident diabetes in obese participants (325) Peripheral neuropathy in individuals with diabetes (330) Increased thyroid volume and increased odds of positive anti-thyroid peroxidase antibodies (353) Hypothyroidism in women (339)
Carbamates	Experiencing more than 10 of 23 neurological symptoms (69,71) AD (83) MM in men (204,211)	Atopic asthma in adult women (309) Allergic rhinitis with or without atopy in adults (314) Farmer's lung (322)
Triazines and triazonines	HL (199) ALL in children (291)	
Pyrethroids	Lower sperm motility and sperm motion parameters (49) Experiencing more than 10 of 23 neurological symptoms (69,71)	High score on the SDQ (107)
Dinitroanilines	Cleft lip palate (27)	
Thiocarbamates	Cleft lip palate (27)	Allergic rhinitis with or without atopy in adults (314)
Petroleum derivatives	Anencephaly (27)	
Hydroxybenzonitriles	Spina bifida (27)	
Phenoxys	MM in men (204) Hay fever in children (307)	Allergies & hay fever in male children (307)
Chlorinated phenols	ALL in children (291)	
Azoles	ALL in children (291)	Allergic rhinitis with or without atopy in adults (314)
Ureas	ALL in children (291)	
Bipyridyls	Allergic rhinitis with or without atopy in adults (314)	

AD: Alzheimer's Dementia BMDI: Bayley's Mental Development Index, PDD: Pervasive Development Disorder MM: Multiple Myeloma HL: Hodgkin Lymphoma ALL: Acute Lymphoblastic Leukemia ADHD: Attention Deficit/Hyperactivity Disorder IQ: Intelligence Quotient SDQ: Social Difficulties Questionnaire GA: Gestational Age

14.1.4 Respiratory outcomes

There were no respiratory outcomes associated with pesticide exposure with good evidence. There was moderate evidence of associations between any pesticide exposure and asthma, wheeze, COPD, hay fever, allergic rhinitis and allergies in specific populations. Insecticide exposure was associated with asthma, allergies, hay fever, allergic rhinitis, sarcoidosis and wheeze in certain populations. Herbicide exposure was associated with asthma, allergies, hay fever and wheeze. Fungicide exposure was associated with allergies, hay fever and wheeze. Allergic rhinitis was associated with exposure to carbamates, thiocarbamates, azoles, and bipyridyls. Phenoxy exposure was associated with hay fever and allergies. Organophosphate and carbamate exposure was associated with asthma, hay fever and Farmer's Lung and organophosphate exposure was also associated with hay fever.

14.1.5 Endocrine outcomes

There was good evidence that the specific organochlorines trans-nonachlor and oxychlordane were associated with diabetes. There was moderate evidence for an association between any pesticide exposure and gestational diabetes. Organochlorine exposure was associated with incident diabetes in obese individuals, peripheral neuropathy in those with diabetes, hypothyroidism in women and thyroid hormone dysfunction.

14.1.6 Other outcomes

There were no other outcomes associated with pesticide exposure with good evidence. There was moderate evidence to suggest hearing loss was associated with insecticide and organophosphate exposure. Insecticide exposure was also associated with rheumatoid arthritis and systemic lupus erythematous in women.

14.1.7 Conclusion

Categorizing the human health effects of pesticides is a complex topic with many different possible exposures and outcomes. Several pesticides exposures have been shown to have significant human health effects. These include an increased risk of reproductive, neurological, oncological, respiratory, endocrine and other outcomes. Many other pesticide exposure and outcome relationships lack sufficient well-designed epidemiological studies to enable the determination of their effect on human health. Recommendations that reduce the use of and exposure to pesticides for the general population and for vulnerable groups (i.e. pregnant women and children) are indicated based on the state of the research evidence at this time. In addition, educational supports for the reduction of and the safe use of agricultural pesticides are important to reduce the risks associated with pesticides in this occupationally exposed group.

15. Glossary of pesticides and health outcomes

15.1 Pesticides

Abbreviations used

2,4-D	(2,4-dichlorophenoxy)acetic acid
2,4-DB	4-(2,4-dichlorophenoxy)butanoic acid
2,4,5-TCP	2,4,5-trichlorophenoxyacetic acid
2,4,5-TP	2-(2,4,5-trichlorophenoxy)propionic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
80/20 mix	carbon tetrachloride/carbon disulfide
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DEET	diethyltoluamide
EPTC	ethyl dipropylthiocarbamate
HCB	Hexachlorobenzene
MCPA	4-chloro-o-tolyloxyacetic acid
OC	Organochlorine
OP	Organophosphate
POP	Persistent Organic Pollutant

Table 74. Pesticides described in the literature reviewed (3)

Pesticide type	Specific Pesticide	Use
Alkanamide	Napropamide	Herbicide
Alkylchlorophenoxy	2,4-D (2,4 dichlorophenoxyacetic acid)	Herbicide
Aromatic hydrocarbon	Naphthalene	Insecticide (obsolete)
Arsenical compound	Lead arsenate	Insecticide
Aryloxyalkanoic acid	2,4-DB	Herbicide
	Dichlorprop	Herbicide
	MCPA[1]	Herbicide
	Mecoprop	Herbicide
Benzimidazole	Benomyl	Fungicide
Benzoic acid	Dicambia	Herbicide
Bipyridylium/ Dipyridyl	Paraquat	Herbicide
Chlorinated hydrocarbon	Dieldrin	Insecticide (obsolete)
Chloroacetamide and Chloroacetanilides	Acetachlor	Herbicide
	Alachlor	Herbicide
	Metoachlor	Herbicide
Chloronitrile	Chlorothalonil[1]	Fungicide
Chlorophenoxy acid	2,4,5-T (2,4,5-trichlorophenoxyacetic acid)	Herbicide
Chlorophenyl	Dichloran/dicloran	Fungicide
Dinitoanilines	Pendimethalin	Herbicide
	Trifluralin	Herbicide
Dinitrophenol	Dintro-cresol	
Diphenyl ester	Oxyfluorfen	Herbicide
Halogenated hydrocarbon	1,3-dichloropropene (DCP)	Nematicide/Fumigant
Imidazolinone	Imazethapyr	Herbicide
Inorganic compound	Copper sulfate	Fungicide
	Hyodrogen Sulfide	Reduced from sulphur
	Mercury	Fungicide
	Methyl bromide/ Bromomethane	Soil fumigant
	Sulphur	Fungicide
Organochlorine	Aldrin	Insecticide (obsolete)
	Chlordane (cis- & trans-nonachlor)	Insecticide
	DDD (Dichlorodiphenyldichloroethane)	DDT metabolite
	DDE (Dichlorodiphenyldichloroethylene)	DDT metabolite
	DDT (Dichlorodiphenyltrichloroethane)	Insecticide (obsolete)
	Dicofol	Acaricide
	Endosulfan	Insecticide/Acaricide
	Heptachlor epoxide	Insecticide (obsolete)
	Hexachlorobenzene	Fungicide
	Hexachlorocyclohexane/Hexachlorohexane	Insecticide
	Lindane	Insecticide
	Mirex	Insecticide (obsolete)
	Oxychlordane	Chlordane metabolite
	Pentachlorophenol	Insecticide & Herbicide & Fungicide
	Toxaphene	Insecticide (obsolete)
Organometal	Fenbutatin-oxide	Acaricide
Organophosphate	Acephate	Insecticide
	Azinphos-methyl	Insecticide
	Chlorpyrifos	Insecticide
	Diazinon	Insecticide
	Dichlorvos	Insecticide
	Dimethoate	Insecticide

Table 74. Pesticides described in the literature reviewed (3)

Pesticide type	Specific Pesticide	Use
	Disulfoton	Insecticide
	Ethoprophos/Ethoprop	Insecticide
	Fonophos	Insecticide
	Malathion	Insecticide
	Naled	Insecticide
	Oxydemeton-methyl	Insecticide
	Parathion	Insecticide
	Parathion-methyl	Insecticide
	Phorate	Insecticide
	Phorate[1]	Insecticide
	Terbufos	Insecticide
	Trichlorfon	Insecticide
Other	Nitrate	Groundwater contaminant from fertilizer
	Piperonyl butoxide	Pesticide synergist Insecticide
	DEET (Diethyltoluamide)	Insecticide & Fumigant
	Ethylene dibromide	
Petroleum derivatives	Petroleum oil	Insecticide
Phenoxypropionic acid	Fenoprop (2,4,5-TP)	Herbicide
Phenylamide	Metalaxyl	Fungicide
Phosphonoglycine	Glyphosate/Glyphosphate	Herbicide
Phosphorothioate	Coumaphos	Insecticide
Phthalic acid	Chlorthal	Herbicide
Phthalimide or Thiophthalimide	Captan	Fungicide
Pipyridylium	Diquat[1]	Herbicide
Pyrethroid	Permethrin	Insecticide
Quinone	Dichlone	Fungicide
Sulfonylurea	Chlorimuron-ethyl	Herbicide
Sulphite ester	Propargite	Acaricide
Thiocarbamate and Carbamates	Aldicarb	Insecticide
	Bufencarb	Insecticide
	Butylate	Herbicide
	Carbaryl	Insecticide
	Carbofuran	Insecticide
	EPTC	Herbicide
	Ferbam	Fungicide
	Maneb/mancozeb[1]	Fungicide
	Metam Sodium	Herbicide & Fungicide & Insecticide
	Methomyl	Insecticide
	Metiram[1]	Fungicide
	Ziram	Fungicide
Triazine and triazonines	Atrazine	Herbicide
	Cyanazine	Herbicide
	Hexazinone[1]	Herbicide
	Metribuzin	Herbicide
	Simazine	Herbicide

[1]Used in PEI in quantities of more than 10,000kg annually.

15.2 Health outcome and other abbreviations used in document

AD	Alzheimer's Disease
ADHD	Attention Deficit/Hyperactivity Disorder
AHS	Agricultural Health Study
ALS	Amyotrophic Lateral Sclerosis
AML	Acute Myeloid Leukemia
AR	Allergic Rhinitis
ASD	Autism Spectrum Disorder
BMDI	Bayley Mental Development Index
BMI	Body Mass Index
BNBAS	Brazelton Neonatal Behavioural Assessment Scale
BPDI	Bayley Physical Development Index
BPH	Benign Prostatic Hyperplasia
BSID	Bayley Scale of Infant Development
CBT	Child Brain Tumour
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
COPD	Chronic Obstructive Pulmonary Disease
DD	Development Disorder
ER +	Estrogen Receptor Positive
ER-	Estrogen Receptor Negative
FEV1	Forced Expiratory Volume in 1 second
FT4	free Thyroxine
FVC	Forced Vital Capacity
G	Grams
HL	Hodgkin Lymphoma
IQ	Intelligence Quotient
IVF	In-Vitro Fertilization
KG	Kilograms
LHC	Lymphohematopoietic Cancer
MCSA	McCarthy Scale of Children's Abilities
ML	Myeloid Leukemia
MM	Multiple Myeloma
NHL	Non-Hodgkin Lymphoma
NOS	Not Otherwise Specified
PD	Parkinson Disease
PDD	Pervasive Development Disorder
PEI	Prince Edward Island
PHASU	Population Health Assessment and Surveillance Unit

PNET	Primitive Neuroectodermal Tumour
PPE	Personal Protective Equipment
RA	Rheumatoid Arthritis
RCC	Renal Cell Carcinoma
SAD	Systemic Autoimmune Disease
SDQ	Strengths and Difficulties Questionnaire
SGA	Small for Gestational Age
SLE	Systemic Lupus Erythematous
SS	Systemic Sclerosis
STS	Soft Tissue Sarcoma
T3	Triiodothyronine
T4	Thyroxine
TGCC	Testicular Germ Cell Carcinoma
Th-1	T-Helper 1
Th-2	T-Helper 2
TSH	Thyroid Stimulating Hormone

16. Appendix 1: Study tables

16.1 Congenital abnormalities

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Congenital abnormalities							
Kielb Int J Hygiene and Enviro Med 2014 (24)	Case-control	817 cases and 2857 controls	Periconceptual maternal occupational pesticide exposure one month pre-conception to 3 months post-conception based on job title	Any pesticide, insecticide only, both insecticide and herbicides or to insecticide, herbicide and fungicide	Isolated craniosynostosis, gastroschisis, diaphragmatic hernia or transverse limb deficiencies	Occupational exposure to insecticides, herbicides and fungicide was associated with gastroschisis among infants of women aged 20 years or older (adjusted (a) OR = 1.88; CI 1.16–3.05), but not for women under age 20 (aOR = 0.48; CI: 0.20–1.16). There were no significant associations for the other defects. Exposure based on job title and interviews regarding exposures.	
Ronda J Occup Enviro Med 2005 (23)	Cohort	587,360 births in Spain	Paternal exposure to pesticides in agriculture	Any exposure	Any congenital abnormality causing fetal death	Paternal agricultural workers had a higher risk of fetal death than non-agricultural workers when their wives were housewives and their children were conceived in the highest season of pesticide use (Apr-Sept) OR 1.68 (CI 1.03-2.73).	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Weselak Repro Toxico 2008 (28)	Cohort	3412 pregnancies	Pre- and post-conception pesticides exposure in farm families	Any pesticide, Fungicides,Insecticides, Herbicides, Triazine, Phenoxy herbicides, Organophosphates, 2,4-D, Cyanazine, Thiocarbamate	Any birth defect	Pre-conception exposure to cyanazine (odds ratio = 4.99, CI 1.63–15.27) and dicamba (OR = 2.42, CI: 1.06–5.53) were associated with increased risk of birth defects in *male* offspring only.No other significant associations were found.	
Winchester Acta Ped 2009 (38)	Cohort	30.11 million births between 1996-2002 in the US	Monthly nitrate, atrazine and other pesticide levels in water	Nitrates, atrazine, other pesticides	Any birth defect	Agricultural chemical concentrations were highest from April to July (Atrazine (A) $p<0.01$, nitrate (N) $p<0.05$ and pesticides (P) $p<0.01$). Births with LMPs between April and July were more likely to experience 11 of 22 birth defect categories (spina bifida, circulatory/respiratory abnormalities, trachea-esophageal defects (P), gastrointestinal defects (A), urogenital defect, cleft lip (A), adactyly (A), club foot, musculoskeletal abnormalities (P), Down's syndrome (A) and other birth defects (A,N,P) $p<0.05$) and total birth defects ($p<0.01$). Significant associations between each chemical and each defect adjusted for the other 2 chemicals are listed after the defect (i.e. A,N or P).	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Neurologic Defects							
Agopian Amer J Med Gene 2013 (30)	Case-Control	16,433 cases from Texas Birth Defects Registry and County level controls	County level estimates of atrazine water levels from US Geological Survey	Atrazine	Hypospadias, cryptorchidism and small penis	In crude analyses, women with medium-low (25^{th} to $<75^{th}$ percentile) or medium (75^{th} to $<90^{th}$ percentile) levels of residential atrazine exposure were at a significantly increased risk of having offspring with any male genital malformation alone(crude OR: 1.18, 95% CI: 1.12–1.25 and crude OR: 1.23, 95% CI: 1.15–1.32, respectively), compared to those with low levels.Those with high levels (above 90^{th} percentile) of exposure were at a significantly decreased risk (crude OR: 0.80, 95% CI: 0.74–0.88), compared to those with low levels. There was a significant association between high levels of atrazine and male genital abnormalities with other major abnormalities (adjusted OR: 1.27, 95% CI: 1.09–1.48), suggesting that high levels may result in multiple abnormalities.	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Brender Ann Epi 2010 (25)	Case-control	184 cases in Mexican American Women and 225 controls	Pesticide use at work, in home or yard around the time of conception and residential proximity to fields	Any	Neural tube defects	With adjustment for maternal education, smoking, and folic acid/folate intake, NTD risk was associated with use of pesticides around the home (OR 2.0 CI, 1.2–3.1), in the yard or garden (OR 2.0 CI, 1.1–3.7), and on self (OR 1.7 CI, 0.96–2.9). After adjustment for multiple sources of pesticide exposure, home use (adjusted OR 1.8 CI 1.1–2.9) and living near cultivated fields (adjusted OR 2.7 CI, 1.4– 5.5) remained associated with NTD risk while occupational exposures and pesticides used on self or in the yard showed minimal or no association with NTD risk. With adjustment for multiple sources of pesticide exposure, reported residential proximity to fields remained strongly associated with anencephaly (OR 3.4 CI, 1.5–7.5) and spina bifida (OR 2.5 CI, 1.1–5.9), whereas home use was only significantly associated with anencephaly (OR 2.4 CI, 1.3–4.2). Dose-response relationship evident with number of sources of pesticide exposure increasing odds of anencephaly and spina bifida.	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Carmichael Pediatrics 2013(41)	Case-control	690 male cases from 1991-2004 in 8 California counties and 2195 controls randomly chosen from the population birth cohort	Early pregnancy exposure to pesticide application within 500m of home address of mother based on pesticide applications and land use	57 chemical groups and 292 chemicals	Hypospadias (abnormal urethral opening in males)	No increase in risk of hypospadias with exposure to increasing number of pesticides. Elevated risk of hypospadias with exposure to monochlorophenoxy acid or ester herbicides (OR highest tertile 2.6 (CI 1.07-6.18)), insecticides aldicab (OR lowest tertile 2.7 (CI 1.04-6.96)), dimethoate (OR lowest tertile 2.5 (CI 1.36-4.39)), **phorate** (OR any exposure 2.8 (CI 1.19-6.44)) and petroleum oil (OR middle tertile 1.9 (CI 1.04-3.62)) and adjuvant polyoxyethylene sorbitol (OR any exposure 3.4 (CI 1.17-9.90)). Elevated risk of mild hypospadias with exposure to 2,6-dinitroaniline (OR lowest tertile OR 2.1 (CI 1.07-4.08)), oxyfluorfen (OR middle tertile 2.0 (CI 1.09-3.77)) and copper sulfate (OR any exposure 2.9 (CI 1.29-6.40)). Elevated risk of moderate to severe hypospadias with exposure to herbicides chloroacetanilide (OR any exposure 2.8 (CI 1.12-6.75)), adjuvants ploylkyloxy (OR lowest tertile 1.9 (CI 1.21-3.10)), and nonyl-phenoxy-poly(ethylene oxy) ethanol (OR lowest tertile 2.0 (CI 1.19-3.36))and insecticides aldicarb (OR any exposure 2.5 (CI 1.03-6.18)) and acephate (OR any exposure 2.6 (CI 1.12-5.96)).	Author correctly notes that there are few significant associations found given the more than 500 tested. Lack of dose-response in many categories (i.e. significance for lowest dose but not for higher dose categories) – the authors suggests that endocrine disruptors may be more potent at lower levels of exposure.
Carmicheal Chemosphere 2010 (44)	Case-control	20 cases and 28 controls in California	Serum samples taken mid-pregnancy	9 persistent pesticides	Hypospadias	No significant associations found	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hypospadias and Cryptorchidism							
Lacasana Occup Enviro Med 2006 (35)	Case-control	151 cases and 151 controls in Mexico	Maternal and paternal occupational exposure	All pesticide exposure	Anencephaly	The children of mothers who worked in agriculture in between 3 months before and one month after the LMP had a greater risk of anencephaly (OR = 4.57, CI 1.05 to 19.96).	
Meyer Enviro Health Persp 2006 (29)	Case-control	354 cases and 727 controls in eastern Arkansas born 1998-2002	Pesticide application within 500m of a subject's home during gestational weeks 6 to 16 from land use data	38 pesticides	Hypospadias	Risk of hypospadias increased by 8% for every 0.05-pound increase in estimated exposure to diclofop- methyl use (OR = 1.08; 95% CI, 1.01–1.15). Any pesticide applications (OR = 0.82; 95% CI, 0.70–0.96) and applications of alachlor (OR = 0.56; 95% CI, 0.35–0.89) and permethrin (OR = 0.37; 95% CI, 0.16–0.86) were negatively associated with hypospadias.	
Nordby et al. Scan J Work Environ Health 2005(36)	Retrospective cohort	105403 female and 131243 male farmers born 1925-1971 and their 300805 children born 1952-1991	Farm production and fungal forecasts (humid and temperate condition) served as a proxy for mancozeb exposure	**Mancozeb**	Neural tube defects	Moderate association of neural tube defects (n=131) with potato cultivation PR 1.6 (95% CI 1.1-2.3) and paternal farm work >500 hours/year PR 1.6 (95% CI 1.1-2.5).	Also in other cancers (thyroid). Proxy exposure-bias towards null.
Pierik Environ Res 2007 (33)	Case-control	219 cases and 564 controls from a US birth cohort 1959-1966	Maternal serum levels	heptachlor epoxide (HCE), hexachlorobenzene (HCB), and β-hexachlorocyclohexane (β-HCCH)	Cryptorchidism	No significant association between cryptorchidism and the studies pesticides, except for hexachlorocyclohexane levels between the 50^{th} and 90^{th} percentiles (OR for 50^{th} to 75^{th} 2.01 (CI 1.10-3.67) OR for 75^{th} to 90^{th} 2.08 (CI 1.08-4.01)) but the p test for trend was not significant (U-shaped curve).	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Rocheleau Birth Defect Res 2011 (40)	Case-control	647 cases and 1496 controls in the US from Oct 1997 to December 2002	Maternal periconceptual occupational exposure to fungicides, insecticides and herbicides	Any	Hypospadias	No significant increased risk of hypospadias with any pesticides, insecticide, fungicide or herbicide exposure in the 1 month before conception or first trimester of pregnancy.	
Rocheleau J Ped Urology 2009 (39)	Meta-analysis	9 studies	Maternal and paternal occupational pesticide exposure	Any	Hypospadias	Elevated risks of hypospadias were associated with maternal occupational exposure (PRR of 1.36, CI 1.04-1.77), and paternal occupational exposure (PRR of 1.19, CI 1.00-1.41).	
Rull AJE 2006 (37)	Case-control	Two pooled case-control studies: 731 cases and 940 controls	Maternal residential proximity within 1,000 m of pesticide applications from the month of and the month after conception	Most frequently used organic pesticides	Neural tube defect (Anencephaly and spina bifida)	Napropamide (OR 3.4 CI 1.0-11.2), benomyl (OR 2.2 CI 1.2-4.0). 1,3-dichloropropene (OR 2.1 (CI 1.0-4.1), acephate (OR 1.7 CI 1.0-2.8), chlorpyrifos (OR 1.5 CI 1.0-2.3), dimethoate (OR 1.7 CI 1.0-2.9), disulfoton (OR 4.0 CI 1.3-12.6), glyphosate (OR1.5 CI 1.0-2.4), naled (OR 2.8 CI 1.3-5.8), oxydemeton-methyl (OR 1.7 (CI 1.0-3.1), fenbutatin-oxide (OR 2.2 CI 1.0-4.8), oxyfluorfen (OR 2.2 CI 1.1-4.7) and methomyl (OR 1.6 (CI 1.1-2.3) application near the home was associated with NTDs after adjustment for study population, maternal ethnicity, educational level, cigarette smoking, and vitamin use. Large number of comparisons.	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Trabert Environ Health Persp 2012 (43)	Case-control	217 sons with cryptorchidism, 197 sons with hypospadias, and 557 sons with neither condition in the US	Serum levels of *trans*-nonachlor and oxychlordane	*trans*-nonachlor and oxychlordane	Hypospadias, cryptorchidism	The quartile-specific ORs and the test for trend for cryptorchidism or hypospadias show no significant associations with *trans*-nonachlor or oxychlordane.	
Waliszewski Bull Environ Contam Taxico 2005 (42)	Case-control	30 cases and 30 controls in Mexico	Serum levels of organochlorines	hexachlorobenzene (HCB), and β-hexachlorocyclohexane (β-HCCH)	Undescended tests	No significant association between the studied pesticides and undescended testes.	
Yang AJE 2014 (27)	Case-control	73 cases with anencephaly, 123 with spina bifida and 785 controls in California	Residential proximity to agricultural pesticide applications during early pregnancy	461 pesticides and 62 chemical groups	Neural tube defects	Chemical groups with significant association with NTDs and cleft palate included petroleum derivatives for anencephaly, hydroxybenzonitrile herbicides for spina bifida. The specific chemicals included 2,4-D dimethylamine salt, methomyl, imidacloprid, and α-(para-nonylphenyl)-ω-hydroxypoly (oxyethylene) phosphate ester for anencephaly; the herbicide bromoxynil octanoate for spina bifida. Adjusted odds ratios ranged from 1.6 to 5.1. Large number of comparisons.	
Orofacial defects							
Agopian J Pediatrics 2013 (32)	Case-control	280 cases from Texas Birth Defects Registry and 3720 County level controls	County level atrazine drinking water exposure estimates	Atrazine	Choanal atresis and stenosis	Compared to offspring of mothers with low levels of estimated residential atrazine exposure, those with high levels had a significant increase in risk for choanal atresia or stenosis (adjusted OR: 1.79, CI: 1.17–2.74). A significant linear trend was also observed with increasing levels of atrazine exposure (adjusted $P = 0.002$).	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Romitti Cleft Palate 2007 (22)	Meta-analysis	19 studies	Exposure to any pesticide	Any	Cleft palate	Maternal occupational pesticide exposure was associated with a pooled increased risk of clefting (OR 1.37 CI 1.04-1.81). No significant increased risk with paternal exposure or residential pesticide exposure.	
Yang AJE 2014 (27)	Case-control	277 with CLP, and 117 with cleft palate only and 785 controls in California	Residential proximity to agricultural pesticide applications during early pregnancy	Any	Cleft lip and cleft lip palate	Chemical groups with significant associations to cleft palate included 2,6-dinitroaniline herbicides and dithiocarbamates methyl iso-thiocyanate for cleft lip palate and the specific chemicals includedtrifluralin and maneb for cleft lip palate. Adjusted odds ratios ranged from 1.6 to 5.1. Large number of comparisons.	
Gastrointestinal defects							
Agopian Matern Child Health J 2013 (31)	Case-control	1,161 cases from Texas Birth Defects Registry and 8,390 County level controls	Maternal county of residence	Atrazine in drinking water	Gastrochisis	Risk for gastroschisis in offspring was significantly increased for women 25 years and older with high levels of residential atrazine exposure compared to low (adjusted OR: 1.97, CI 1.19–3.26). This association was not observed among women <25 years.	
Felix Birth Defects Res 2008 (26)	Case-control	47 cases and 202 controls in the Netherlands	Maternal exposure to herbicides or insecticides from 1 month before conception to the end of the 1st trimester	Any	Esophageal atresia with or without tracheoesophageal fistula (EA/TEF) and congenital diaphragmatic hernia (CDH)	Contact with herbicides or insecticides was associated with EA/TEF in univariate analysis (OR 2.0; CI: 1.0–4.1).	

Congenital abnormalities and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Congenital hypothyroidism							
Nagayama Chemosphere 2007 (34)	Case-control	34 cases and 102 controls in Fukuoka, Japan from 2001-2004	Breast milk organochlorine concentration	Organochlorines (hexachlorocyclohexanes (HCH), chlordane, hexachlorobenzene (HCB))	Congenital hypothyroidism/cretinism	Risk of cretinism was significantly increased with exposure to HCB (OR 22, p=0.004) and chlordane (OR 6.6, p=0.006) but not with HCH (OR 2.8, p=0.07) after adjustment for maternal age and parity. Concentration of organochlorine compounds was 1.9-2.5 times higher in the breast milk of mothers with infants with cretinism.	

16.2 Fetal growth

Fetal growth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Barr Total Environ 2010(11)	Prospective cohort	150 women having elective cesarean deliveries in New Jersey	Maternal and cord blood serum biomarkers	chlorpyrifos, diazinon, carbofuran, **chlorothalonil,** dacthal, metolachlor, trifluralin and diethyl-m-toluamide (DEET).	Birth weight, abdominal circumference, birth length and head circumference	Significant associations between high metolachlor (75^{th} percentile +) cord blood levels and lower birth weight (p=0.05) and higher dichloran (75^{th} percentile +)cord blood concentration and increased abdominal circumference in the newborn (p=0.031)	Cut point used (75^{th} percentile) could have been used to show significance...no associations between maternal blood levels and birth outcomes, small sample size.
Fenster Environ Health Persp 2006 (20)	Cohort	385 low-income Latinas in Salinas Valley, California	Maternal serum organochlorine levels	Hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCCH), γ-hexachlorocyclohexane (γ-HCCH), dieldrin, heptachlor epoxide, oxychlordane, *trans*-nonachlor, and mirex.	Birth weight or crown–heel length	There were no adverse associations between maternal serum organochlorine levels and birth weight or crown–heel length. Also in preterm birth.	
Migeot Environ Research 2013(14)	Cohort	11,446 women-neonate dyads	Atrazine and nitrates in community drinking water	Atrazine presence or absence and tertiles of nitrate concentrations	Small for Gestational Age birth weight (below 10^{th} percentile for sex and gestational age) excluding birth by Cesearan section	No significant differences in SGA with mixed atrazine and nitrate exposures..	

Fetal growth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Mink J Toxico Environ Health 2012 (21)	Review	4 cohort studies	Biomarkers	Chlorpyrifos	Birth weight, birth length, head circumference	No association between self-reported exposures and birth outcomes. There were no consistent associations across studies of fetal growth outcomes and chlorpyrifos exposure.	
Ochoa-Acuna Environ Health Perspec 2009 (15)	Retrospective cohort	24,154 births in Indiana from 1993 to 2007	Atrazine concentration in 19 water systems based on mother's residence at time of birth	Atrazine	Small-for-Gestational-Age (SGA) and preterm birth	Atrazine in drinking water during the third trimester and the entire pregnancy was associated with a significant increase in the prevalence of SGA. Atrazine in drinking water > 0.1 μg/L during the third trimester resulted in a 17–19% increase in the prevalence of SGA compared with the control group (< 0.1 μg/L). Mean atrazine concentrations over the entire pregnancy > 0.644 μg/L were associated with higher SGA prevalence than in the control group (adjusted Prevalence Ratio = 1.14; 95% confidence interval, 1.03–1.24). Also in preterm labor.	
Petit AJE 2012 (17)	Cohort	1,213 births in France	Exposure to agricultural activities, nonorganic diet, household insecticide use on plants, and household insecticide use against insects	Any insecticide	Birth weight, head circumference	No significant associations between birth outcomes and insecticides exposure (both residential and agricultural).	

Fetal growth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Petit Environ Health 2010 (13)	Prospective cohort	3,421 births in Brittany, France	Residential proximity to agricultural activity	Agricultural exposure	Birth weight, growth restriction, head circumference	Infant born in a municipality where peas were grown had a smaller head circumference at birth than those in municipalities not growing peas (-0.2 cm, p = 0.0002). Risk of an infant with a small head circumference was higher when the mother lived in a municipality where peas where grown (OR = 2.2; CI = 1.2-3.6).No other significant associations were found with birth length or birth weight.	
Rauch Enviro Health Perspec 2012 (18)	Prospective birth cohort	306 mother-infant dyads	6 metabolites of organophosphate insecticides obtained from two maternal urine samples.	Sum of the 6 metabolites (ΣDAP)	Birth weight and gestational age at birth	A 10-fold increase in ΣDAP concentrations was associated with a decrease in covariate-adjusted gestational age [–0.5 weeks; 95% confidence interval (CI): –0.8, –0.1]. The same 10-fold increase significantly reduced birth weight (–151 g; CI: –287, –16); a finding thatwas attenuated to being non-significant after adjusting for gestational age. There was a greater decrease in birth weight with increasing urinary ΣDAP concentrations for African-American (–188 g; CI: –395, 19) than for white (–118 g; CI: –296, 60) newborns.	
Sagiv Epidemiology 2007(19)	Cohort	722 infants born 1993-1998 to residents of Bedford, Mass.	Cord blood samples	Organochlorines: hexachlorobenzene [HCB]	Birth weight, crown-heel length and head circumference	No associations were found for HCB for any measures of birth size.	

Fetal growth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Sathyanarayana J Agromedicine 2010 (12)	Cross-sectional	2246 farm women whose most recent singleton birth occurred within 5 years of enrollment (1993–97) in the Agricultural Health Study	27 individual pesticides used on the farm in the first trimester based on the following activities:1. No exposure 2. Indirect exposure 3. Residential exposure and 4. Agricultural exposure.	Alachlor Atrazine Chlorimuron-ethyl Cyanazine Dicamba Glyphosate Imazethapyr Metolachlor Paraquat Petroleum Oil Pendimethalin Trilfluralin 2,4-D Captan Metalaxyl Carbaryl Chlordane Chlorpyrifos Coumaphos Diazinon Dichlorvos Fonofos Malathion Permethrin on crops Permethrin on animals Phorate Terbufos	Birth weight after adjustment for site, preterm birth, medical parity, maternal BMI, height and smoking	First-trimester pesticide-related tasks were not associated with birth weight. Ever use of the pesticide carbaryl in the agricultural setting was associated with decreased birth weight (−82 g, 95% CI = −132, −31). The study only considered first trimester use.	
Snijder Hum Repro 2012 (10)	Prospective cohort	4680 women in the Netherlands	Occupation exposure to pesticides	Job-based	Fetal weight, head circumference, fetal length, placental weight	Occupational exposure to pesticides was associated with a significant reduction in fetal length (b -0.035cm, p=0.016), placental weight (b -65.90g (CI -129.86 to -1.94)) after adjustment for confounders. No associations were seen for fetal weight or head circumference.	

Fetal growth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Villanueva Occup Environ Med 2005(16)	Retrospective cohort	3510 births that took place from 1 October 1997, to 30 September 1998 in Spain	Atrazine levels from 2661 water treatment plant samples over the last 10 years	Atrazine	Preterm delivery, low birth weight and small-for-gestational age	Atrazine levels in water were not associated with an increased risk of LBW or SGA status. There was an increased risk of SGA status in cases in which the third trimester overlapped in whole or in part with the May–September period (peak atrazine levels), compared with those in which the third trimester occurred totally from October to April (OR = 1.37, 95% CI 1.04 to 1.81). If the entire third trimester took place from May to September, the OR was 1.54 (95% CI 1.11 to 2.13). Very low population exposure in general.	

16.3 Fetal loss and spontaneous abortion

Fetal loss and spontaneous abortion and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Mueller Environ Health Perspec 2007 (66)	Case-Control	7,054 women experiencing fetal death after 20 weeks and 10 controls per case in Washington State	Distance at maternal residence at delivery to nearest hazardous waste site	Any	Fetal death	The risk of fetal death increased among women residing ≤1 mile from pesticide-containing sites (OR = 1.28; 95% CI, 1.13–1.46)	

16.4 Infertility

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Buck Louis Environ Health Perspec 2013 (53)	Cohort	501 couples in Michigan or Texas	Serum levels of 9 organochlorine pesticides	hexachlorobenzene (HCB), β-hexachlorocyclo- hexane (β-HCH), γ-hexachlorocyclohexane (γ-HCH), oxychlordane, *trans*-nonachlor and mirex]	Time to pregnancy	HCB levels in women were associated with reduced crude odds of getting pregnant OR 0.87 (CI 0.77-1.00). No other significant associations.	
Chevrier Epidemiology 2013 (54)	Retrospective Cohort	3,421 pregnant women in France	14 organochlorine pesticides	α-hexachlorocyclohexane, β-hexachlorocyclohexane [βHcH], γ-hexachlorocyclohexane [γHcH], hexachlorobenzene [HcB], heptachlor, heptachlor epoxide [Hce], aldrin, diel- drin, α-endosulfan, β-endosulfan	Time to pregnancy	The fecundability OR decreased with βHcH at medium (OR 0.72 CI 0.52-1.00) and high (OR 0.61 CI 0.43-0.86) levels (p trend=0.005), HcB at high levels (OR 0.67 CI 0.48-0.95) (p trend=0.02), heptachlor epoxide above the LOD (OR 0.76 CI 0.58-1.00). Other associations not significant.	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Clementi Repro Toxi 2008 (63)	Cohort	Fertility rate of resident women in 3 provinces in Italy	According to the estimated quantities of sprayed pesticides, the area was divided in three sub-areas with expected low, intermediate and high pesticide exposure.	Any	Fertility rate	No significant differences in the fertility rate between areas.	
Cole Repro Toxi 2006 (56)	Cohort	41 couples in Hamilton, Canada	Serum organochlorine levels and environmental exposures	Benzene hexachloride, Hexachlorobenzene, Oxychlordane	Fecundability odds ratio	Significantly increased length of time to pregnancy with the highest tertile of maternal benzene hexachloride levels (fecundability OR 0.30 CI 0.10-0.89) with a positive trend of increasing time to pregnancy with increasing levels ($p<0.01$) but no association in multivariate analysis. No other significant associations with the pesticides studied.	
De Fleurian J Andrology 2009 (62)	Cohort	402 men consulting for couple infertility in France	Self-reported physical or chemical occupational exposures	Any	Semen quality	No significant association between semen impairment and exposure to pesticides (OR 3.6 CI 0.8-15.8).	
Gracia AJE 2005 (61)	Case-control	650 cases and 698 controls across the US	Self-reported occupational exposure	Any	Male infertility	No significant association between male infertility and occupational exposure to pesticides (OR 1.1 CI 0.80-1.5).	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Harley J Occup Environ Med 2008 (48)	Cohort	402 pregnant women in a migrant farm community in Salinas Valley, California	Self-reported maternal and paternal home and occupational pesticide exposure before conception		Time to pregnancy	Maternal occupational pesticide exposure (fecundability (f) OR=0.8 CI: 0.6, 1.0), home pesticide use (fOR=0.6 CI: 0.4, 0.9), and residence within 200 feet of an agricultural field (fOR=0.7 CI: 0.5, 1.0) were associated with reduced fecundability (i.e. longer TTP). These findings persisted when subsets of the data were analyzed (i.e. primaparous women, couples actively trying, etc...)	
Jurewicz Int J Occup Med Environ Health 2009 (354)	Review	18 studies		Any pesticide	Semen quality	Clear effects on male fertility have been demonstrated for some pesticides: dibromochloropropane, ethylene dibromide, organophosphorus, alochlor, me- tochlor, 2,4-D, atrazine, fenvalerate, carbaryl, chlorpyrifos. There are several indications that some pesticides may impair semen quality in humans, but weak exposure assessment in most studies precludes proper identification of responsible agents and evaluation of exposure-response relations.	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Kadhel Repro Sciences 2012 (59)	Systematic Review	22 studies followed Cochrane guidelines	Organochlorines (OCs)	Aldrin, Chlordan,Chlordecone, Dichlorodiphenyldichloroethane, Dichlorodiphenyldichloroethylene, Dichlorodiphenyltrichloroethane , Dieldrin, Dioxins, Endosulfan, Endrin, Furans, Heptachlor, Hexachlorobenzene, Hexachlorocyclohexane, Mirex, Polychlorinated biphenyls, Toxaphene	Female fertility in an IVF context	Overall, rates of pregnancy following IVF were not significantly affected by exposure to OCs, but there was some evidence to suggest that increasing OCs decreased oocyte or embryo quality and implantation. The conclusions are limited by the variations in the protocols used, OCs studied, and the quality of the studies.	
Luderer Enviro Research 2013 (64)	Cohort	457 adults born 1981-1982 in Hawaii	In utero exposure to hepatachlor epoxide contaminated cow's milk during 15 months in 1981-82	Hepatchlor epoxide	Reproductive function, age of puberty	There were no strong associations of heptachlor epoxide exposure during gestation and lactation with reproductive endpoints. In females, heptachlor epoxide exposure was associated with a longer luteal phase length and a slower drop in the ratio of estradiol to progesterone metabolites after ovulation. Breastfeeding and drinking more than 12 glasses/milk per week versus 0-5 glasses was associated with significantly earlier ages at menarche for women (b -1.027 CI -2.008 to -0.046).	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Mahalingaiah Enviro Health Perspec 2012(55)	Cohort	720 women undergoing 774 in virto fertilization (IVF) cycles in Boston	Maternal serum levels	Hexchlorobenzene	IVF outcomes	Compared with the lowest quartile (Q1) of HCB, the lipid- and multivariable-adjusted OR for failed implantation was significantly elevated for those with higher HCB quartiles [Q2–Q4; adjusted ORs: for Q2, 1.71; CI 1.03-2.82; for Q3, 2.30; CI: 1.39-3.81; for Q4, 2.32; CI: 1.38-3.90] and showed a significantly increasing trend (p = 0.001). No statistically significant associations were observed between HCB and chemical pregnancy or spontaneous abortion.	
Martenies Toxicology 2013 (50)	Systematic review	17 studies		Hexachlorocyclohexane (HCH) and abamectin. Pyrethroids and organophosphates included as entire classes	Human sperm parameters (concentration, motility and morphology)	A majority of the studies reported significant associations between pesticide exposure and sperm parameters. A decrease in sperm concentration was the most commonly reported finding among all of the pesticide classes. Decreased motility was associated with exposures to each of the pesticide classes, although these findings were less frequent across studies. An association between pesticide exposure and sperm morphology was only reported by 2 studies.Based on 4 studies, exposure to pyrethroids at environmentally relevant levels may impact semen concentration. Organophosphate pesticide exposure may be associated with declines in semen quality. Also a discussion of organochlorines and genetic modifications not included here.	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Meeker Environ Health Perspec 2004 (52)	Cohort	272 males attending a Massachusetts infertility clinic with no reported occupational pesticide exposure	Urinary metabolites	Carbaryl/Naphthalene (C/N) and Chlorpyrifos (C) metabolites	Semen quality (sperm concentrations, percent motile sperm, percent sperm with normal morphology and sperm motion parameters)	For increasing C/N tertiles, adjusted ORs were significantly elevated for below-reference sperm concentration (OR for low, medium, and high tertiles = 1.0, 4.2, 4.2, respectively; *p*-value for trend = 0.01) and percent motile sperm (1.0, 2.5, 2.4; *p*-value for trend = 0.01). The sperm motion parameter most strongly associated with C/N was straight-line velocity. Sperm morphology was not significantly associated with both C and C/N and sperm concentration and motility was not significantly associated with C.	
Meeker Human Repro 2008 (49)	Cohort	207 men attending a Massachusetts infertility clinic	Urinary metabolites	Pyrethroid insecticides [urinary pyrethroid metabolites [3-phenoxybenzoic acid (3PBA) and cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (CDCCA and TDCCA)]	Semen quality, sperm motion parameters and sperm DNA damage with the neutral comet assay	There were significant inverse associations between TDCCA and sperm motility (p trend =0.01) and sperm motion parameters (p trend <0.04) when adjusting for CDCCA and other covariates. There were dose-dependent increased odds for below reference sperm concentration (OR at for above 75th percentile 2.72 (CI 1.07-6.92) versus below 50th percentile)for TDCCA (p trend =0.05). Among the comet assay measures, 3PBA was associated with increased sperm DNA damage (p trend=0.02).	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Recio-Vega J App Toxicology 2008 (51)	Cohort	52 men who provided repeat semen samples in Mexico	Urinary pesticide levels and organophosphate occupational exposure	Organophosphate (OP) pesticides divided into 3 groups: 1)Non-occupationally exposed 2) Agricultural workers but not OP sprayers 3) OP sprayers	Semen quality, concentration and count	The poorest semen quality (volume p=0.002, sperm count p=0.025) was found among the subjects in Group 3 compared to Group 1. The lowest sperm concentration and sperm counts were found in the spring when the highest OP spraying occurred and the highest sperm counts and concentration were found in the winter low spraying season.	
Snijder Hum Repro Update 2012 (10)	Systematic review	7 studies considering both male and female pesticide exposures	Overall chemical exposures	Occupational exposure	Time to pregnancy (TTP)	Adverse effects of occupational pesticide exposure on TTP based on reported fecundability ratios in 6 of 7 studies that included both male and female exposures.	
Swan Int J Andrology 2006 (60)	Case-control	25 cases and 25 controls at 4 US prenatal clinics between 1999 and 2001	Urinary pesticide metabolite levels	Alachlor, atrazine, metolachlor, acetachlor, 2,4-D, malathion, DEET and diazinon	Low sperm quality	Pesticide metabolite levels were elevated in cases compared with controls for the herbicides alachlor and atrazine, and for the insecticide diazinon (2-isopropoxy-4-methyl-pyrimidinol) (p-values for Wilcoxon rank test = 0.0007, 0.012, and 0.0004 for alachlor, atrazine and diazinon respectively). Men with higher levels of alachlor or diazinon were significantly more likely to be cases than men with low levels [odds ratios (OR) = 30.0 (CI 4.3-210), 16.7 (CI 2.8-98.0) for alachlor and diazinon respectively], as were men with atrazine over the limit of detection (OR = 11.3 (CI 1.3-98.9). Small sample size.	

Infertility and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Yoshinaga Andrology 2014 (65)	Cross-sectional	322 male university students in suburban Tokyo	Pyrethroid insecticides	Urinary [3-phenoxybenzoic acid (3-PBA)]	Serum levels of reproductive hormones (follicle-stimulating hormone, luteinizing hormone, testosterone, sex hormone-binding globulin, inhibin B and calculated free testosterone)	91% of participants had detectable 3-PBA. No association between urinary 3-PBA and serum reproductive hormone levels.	
Langer Endocrine Regulation 2014 (57)	Cross-sectional	248 males and 330 females aged 21-40 years (young) and 586 males and 889 females aged 41 to 75 years (old) in Eastern Slovakia	Serum levels	15 PCB congeners, p,p'-DDE and hexachlorobenzene (HCB)	Testosterone levels	Increased HCB levels were significantly associated with decreased testosterone levels in young and old males $p<0.01$. Also in diabetes and other endocrine.	

16.5 Preterm birth

Preterm birth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Cioroiu Sci Tot Environ 2010 (45)	Cross-sectional	63 mothers	Colostrum concentrations	Hexachlorocyclohexanes (HCHs) isomers and hexachlorobenzene (HCB)	Normal or preterm labor	No tests for significant differences between chemicals. The sum of hexachlorocyclohexanes (HCHs) isomers was slightly higher in preterm labor.	
Fenster Environ Health Persp 2006 (20)	Cohort	385 low-income Latinas in Salinas Valley, California	Maternal serum organochlorine levels	Hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCCH), γ-hexachlorocyclohexane (γ-HCCH), dieldrin, heptachlor epoxide, oxychlordane, *trans*-nonachlor, and mirex.	Length of gestation	There was a decreased length of gestation with increasing levels of lipid-adjusted HCB (adjusted β= –0.47 weeks; $p = 0.05$). No associations between other pesticides and gestation length. Also in fetal growth.	
Ferguson J Toxico Environ Health 2013 (46)	Comprehensive review			hexachlorobenzene (HCB) or hexachlorocyclohexane (HCH) and other organochlorines, non-persistent pesticides	Preterm birth	There is insufficient data to make conclusions about hexachlorobenzene (HCB) or hexachlorocyclohexane (HCH) and preterm birth but initial evidence suggest that there is only an association at level much higher than background United States level. No conclusions about other organochlorines. Mixed study findings for studies examining organophosphates and atrazine.	
Ochoa-Acuna Environ Health Perspec 2009 (15)	Retrospective cohort	24,154 births in Indiana from 1993 to 2007	Atrazine concentration in 19 water systems based on mother's residence at time of birth	Atrazine	Small-for-Gestational-Age (SGA) and preterm birth	No association with preterm birth. Also in fetal growth.	
Rauch Enviro Health	Prospective birth cohort	306 mother-infant dyads in	6 metabolites of organophosphate	Sum of the 6 metabolites (ΣDAP)	Birth weight and	A 10-fold increase in ΣDAP concentrations was associated with a	

Preterm birth and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
perspec 2012 (18)		Cincinnati, Ohio	insecticides obtained from two maternal urine samples.		gestational age at birth	decrease in covariate-adjusted gestational age [–0.5 weeks; 95% confidence interval (CI): –0.8, –0.1]. The relationship between ΣDAP concentrations and gestational age was stronger for white (–0.7 weeks; CI: –1.1, –0.3) than for African-American (–0.1 weeks; 95% CI: –0.9, 0.6) newborns.	
Rinsky Public Health Reports 2012 (47)	Retropective cohort	71,768 Kentucky births from 2004-2006	Atrazine levels in public drinking water divided in 3 exposure groups based on maternal county of residence	Atrazine	Preterm birth	An increase in the odds of preterm birth was found for women residing in the counties included in the highest atrazine exposure group compared with women residing in counties in the lowest exposure group, while control- ling for covariates. Analyses using the three exposure assessment approaches produced odds ratios ranging from 1.20 (95% confidence interval [CI] 1.14, 1.27) to 1.26 (95% CI 1.19, 1.32), for the highest compared with the lowest exposure group. Limitations in precision of exposure measurement.	
Villanueva Occup Environ Med 2005(16)	Retrospective cohort	3510 births that took place from 1 October 1997, to 30 September 1998 in France	Atrazine levels from 2661 water treatment plant samples over the last 10 years	Atrazine	Preterm delivery, low birth weight and small-for-gestational age	Atrazine levels in water were not associated with prematurity. Very low population exposure in general.	

16.6 Parkinson's disease

Parkinson's and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Freire Neurotoxicology 2012(78)	Systematic Review	23 case-control studies, 12 studies with other designs		Pesticide exposure	Parkinson Disease	Increased risk of PD in 13/23 case-control and 10/12 other design studies. Associations in six studies between PD and exposure to chlorpyrifos and organochlorines. Other studies show associations between PD and exposure to paraquat, maneb or a combination of the two. Frequent limitations to studies include the use of prevalent rather than incident cases, weak exposure assessment and the possibility of recall bias.	
Kamel AJE 2006 (79)	Cohort	83 prevalent and 78 incident cases of Parkinson's disease among a cohort of 55,931 Agricultural Health Study participants followed from 1993-1997 to 1999-2003	Self-reported occupational exposure	50 specific pesticides	Parkinson's disease	Incident PD was associated with cumulative days of pesticide use at enrollment (Q4 vs. Q1 OR 2.3 CI 1.2-4.5 p trend 0.009) and with trifluralin (OR 1.7 CI 1.0-3.2) and 2,4,5-T (OR 1.8 CI 1.0-3.3). Prevalent PD was associated with paraquat (OR 1.8 CI 1.0-3.4), cyanazine OR 2.6 CI 1.4-4.9) Prevalent PD was not associated with overall pesticide use. Incident or prevalent PD was not associated with ever pesticide use.	
Noyce Annal Neuro 2012(76)	Meta-analysis	36 case-control studies and 2 cohort studies		Ever exposure to pesticides	Incident Parkinson Disease	Summed RR 1.77 (CI 1.48-2.12) with exposure to pesticides.	
Parron Toxico Appl Pharm 2011(80)	Ecological	4 high pesticide use districts and 6 low	Pesticide sales	Pesticides sales and by insecticide, fungicide, herbicide and plant growth	Hospital discharge diagnosis of Parkinson's	Compared to the low pesticide use district, the high pesticide use districts had an increased prevalence OR for Parkinson's disease (PD) (OR 1.30 CI 1.22-1.39). After adjustment for age and gender, residence in	

Parkinson's and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		pesticide use districts in Spain		regulator	disease (PD),	high pesticide areas was not associated with Parkinson's. Also in depression and memory disorders.	
Pezzoli and Cereda Neurology 2013(74)	Meta-analysis	89 studies (6 cohort and 83 case-control)	Varied depending on study, included at least one risk value (RR or OR) and a confidence interval	Paraquat, **Maneb/mancozeb**, all pesticides, herbicides and solvents	Parkinson disease (PD)	PD significantly associated with farming and pesticides when diagnosis self-reported. In high quality case-controls studies PD risk increased with exposure to any pesticide (OR 1.58 (CI 1.34-1.86)), herbicide (OR 1.36 (CI 1.11-1.66)) or solvent (OR 1.58 (CI 1.23-2.04)) with no associations reported for fungicides, rodenticides, organochlorines and organophosphates. Paraquat (OR 1.72 (CI 1.28-2.32)) and **maneb/mancozeb (OR 2.18 (CI 1.19-3.98)** exposure associated with 2-fold increase in risk of PD. Inclusion of only high quality case-control studies resulted in no association being found between insecticides, farming and well water drinking and PD but a significant increase in risk for rural living (RR 1.51 (CI 1.13-2.03)). Cohort study association with farming (RR 1.33 (CI 1.14-1.56)). Exposure to higher lifetime doses and greater number of compounds increased risk of PD in general and having a high risk genotype and pesticide exposure increased risk of PD by 3- to 14-fold (not part of meta-analysis).	Well done meta-analysis., assessed any type exposure mainly plus several specific compounds using Cochran Q and P statistics and the Duval and Tweedie non-parametric trim and fill procdedure to adjust for publication bias.
van Maele-Fabry Enviro International 2012(77)	Meta-analysis	12 cohort studies		Occupational pesticide exposure	Parkinson Disease	Overall increased risk of Parkinson's with occupational pesticide exposure RR 1.28 (CI 1.03-1.59). Studies where a neurologist confirmed the PD diagnosis that considered plantations only, examined incident instead of prevalent PD and had participants	

Parkinson's and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						from outside North America or Europe had higher RRs. Herbicides, fungicides and paraquat were not found to be significant subclasses.	
van der Mark Enviro Health Persp 2012(75)	Meta-analysis	39 case-control studies, 4 cohort studies and 3 cross-sectional studies	Job based or self-reported	Any	Parkinson Disease	Overall RR 1.62 (CI 1.40-1.88) for ever versus no exposure. Job title measure made for higher RR (2.5 CI 1.5-4.1) than self-reported exposures (RR 1.5 (CI 1.3-1.8). Subclass estimates showed a significant association with herbicides (RR 1.40 CI 1.08-1.81) and insecticides (RR 1.50 CI 1.07-2.11) but not fungicides (RR 0.99 CI 0.71-1.40).	

16.7 ALS

Amyotrophic lateral sclerosis (ALS) and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Kamel Neurotoxicology 2012 (81)	Cohort and meta-analysis	41 cases from death certificates and 84,698 Agricultural Health Study controls plus 8 case-control studies in the meta-analysis	Self-reported farm exposure	Any use, organochlorines, pyrethroids, herbicides and fumigants with 50 specific pesticides	ALS	For the AHS cohort, there were no significant associations between any pesticides or pesticide classes.ALS was associated with any pesticide exposure (OR 1.9 CI 1.1-3.1) in the meta-analysis of published ALS studies.	
Pamphlett Eur J Neurol 2012(82)	Case-control	787 cases with Sporadic Motor Neuron Disease (SMND) and 778 non-related controls	Occupational herbicide or pesticide exposure	Any	Sporadic Motor Neuron Disease and ALS	Men were more likely to get SMND with occupational exposure to herbicides or pesticides (OR 1.96 CI 1.46-2.61). Herbicide and pesticide exposure were associated with ALS in men (OR 1.77 CI 1.30-2.39) and women (OR 1.43 CI 1.03-1.99).	

16.8 Memory disorders

Memory disorders and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Baldi Occup Environ Med 2011(68)	Cohort	929 French farmers followed from 1997-1998 to 2001-2003 (614 completed follow-up)	Lifelong pesticide exposure (directly exposed, indirectly exposed or non-exposed)	Occupational overall pesticide exposure	Nine neurobehavioral tests	Follow-up analysis confirmed that the risk of obtaining a low performance on the tests was higher in exposed participants, with ORs ranging from 1.35 to 5.60, with many including 1.0 in the lower CI. Evolution of performances over the follow-up period demonstrated that exposed participants had the worst decreases in performance. The risk of having a two-point lower score on the Mini-Mental State Examination (MMSE) was 2.15 (95% CI 1.18 to 3.94) in exposed subjects. Direct pesticide exposure was associated with an increased risk of worsening MMSE (OR 1.97 CI 1.09-3.59) and indirect exposure with a reduction on the STb (Stroop bad answers) (OR 2.08 CI 1.09-3.96).	
Hayden Neurology 2010(83)	Cohort	3,084 residents of Cache County, UT assessed at 3, 7 and 10 years	Occupational exposure to pesticides	Any, organophosphates, carbamates, organochlorines and methyl bromide	Cognitive status, incident dementia and Alzheimer's Disease (AD)	Pesticide exposure increased the risk of all-cause dementia (HR 1.38 CI 1.09-1.76) and AD (HR 1.42 CI 1.06-1.91). The risk of AD was higher with organophosphate exposure (HR 1.53 CI 1.05-2.23) than organochlorine exposure (HR 1.49 CI 0.99-2.24). All results adjusted for age, sex, education, genotype and baseline cognitive status.	
Ismail Occup Enviro Med 2012(67)	Meta-analysis	17 studies of agricultural workers	Organophosphate exposure	Chronic Low-level occupational organophosphate exposure	Neurobehavioral deficits	All tests and measures of the neurobehavioral functions of attention, visuomotor integration, verbal abstraction and perception constructs showed significant reductions for exposed participants. One out of three tests of memory, two of five tests of sustained	

Memory disorders and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						attention, and four of eight tests of motor speed constructs also showed significant reductions. The significant effect sizes are small or moderately large, ranging from −0.16 to −0.71.	
Kamel Enviromental Health Perspective 2005 (69)	Cross-sectional	18,782 male Caucasian pesticide applicators enrolled in the Agricultural Health Study 1993 to 1997	Self-reported occupational pesticide use	50 individual pesticides	23 neurologic symptoms in the domains of affect, cognition, sensory, motor, autonomic and other, experiencing 10 or more of the symptoms in the past year compared to less than 10	There were significant associations between experiencing more than 10 of the neurological symptoms in the past year and cumulative lifetime days of insecticide use: ORs 1.64 (CIs 1.36–1.97) for 1–50 days, 1.89 (1.58–2.25) for 51–500 days, and 2.50 (2.00–3.13) for > 500 days, compared with never users. Among insecticides, associations with greater than 10 neurological symptoms were strongest for organophosphates and organochlorines followed by carbamates and then by pyrethroids, with all categories having significant ORs. Also associated with greater than 10 neurological symptoms were fumigants [> 50 days, 1.50 (1.24–1.81)] and fungicides [> 50 days, 1.23 (1.00–1.50). Exposure to any pesticide was significantly associated with headache, tension, insomnia, irritability, dizziness, numbness in hands or feet, depression, difficulty concentrating, twitches in arms or legs, fast heart rate, poor balance, poor night vision, tremor in hands, blurred double vision, changes in smell or taste, difficulty speaking and loss of consciousness. Associations with all insecticides, organophosphates, organochlorines and fumigants are list but omitted here for brevity.	

Memory disorders and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Kamel Hum Experi Toxico 2007(71)	Cross-sectional	18,782 male Caucasian pesticide applicators enrolled in the Agricultural Health Study 1993 to 1997	Self-reported occupational pesticide use	50 individual pesticides	23 neurologic symptoms in the domains of affect, cognition, sensory, motor, autonomic and other, experiencing 10 or more of the symptoms in the past year compared to less than 10	There were significant associations between experiencing more than 10 of the neurological symptoms in the past year and the application of more than 65 lifetime days of pesticides use (ORs 1.1-1.2 Lower CI 1.0-1.1 Upper CI 1.3), application of insecticides (OR 1.8 CI 1.5-22), fungicides (OR 1.3 CI 1.2-1.4), and fumigants (OR 1.3 CI 1.2-1.4), use of organphosphates (OR 1.5 CI 1.3-1.7), organochlorines (OR 1.7 CI 1.6-1.9), carbamates (OR 1.4 CI 1.3-1.6) and pyrethroids (OR 1.3 CI 1.2-1.4). Herbicides were not associated with having more than 10 neurological symptoms in the past years. Significant dose-response relationships were apparent for insecticides, organophosphates or organochlorines.	
Mackenzie Ross Neurotoxicology 2010(72)	Cross-sectional	127 exposed sheep farmers and 78 controls	Self-reported work and exposure history	Organophosphates	Neuropsychological or psychiatric impairment (anxiety, depression, tests of memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for the effects of mood)	Exposed subjects performed significantly worse than controls on tests of memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for the effects of mood. Also in depression.	
Parron Txico Appl Pharm 2011(80)	Ecological	4 high pesticide use districts and 6 low pesticide use districts in Spain	Pesticide sales	Pesticides sales and by insecticide, fungicide, herbicide and plant growth regulator	Hospital discharge diagnosis of Alzheimer disease (AD), multiple sclerosis (MS), cerebral degeneration (i.e., Pick disease, frontotemporal dementia, senile dementia, hydrocephalus-induced	Compared to the low pesticide use district, the high pesticide use districts had an increased prevalence OR for Alzheimer disease (AD) (OR 2.10 CI 1.96-2.25), multiple sclerosis (MS) (OR 1.23 CI 1.05-1.43) and low prevalence OR for cerebral degeneration (OR 0.71 CI 0.65-0.77). After adjustment for age and gender, residence in high pesticide areas was associated with	

Memory disorders and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
					neural degeneration, Lewy bodies dementia), polyneuropathy (peripheral neuropathies of any kind), affective psychosis (manic, depressive, mixed type or bipolar disorders).	Alzheimer disease (AD) (OR 1.65 CI 1.52-1.80) and low prevalence OR for cerebral degeneration (OR 0.46 CI 0.42-0.50), affective psychosis (OR 0.71 CI 0.63-0.80) and polyneuropathies (OR 0.68 CI 0.58-0.79). Also in depression and Parkinsons.	
Rohlman Neurotoxicology 2007(70)	Cross-sectional	175 Hispanic adults (n=119) and adolescents (n=56)	Working in agricultural or working with pesticides	Self-reported occupational exposure	Neurobehavioral test battery consisting of 10 computer-based tests measuring attention, response speed, coordination and memory	For females, as years working in agriculture increased, performance on the Symbol-Digit and Reaction Time measures decreased; this effect was not significant for males. For males there was no effect on Symbol-Digit or Reaction Time. Scores on Digit Span forward and Digit Span reverse were significantly lower for men who had handled pesticides (0.51 points lower for forward, p = 0.02 and 0.52 points lower for reverse, p = 0.02). Match-to-Sample scores were also lower (2.04 points) for men who reported handling pesticides in the past compared to men who had never reported handling pesticides (p = 0.02). The percentage of hits on the Continuous Performance test also showed a decrease for men who handled pesticides (6.4 percentage points, p = 0.047). Men who reported mixing/applying pesticides in the past month had an average Match-to-Sample score 2.68 points lower than participants with no experience handling pesticides (p = 0.015). The percentage of hits and d-prime score for the Continuous Performance test also showed decreased performance, 15.8 percentage points on	

Memory disorders and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						percent hits and 0.79 points lower on d-prime score, for men mixing/applying pesticides in the past month compared to men with no pesticide handling ($p = 0.001$ and $p = 0.012$, respectively).	
Starks Neurotoxicol Teratol 2012(73)	Cross-sectional	701 male pesticide applicators between 2006 and 2008 in Agricultural Health Study Cohort		Ever-use and lifetime days of use of 16 OP pesticides	Neurobehavioral tests to assess memory, motor speed and coordination, sustained attention, verbal learning and visual scanning and processing	Ethoprop was significantly associated with reduced performance on a test of motor speed and visual scanning. Malathion was significantly associated with poor performance on a test of visual scanning and processing. There was significantly better test performance for five OP pesticides. Specifically, chlorpyrifos, coumaphos, parathion, phorate, and tetrachlorvinphos were associated with better verbal learning and memory; coumaphos was associated with better performance on a test of motor speed and visual scanning; and parathion was associated with better performance on a test of sustained attention. No strong overall associations noted.	
Zaganas Toxicology 2013(355)	Review				All memory disorders and Parkinson's	Mixed findings, used to locate three additional studies.	

16.9 Depression

Depression and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Beard Enviro Rese 2013(86)	Cohort	16,893 wives without	Use of pesticides	Ever use, use of 11 classes and 50 specific	Self-report of physician diagnosed	No association between the correct use of pesticides by	

Depression and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		depression in 1993-1997 and who completed a follow-up phone interview 2005-2010		pesticides by wives and husbands	depression	husbands or wives and female depression. Phenoxy and triazine herbicides were significantly inversely associated with depression (RRs 0.71 (CI 0.58-0.88) and 0.69 (CI 0.49-0.96) respectively, perhaps due to healthy worker effect. Other pesticides specifically associated with depression included metalaxyl (RR 1.61 CI 1.03-2.52) and permethrin for crops (RR 1.44 CI 1.02-2.03) and inversely associated with carbofuran (RR 0.31 CI 0.14-0.67), trifluralin (RR 0.71 CI 0.50-0.99), metribuzin (RR 0.47 CI 0.23-0.98), imazethapyr (RR 0.58 CI 0.35-0.95), cyanazine (RR 0.50 CI 0.30-0.84), atrazine (RR 0.61 CI 0.41-0.90) and 2,4-D (RR 0.72 CI 0.58-0.89).	
Beseler Enviro Health Persp 2008(85)	Case-control	534 cases and 17,051 controls in AHS 1993-1997	Lifetime pesticide exposure was categorized in three mutually exclusive groups: low (< 226 days, the reference group), intermediate (226–752 days), and high (> 752 days).	Any, Herbicides, insecticides, organophosphates, carbamates, organochlorines, fungicides, fumigants	Self-report of physician diagnosed depression	Regular lifetime pesticide exposure in the low, intermediate and high groups was not associated with depression but after excluding participants with pesticide poisoning events there was a significant association between high lifetime pesticide exposure and depression OR 1.54 (CI 1.16-2.04). Ever use of insecticides (OR 2.05 CI 1.29-3.27), organophosphates (OR 1.78 CI 1.27-2.5), organochlorines (OR 1.32 CI	

Depression and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						1.09-1.59), fungicides (OR 1.24 CI 1.01-1.53) and fumigants (OR 1.35 CI 1.07-1.69) were associated with depression.	
Beseler J Occup Enviro Med 2006 (88)	Case-control study nested within a cohort	29,074 female spouses of private pesticide applicators enrolled in the Agricultural Health Study 1993-1997.	Never mixed/applied pesticides, low pesticide exposure (up to 225 lifetime days), high exposure (more than 225 days)	Any	Self-report of physician diagnosed depression requiring medication	No association between depression and low or high cumulative pesticide exposure.	
Freire Int J Hyg Enviro Health 2013 (84)	Systematic review	11 studies on depression and 14 studies on suicide	Various	Various	Depression or anxiety	Significantly increase risk of suicide in 4 studies of areas of intensive pesticide use (ORs 1.30-4.13). Increased risk of suicide with agricultural occupation in 4 of 5 studies (ORs 1.30-4.13). Increased risk of suicide with lifetime use of chlorpyrifos (OR 2.37) in 1 study. Limited evidence for effects of chronic low dose exposure.	
Mackenzie Ross Neurotoxicology 2010(72)	Cross-sectional	127 exposed sheep farmers and 78 controls	Self-reported work and exposure history	Organophosphates	Neuropsychological or psychiatric impairment (anxiety, depression)	Over 40% of the exposed cohort reported anxiety and depression compared to less than 23% of controls. Also in memory disorders.	
Parron Toxico Appl Pharm 2011(80)	Ecological	4 high pesticide use districts and 6 low pesticide use districts in Spain	Pesticide sales	Pesticides sales and by insecticide, fungicide, herbicide and plant growth regulator	Suicide attempts.	Compared to the low pesticide use district, the high pesticide use districts had an increased prevalence OR for suicide attempt (OR 1.87 CI 1.67-2.08). After adjustment for age and	

Depression and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						gender, residence in high pesticide areas was associated with suicide attempt (OR 1.76 CI 1.49-2.08). Also in memory and Parkinson's.	
Weisskoft AJE 2013(87)	Cross-sectional	567 farmers aged 37 to 78 years	Self-reported pesticide use history	Herbicides, insecticides or fungicides	Self-reported treatment or hospitalization for depression	Herbicide use for over 19 years was associated with depression (Hazard Ratio (HR) 2.31 CI 1.05-5.10) but not with shorter use (<19 years, HR = 2.24 CI: 0.80- 6.25). No association with fungicide of insecticide use. Similar results with increasing intensity of herbicide use ((<137 hours, HR = 2.39 CI: 0.89-6.41; ≥137 hours, HR = 4.14 CI: 1.42-12.12).	

16.10 Neurodevelopmental and behavioural health outcomes in children

Neurologic outcomes in children and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Burns J Toxico Enviro Health part B 2013(356)	Review					Guide to evaluating epidemiological studies of human effects of pesticides.	
Jurewicz Int J Occup Med Enviro Health 2008(91)	Review	18 articles		All		Children exposed to organophosphate pesticides (OP), prenatally and during childhood, may have difficulties with short-term memory, and may show increased reaction time, impaired mental development or pervasive developmental problems. In newborns, the effects of OP exposure are mainly an increased number of abnormal reflexes, while adolescents show increased mental and emotional problems. Studies investigating association between exposure to organochlorine pesticides and neurodevelopmental effects have inconsistent results. No consistent impairments in mental and psychomotor functions are reported.	
Korrick Curr Opin Ped 2008(100)	Review	12 cohort studies		Organochlorines		Inconsistent results for the effect of organochlorines on human neurodevelopment. Limited associations between prenatal HCB exposure and ADHD-associated symptoms in Spanish but not US	

Neurologic outcomes in children and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						children.	
Liu Workplace Health 2012(357)	Review	No new information, includes studies already reviewed					
Rosas Curr Opin Ped 2008(101)	Review	7 studies		Organophosphates		Higher in-utero organophosphate exposure leads to an increased number of abnormal neonatal reflexes. Variable influences on psychomotor and mental development depending on the specific compound and age of measurement. Increased risk of pervasive development disorder.	

16.11 Neurologic outcome in newborns

Neurologic outcomes in children up to age 3 and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Rauh Pediatrics 2006(93)	Prospective cohort	254 children followed through the first 3 years of life	Chlorpyrifos levels in umbilical cord plasma	Chlorpyrifos	Cognitive and motor development at 12, 24, and 36 months (measured with the Bayley Scales of Infant Development II) and child behavior at 36 months (measured with the Child Behavior Checklist)	Children with high levels of chlorpyrifos (above 6.17pg/g plasma) scored 6.5 points (p=0.01) lower of the Bayley Psychomotor Dvelopment Index (BPDI) and 3.3 points (p=0.06) lower on the Bayley Mental Development Index (BMDI) by age 3. Also by age 3, they were more likely to have BPDI (OR 2.4 CI 1.12-5.08) and BMDI (OR 4.9 CI 1.78-13.72) delays, attention problems, ADHD problems and pervasive development disorder problems (all p<0.05).	
Horton Pediatrics 2011(95)	Cohort	A birth cohort of 348 infants in New York City	Permethrin levels measured in maternal and umbilical cord plasma collected on delivery and permethrin and piperonyl butoxide levels measured in personal air collected during pregnancy	Permethrin and piperonyl butoxide	36-month cognitive and motor development (using the Bayley Scales of Infant Development (BSID),second edition)	No association between Permethrin exposure and BSID score. Children highly exposed to piperonyl butoxide in their prenatal air samples (above 4.34ng/m^3) score 3.9 points (CI -0.25 to -7.49) lower on the Mental Development Index than lower exposure children.	

Neurologic outcomes in children up to age 3 and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Eskenazi Enviro Health Persp 2007(92)	Cohort	Birth cohort of Californian children assessed at 6 (n=396), 12 (n=395) and 24 (n=372) months	Six nonspecific dialkylphosphate (DAP) metabolites in maternal and child urine as well as metabolites specific to malathion (MDA) and chlorpyrifos (TCPy) in maternal urine	Organophosphates	Bayley Scales of Infant Development [Mental Development (MDI) and Psychomotor Development (PDI) Indices] and mother's report on the Child Behavior Checklist (CBCL)	At 24 months of age, prenatal DAP levels were negatively associated with MDI (per 10-fold increase in DAP beta=-3.5 points CI -6.6 to -0.5) but child DAP levels were positively associated with MDI (per 10-fold increase in DAP beta=2.4 points CI 0.5 to 4.2). Increase odds of pervasive development disorder for 10-fold increases in prenatal and child DAPs (prenatal OR 2.25 CI 0.99-5.16 child OR 1.71 CI 1.02-2.87).	

16.12 Neurologic outcomes in children up to age three

Neurologic outcomes in newborns and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Young Neurotoxico 2005(90)	Cohort	381 infants less than 2 months old	Urinary levels of dialkylphosphate (DAP) metabolites measured twice during pregnancy and post-delivery	Organophosphates	Brazelton Neonatal Behavioral Assessment Scale (BNBAS)	Among the >3 day old infants, increasing average prenatal urinary metabolite levels were associated with both an increase in number of abnormal reflexes (total DAP: adjusted b = 0.53, 95% CI = 0.23, 0.82) and the proportion of infants with more than three abnormal reflexes (total DAP: adjusted OR = 4.9, 95% CI = 1.5, 16.1).	
Engel AJE 2007(89)	Cohort	311 neonates in New York City	Urinary levels of six dialkylphosphate metabolites and Malathion Dicarboxylic Acid (MDA).	Organophosphates	Brazelton Neonatal Behavioral Assessment Scale (BNBAS)	There were an increased in number of abnormal reflexes with MDA levels above the LOD (OR 2.24 CI 1.55-3.24) and higher levels of total diethylphosphates (OR 1.49 CI 1.12-1.98) and total dialkylphosphates (OR 1.32 CI 0.99-1.77).	

16.13 Neurologic outcomes in children over age three

Neurologic outcomes in children over age 3 and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Puertas Neurotoxicology 2010 (97)	Cohort	Birth cohort (n=104) in Spain recruited 2000-2002	Mirex placenta levels	Mirex (OC)	McCarthy Scales of Children's Abilities (MSCA)	Prenatal exposure to detectable levels of mirex was associated with reduced working memory (beta -5.15 points, p=0.02) and reduced quantitative area score (beta -7.33 points, p=0.04) at age 4 years. No significant association between other areas of MCSA and prenatal mirex exposure.	
Rauh Enviro Health Persp 2011(94)	Cohort	265 children in New York City followed to age 7	Umbilical cord blood plasma levels of chlorpyrifos	chlorpyrifos	Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)	For each standard deviation increase in CPF exposure (4.61 pg/g), Full-Scale intelligence quotient (IQ) declined by 1.4% (p=0.02) and Working Memory declined by 2.8% (p<0.0001).	
Rauh PNAS 2012(358)	Cohort	40 children evaluated at 5.9-11.2 years	Chlorpyrifos in cord blood divided in low and high exposure groups	Chlorpyrifos	MRI of brain	Not included as MRI imaging studies not epidemiological studies.	
Ribas-Fitó Enviro Health Perspec 2007(96)	Cohort	2 birth cohort (n=475) in Spain between 1997-1999	Organochlorine levels in cord blood	Hexachlorobenzene	California Preschool Social Competence Scale and the Attention-Deficit Hyperactivity Disorder (ADHD) completed by teachers.	Children with higher concentrations of HCB (> 1.5 ng/mL) at birth had a statistically significant increased risk of having poor Social Competence scores [RR = 4.04; CI 1.76–9.58). No association was found between HCB and the cognitive and psychomotor performance of these children at age 4. Also in ADHD.	
Ruckart Enviro Health Perspec	Cohort	Children (n=147	urinary *para*-nitrophenol levels	organophosphate	Pediatric Environmental	No persistent deficits in PENTB scores between exposed and	

Neurologic outcomes in children over age 3 and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
2004(98)		Mississippi, 104 Ohio) exposed to illegally sprayed Methyl parathion (MP) as pest control and an unexposed comparison group (n= 218 Mississippi, n=183 Ohio)	and environmental wipe samples for MP		Neurobehavioral Test Battery (PENTB)	unexposed children who performed lower than expected in year 1 versus year 2. In individual tests did not show consistent differences in results between exposed and unexposed children. Effects were seen for task of short-term memory and attention and the frequency of behavioural and motor skill problems was higher. Interesting use of 90% CIs.	
Sioen Enviro Int 2013(99)	Cohort	270 children followed from birth to 7-8 years	Cord blood levels of HCB	Organochlorines	Strengths and Difficulties Questionnaire (SDQ)	No association between cord blood HCB levels and abnormal SDQ values at age 7 to 8 years.	

16.14 Pervasive developmental disorder (PDD) and autism

Pervasive developmental disorder (PDD) and autism and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
DeCock Acta Pedia 2012 (102)	Review	21 articles			Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD)	Increased risk of ASD with exposure to pesticides. Increased risk of ADHD with exposure to dialkyl phosphate and chlorpyrifos.	
Furlong Enviro Int 2014 (103)	Cohort	404 mother infant pairs with OP metabolite levels , 136 of whom completed the SRS	Urinary biomarkers of prenatal Organophosphate (OP) exposure	OPs	Impaired reciprocal behavior measured by the Social Responsiveness Scale (SRS), a 65-item (each on a 4 point scale) caregiver rating scale where higher score indicates poorer behavior	No significant associations overall or for whites, Hispanics or girls. Poorer social responsiveness for each 10-fold increased in OP metabolites in African-Americans (β=5.1 points CI 0.8-9.4) and boys (β=3.5 points CI 0.2-6.8).	
McGovern Enviro Health Persp Comment 2007 (106)	Discusses Roberts et al. (2007). Points out the small samples size that the conclusions are based on but also the interesting associations with organochlorine application and possible further study.						
Roberts Enviro Health Persp 2007 (104)	Case-control	465 cases and 6,975 controls in California	Proximity to residential pesticide application	54 specific individual pesticides according to application records	Autism Spectrum Disorder (ASD)	Application of dicofol and endosulfan during pregnancy weeks 1 to 8 was possibly associated with later development of ASD (no ORs provided). Children of mothers living within 500m of fields with highest quartile of organochlorine poundage compared to children of mothers not near field site had increased ASD risk (OR 6.1 CI 2.4-15.3).	
Roberts Stats in	Describes a Bayesian modeling approach to the Roberts et al. (2007) data.						

Pervasive developmental disorder (PDD) and autism and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Med 2012 (359)							
Shelton Enviro Health Perspec 2014(105)	Case-Control	970 participants (486 with autism spectrum (ASD), 168 with Developmental Delay (DD) and 316 controls)	Retrospective pesticide application reports during pregnancy in California	organophophates, organochlorines, pyrethroids, and carbamates	ASD, DD	Proximity within 1.25km to organophosphates at some point during gestation was associated with an increased risk for ASD (aOR 1.60 CI 1.02-2.51). Risk for DD was increased (aOR 2.48 CI 1.04-5.91) in those within 1.25km of carbamate applications, but no specific vulnerable period was identified. ORs decreased as the buffer zone increased. Risk of ASD was higher for third-trimester exposures to organophosphates (OR = 2.07 CI: 1.23- 3.50), and second-trimester chlorpyrifos applications (OR = 3.31 CI: 1.48- 7.42) within 1.5 km. Children of mothers residing near pyrethroid insecticide applications just before conception (ASD at 1.5km OR 1.82 CI 1.00-3.31) or during third trimester (ASD at 1.5km OR 1.87 CI 1.02-3.43 DD at 1.75km OR 2.34 CI 1.18-4.67) were at greater risk for both ASD and DD.	

16.15 Attention deficit disorders

Attention Deficit and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Bouchard Pediatrics 2010(108)	Cross-sectional	1,139 children age 8 to 15 years from the US National Health and Nutrition Examination Survey (2000-2004)	Urinary dialkyl phosphate (DAP) metabolites	Organophosphates	ADHD based on diagnostic criteria	A 10-fold increase in DMAP concentration was associated with an odds ratio (OR) for ADHD of 1.55 (CI 1.14–2.10), after adjusting for sex, age, race/ethnicity, poverty-income ratio, fasting duration, and urinary creatinine concentration.	
Fortenberry Int J Hyg Enviro Health 2014(112)	Cohort	187 mother-child pairs	In utero exposure to chlorpyrifos, chlorpyrifos- methyl, and/or 3,5,6-trichloro-2-pyridinol (TCPY) measured by third trimester urinary TCPY concentrations	Chlorpyrifos, chlorpyrifos- methyl	ADHD at age 6 to 11 assessed using Con-ners' Parental Rating Scales-Revised (CRS-R), Conners' Continuous Performance Test (CPT), and Behavior Assessment System for Children-2 (BASC-2)	There were no significant associations between tertiles of maternal TCPY concentrations and ADHD-related outcomes in children.	
Marks Enviro Health Persp 2010(109)	Cohort	Birth cohort of whom 331 children were assessed at age 3.5 and 323 children followed-up at age 5 living in California	Urinary dialkyl phosphate (DAP) metabolites	Organophosphates	ADHD measured by Child Behavior Checklist (CBCL), NEPSY- II visual attention sub- test to children at 3.5 years and the Conners' Kiddie Continuous Performance Test (K- CPT) at 5 years yielding a standardized attention deficit/hyperactivity	Prenatal DAPs were significantly related at age 5 years [CBCL attention problems: $\beta = 0.7$ points; CI 0.2–1.2; ADHD: $\beta = 1.3$; CI, 0.4–2.1]. Prenatal DAPs adjusted for sex and a number of other variables were associated with scores on the K- CPT ADHD Confidence Index > 70th percentile [OR =	

Attention Deficit and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
					disorder (ADHD) Confidence Index score .	5.1; CI, 1.7–15.7] and with a composite ADHD indicator of the various measures (OR = 3.5; CI, 1.1–10.7). Stratification by sex showed non-significant results for girls and increased risk of ADHD (OR 6.4 CI 1.1-39.0), K- CPT ADHD Confidence Index > 70th percentile (OR 10.1 CI 1.6-65.3), and composite ADHD indicator (OR 11.1 (CI 1.8-66.5) for boys. Wide CIs on the sex stratification. No significant associations on postnatal DAP concentrations and ADHD.	
Oulhote and Bouchard Enviro Health Persp 2014(107)	Cross-sectional	779 children aged 6 to 11 from the Canadian Health Measures Survey (2007-2009)	Urinary metabolites of organophosphates and pyrethroid pesticides	Pyrethroids and organophosphates	High scores on Strengths and Difficulties Questionnaire (SDQ) – higher scores may indicate behavioral problems	Organophosphate metabolites were not significantly associated with high SDQ scores. The pyrethroid metabolite *cis*-DCCA was significantly associated with high scores for total difficulties on the SDQ (OR for a 10-fold increase = 2.0 CI 1.1-3.6).	
Quirós-Alcalá Enviro Health Persp 2014(111)	Cross-sectional	1,659-1,680 children age 6 to 15participating in the US National Health and Nutrition	Urinary metabolite biomarkers	Pyrethroid	Parent reported Learning Disability (LD) and Attention Deficit/Hyperactivity Disorder (ADHD)	No significant association between parent-reported LD or ADHD and urinary pyrethroid exposure after adjustment for significant confounders.	

Attention Deficit and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		Examination Survey (1999-2002)					
Ribas-Fitó Enviro Health Perspec 2007(96)	Cohort	2 birth cohorts (n=475) in Spain between 1997-1999	Organochlorine levels in cord blood	Hexachlorobenzene	Attention-Deficit Hyperactivity Disorder (ADHD) completed by teachers.	Children with higher concentrations of HCB (> 1.5 ng/mL) at birth had a statistically significant increased risk of meeting ADHD diagnostic criteria (RR = 2.71 CI 1.05–6.96). Also in neurologic outcomes.	
Xu Occup Enviro Med 2011(110)	Cross-sectional	2546 children aged 6 to 15 years participating in the 1999-2004 National Health and Nutrition Examination Survey	Urinary trichlorophenols (2,4,5-TCP and 2,4,6-TCP, metabolites of hexachlorobenzene (HCB) and hexachlorocyclohexanes (HCH))	Organochlorine	Parent-reported ADHD	Children with high levels (>=3.58 mg/g) of urinary 2,4,6-TCP had a increased risk of parent-reported ADHD compared to children with levels below the limit of detection (OR 1.77, CI 1.18 to 2.66, respectively; p for trend 0.006 over undetectable, low and high categories) after adjusting for covariates. No association was found between urinary 2,4,5-TCP and parent-reported ADHD.	

16.16 Child IQ and Learning

Learning disorders, mental retardation and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Bouchard Enviro Health Perspec 2011(114)	Cohort	329 children in Salinas California	Dialkyl phosphate (DAP) urinary metabolites measured in pregnancy and at ages 6 months, 1,2, 3.5 and 5 years	Organophosphates	Wechsler Intelligence Scale for Children, 4th edition	Analyses were adjusted for maternal education and intelligence, Home Observation for Measurement of the Environment score, and language of cognitive assessment. A 10-fold increase in averaged maternal DAP concentrations were associated with poorer scores for Working Memory (β-4.3 CI -7.7 to -0.9), Processing Speed (β-3.4 CI -6.8 to -0.1), Verbal Comprehension (β-5.3 CI -8.6 to -2.0), Perceptual Reasoning (β-4.0 CI -7.9 to -0.1), and Full-Scale intelligence quotient (IQ) (β-5.6 CI -9.0 to -2.2). Children in the highest quintile of maternal DAP concentrations had an average deficit of 7.0 IQ points compared with those in the lowest quintile. However, children's urinary DAP concentrations were not consistently associated with cognitive scores.	
Engel Enviro Health Persp 2011 (113)	Cohort	404 mother infant pairs with OP metabolite levels, of whom completed 12 month (n=200), 24 months (n=276) and 6-9 year (n=169) assessments	Urinary biomarkers of prenatal organophosphate exposure	Prenatal total dialkylphosphate metabolite level	Cognitive development (Bayley Scales of Infant Development Mental Development Index (MDI) , 2nd edition, mean score of 100 and the Wechsler Intelligence Scales for	A 10-fold increase in prenatal total dialkylphosphate metabolite level was associated with a decrement in mental development at 12 months among African-Americans and Hispanics (β=-3.29 CI -5.88 to -0.70). The reverse pattern was present for whites (β=4.77 CI 0.69-8.86). A 10-fold increase in prenatal total dialkylphosphate metabolite level was not significantly associated with a decrement in mental development at 24 months. No significant changes in WIS scores at 6 to 9 years.	

Learning disorders, mental retardation and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
					Preschool and Children)		
Sanchez-Lizardi J Pedia Psycho 2008(115)	Cross-sectional	48 Hispanic children in an agricultural community in Southern Arizona	Urinary biomarkers	Organophosphate pesticides	Wisconsin Card Sorting Test and other cognitive measures	Higher OP concentration were associated with poorer speed of attention, sequencing, mental flexibility, visual search, concept formation, and conceptual flexibility. There were significant positive correlations between the OP metabolite concentration levels and the total Number of Errors made (r =.31, p= .03); the Number of Perseverative Responses (r=.34, p=.01); the Number of Perseverative Errors (r=.35, p=.01); the Conceptual Level Responses provided (r=.38, p=.01); and, the Failure to Maintain Set (r=.38, p=.02). The removal of the two highest samples made the results non-significant.	

16.17 Adult leukemia

Adult leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hoffman Mer J Indus Med 2008 (193)	Case-control	1,430 cases and 3,041 controls	Self-reported residential exposure and residential dust samples	Any	ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia; CMD, chronic myeloproliferative diseases; MM, multiple myeloma; plasmocytoma; NHL_{lowC}, lowgrade malignant non-Hodgkin's lymphoma, including chronic lymphocytic leukemia (CLL); NHL_{high}, highgrade malignant non-Hodgkin's lymphoma.	Results not reported by case/control status. Also in lymphoma.	
Jones Enviro Research 2014(194)	Cohort	37,099 Iowa women aged 55-65 at enrollment in 1986, 7262 living on a farm and 2744 in a rural area (not on a farm).	GIS residence addresses and crop acreage/pasture land within 750m of residence		Lymphohematopoietic cancers by cancer registry linkage	The risk of acute myeloid leukemia (AML) was higher among women living on farms (HR 2.23 CI: 1.25–3.99) but not with rural living compared with women living in towns of > 10,000 population. No significant associations between pasture or row crop acreage within 750m and AML, chronic lymphocytic leukemia, small lymphocytic leukemia, and overall leukemia risk. Also in lymphoma.	
Kokouva BMC	Case-control	354 cases and 455 sex-	Exposure to	Any	lymphohaematopoietic	Pesticide exposure was	

Adult leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Public Health 2011(196)		and age-matched hospital based controls.	pesticides via self-report from farming applications		cancers (LHC)	independently associated with total LHC cases (OR 1.41 CI 1.00 - 2.00, p trend=0.004) and leukemia (OR 2.05 CI 1.02-4.12, p trend=0.002) after controlling for age, smoking and family history (cancers, LHC and immunological disorders). Smoking during pesticide application increased to risk of LHC, myelodysplastic syndrome and leukemia and eating during pesticide application increased the risk of leukemia. No significant associations between LHC and the insecticide, fungicide or herbicide categories and the carbamates, organophosphates and organochlorine categories. Also in lymphoma.	
Merhi Cancer Causes Control 2007(192)	Meta-analysis	13 case-control studies published 1990 to 2005	Occupational pesticide exposure	Any	Non-Hodgkin lymphoma (NHL), leukemia and multiple myeloma	No significant association between occupational pesticide exposure and leukemia (OR 1.35 CI 0.9-2). Myelodysplastic syndromes were significantly related to pesticide exposure (OR 2.97 CI 1.67-5.31). Increased odds of combined hematopoietic cancers (OR 1.3 CI 1.2-1.5) with occupational pesticide exposure.	
Miligi Annl NY Acad Scien 2006(195)	Case-control	1925 cases and 1232 controls (random population sample)	Pesticide exposure by self-report	Any	Incident hematolym phopoietic malignancies	Non-Hodgkin's lymphoma (NHL) was significantly associated with the use of 2,4-D without protective equipment (OR 4.4 CI 1.1-29.1). No	

Adult leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						significant associations between NHL, leukemia, CLL and any pesticides use (including herbicides, fungicides, fumigants, insecticides, phenoxy herbicides, MCPA, 2,4-D (with protective equip)). Also in lymphoma.	
Mills et al. Cancer Causes and Control 2005 (197)	Nested case-control within a cohort study	131 cases of lymphohematopoeitic cancers (LHC) and 5 age-matched controls for each case from the cohort of 139,000 Hispanic farm workers in California	Linking county and month and crop of job history from union records with pesticide use reports from California Department of Pesticide Regulation	Methyl bromide, Diazinon, malathion, dchloro-propane, captan, simazine, **chlorothalonil**, mancozeb, methyl parathion, bitrofen, propyzamide, toxaphene, trifluralin, 2,4-D, Maneb	LHC, including non-Hodkins lymphoma (NHL) and lymphocytic and granulocytic leukemia	Elevated LHC risk in workers cultivating vegetables (OR 1.67 (CI 1.12-2.48)), increased risk of leukemia with mancozeb exposure (OR 2.35 (CI 1.12-4.95)) and toxaphene exposure (OR 2.20 (CI 1.04-4.65)). Increased risk in women for leukemia with exposure to malathion (OR 4.91 (CI 1.21-19.89)), **chlorothalonil** (OR 4.78 (CI 1.11-20.44)) and trifluralin (OR 4.51 (CI 1.24-16.38)). Also in lymphoma.	
Van Maele Cancer Cause Control 2007 (191)	Meta-analysis	17 cohort and 16 case-control studies published 1979 to 2005	Occupational pesticide exposure	Any	Myeloid leukemia (ML)	The overall meta-rate ratio estimate (meta-RR) for the cohort studies was 1.21 CI 0.99–1.48). After stratification of cohort studies by specific ML subtype, an increased risk of acute myeloid leukemia (AML) was found (meta-RR: 1.55; 95% CI: 1.02–2.34). An increased risk of chronic myeloid leukemia (CML) was found among men (meta-RR: 1.39 CI: 1.03–1.88) and farmers or agricultural workers (meta-RR:	

Adult leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						1.38 CI: 1.06–1.79).	

16.18 Lymphoma

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Bräuner Enviro Health Persp 2012 (216)	Case-control nested within a cohort	256 cases within a cohort of 57,053 Danish people and 256 random controls	Organochlorine concentration in pre-diagnostic adipose tissue	8 pesticides [*p*,*p*´-DDT, *p*,*p*´-dichloro-diphenyldichloroethylene (*p*,*p*´-DDE), β-hexachlorocyclohexane, dieldrin, hexachloro-benzene, *cis*-nonachlor, *trans*-nonachlor, and oxychlordane]	NHL	No significant association with interquintile range increases for cis-nonachlor (linear estimate OR 1.13 (CI 0.94-1.36),5th quintile significant OR 2.60 (CI 1.08-6.27)) and oxychlordane (linear estimate OR 1.11 CI 0.89-1.38, 3rd and 4th quintile ORs significant at 1.87 (CI 1.00-3.49) and 2.81 (CI 1.28-6.14) respectively). When stratified by sex, these associations remained significant only for men but with wide CIs and a non-significant Wald's test for interaction. Significant dose-response trend for cis-nonachlor in categorical models. No significant associations for ß-hexachlorocyclohexane, dieldrin, trans-nonachlor, hexachlorobenzene or the sum of the chlordanes,	
Cocco Occup Enviro Med 2008(219)	Case-control	174 cases of NHL and 203 controls	Serum levels	17 organochlorine pesticides	Non Hodgkin Lymphoma (NHL)	No evidence of an association between plasma organochlorine levels and NHL.	
Colt Cancer Epi Biomark Preven 2006(220)	Case-control	1,321 cases and 1,057 controls aged 20 to 74 years in Iowa, Los Angeles, Detroit and Seattle	Vacuum cleaner dust samples and questionnaires	Residential insecticide exposure	Non-Hodgkin Lymphoma (NHL)	Homes treated for termites had an elevated risk for NHL (OR 1.3 CI 1.0-1.6) but only for homes treated before the 1988 chlordane ban.Among respondents with carpet dust samples, there was a significant trend of increasing risk with increasing levels of α-chlordane (Ptrend = 0.04)	
Colt Epidemiology 2005(218)	Case-control	603 cases and 443 controls aged 20 to 74 years between 1998 and 2000 Iowa, Los Angeles,	Vacuum bag dust in subject who had owned most of their carpets for at least 5 years	Residential organochlorine exposure (chlordanes or pentachlorophenol)	Non-Hodgkin Lymphoma (NHL)	No significant associations between the chlordanes or pentachlorophenol and NHL.	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		Detroit and Seattle					
Cooper Enviro Health Persp 2008(200)	Review	15 adult case control studies (11 of pentachlorophenol and 4 of chlorophenol), 2 occupational cohort groups and 2 childhood cancer studies	Occupational or parental occupational exposure	Pentachlorophenol (fungicide) and chlorophenols	NHL, HL, Soft Tissue Sarcoma (STS), Multiple Myeloma, childhood leukemia, brain cancer and lymphoma	Case-control: NHL and Pentachlorophenol: 1 study with no association, 1 study with increased risk with high level exposure (1 week continuous or 1 month total) (OR 8.8 CI 3.4-24), NHL and chorophenols: 1 study increased risk only with fencing work (OR 2.0 CI 1.3-3.01) and second study with increased risk for wood preservers and manufacturers but not lumber graders NHL and HL and chlorophenols, 1 study no significant association STS and pentachlorophenols, 2 studies with no relevant cases, 1 study with no significant association, 2 studies with increased risk from high exposure to pentachlorophenols (OR 2.8 CI 1.5-2.4) in one and lumber grader (OR 2.7 CI 1.1-6.4) in another, meta-analysis of all 4 studies (OR 2.8 CI 1.5-5.4) MM and chlorophenols, 1 study with no association STS and chlorophenols, 4 studies, significant increased risk in 2 studies (OR 3.3-6.6) and with high exposure in a third (OR 5.24 CI 1.69-16.3) Cohort: 2 cohorts, 1 with no significant association, 2nd cohort showed significant increased risk NHL with 2-5 years exposure and 20 year latency (OR 2.1 CI 1.1-3.7), increased risk of MM with more than 5 years exposure and 20 year latency (OR 3.8 CI 1.2-12.3) and no association with liver cancer Also in child leukemia.	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
De Roos Cancer Research 2005 (217)	Case-Control	100 untreated cases and 100 controls aged 20 to 74 years between 1998 and 2000 Iowa, Los Angeles, Detroit and Seattle	Serum biomarker levels	13 organochlorines [p ,p V- DDE, o ,p V-DDT, p ,p V-DDT, aldrin, ß-hexachlorocyclohexane (ß-HCCH), γ-hexachlorocyclohexane (γ-HCCH), dieldrin, endrin, hexachlorobenzene (HCB), heptachlor epoxide, mirex, oxychlordane, and transnonachlor (tNONA)]	Non-Hodgkin Lymphoma (NHL)	No significant association between NHL and dieldrin,ß-HCCH, heptachlor epoxide, oxychlordane, and transnonachlor (tNONA).	
Eriksson Int J Cancer 2008 (213)	Case-control	910 cases and 1016 controls in Sweden from 1999 to 2002	Self-reported pesticide exposure	Multiple individual pesticides	Non-Hodgkin Lymphoma (NHL)	Exposure to herbicides was associated with an increased risk of NHL(OR 1.72, CI 1.18–2.51). For pheoxyacetic acids the highest risk was calculated for MCPA(OR 2.81CI 1.27–6.22) and all cases contributing to this had a latency period >10 years. Exposure to glyphosate was associated with NHL OR 2.02 (CI 1.10–3.71) and with >10 years latency period OR 2.26(CI 1.16–4.40). Removal of pheoxyacetic acids and glyphosate-exposed cases from the herbicide category rendered the association between herbicides and NHL non-significant. Impregnating agents (chlorophenols, arsenic, creosote, tar and others) were also associated with NHL(OR 1.57 CI 1.07–2.30).	
Fazzi Ann Hematol 2010 (221)	Ecological	370 deaths from NHL Province of Pisa, Italy from 1987 to 1992 (1st sample) and 281 NHL	Land use data used to calculate a cumulative concentration index (Cw) 1988-1990	Herbicide percolation	Non-Hodgkin Lymphoma (NHL)	Moderate correlation between geofunctional area herbicide percolation and NHL mortality rates (Spearman's rank test=0.355, $p<0.05$) in the 1st sample. In the 2nd sample, there was a statistically significant correlation ($\rho = 0.53$; $p < 0.0005$) between the standardized incidence rate of NHLs and Cw index, with most cases reported in areas with Cw> 12 µg/g and least cases reported in areas with Cw < 6. The	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		cases 1999-2003 (2nd sample)				correlation was observed for low-grade NHLs (ρ = 0.61, p < 0.0001), but not for high-grade NHLs (ρ=0.14, p=0.40).	
Hardell Oncology Reports 2009(214)	Case-control	99 cases of NHL and 99 population-based controls in Sweden	Serum levels	hexachlorobenzene (HCB), seven subgroups of chlordanes (cis-heptachlorepoxide, cis-chlordane, trans-chlordane, oxychlor- dane, MC6, trans-nonachlordane, cis-nonachlordane)	Non-Hodgkin Lymphoma (NHL)	High sum of chlordanes (OR 2.3 CI 1.2-4.5), oxychlordane (OR 2.1 CI 1.1-4.0), MC6 (OR 2.8 CI 1.4-5.6)and trans-nonachlordane (OR 2.4 CI 1.2-5.0) were associated with increased odds of NHL. There were increased odds of NHL with a combination of a high Epstein-Barr IgE antibody level and high level of HCB (high HCB OR 5.3 CI 1.9-15 vs. low HCB OR 3.9 CI 1.5-10) and sum of chlordanes (High sum chlordane OR 6.8 CI 2.3-20 versus low sum chlordane OR 1.8 CI 0.7-4.7).	
Hartge Cancer Epi 2005(222)	Case-control	1,321 cases and 1,057 controls aged 20 to 74 years between 1998 and 2000 Iowa, Los Angeles, Detroit and Seattle	Self-reported home herbicide use on homes occupied since 1970 and	Vacuum bag dust for 2,4-dichlorophenoxy-acetic acid and dicamba in subjects who had owned most of their carpets for at least 5 years (n=679 cases and 510 controls)	NHL	No association between self-reported herbicide use or vacuum bag dust sample of 2,4-D or dicamba herbicide levels and NHL.	
Hoffman Mer J Indus Med 2008 (193)	Case-control	1,430 cases and 3,041 controls	Self-reported residential exposure and residential dust samples	Any	ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia; CMD, chronic myeloproliferative diseases; MM, multiple myeloma; plasmocytoma	Results not reported by case/control status.	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
					; NHL_{lowC}, lowgrade malignant non-Hodgkin's lymphoma, including chronic lymphocytic leukemia (CLL); NHL_{high}, highgrade malignant non-Hodgkin's lymphoma.		
Hohenadel Int J Enviro Res & Public Health 2011 (206)	Case-control	513 newly diagnosed NHL cases and 1,506 frequency age and sex matched controls in 6 Canadian provinces	Lifetime exposure to more than 10 hours of pesticide use	Multiple pesticides	Non-Hodgkin Lymphoma (NHL)	In multiple logistic regression analyses, risk of NHL increased with the number of pesticides used (p trend= 0.01). Similar results were obtained in analyses restricted to herbicides (p trend= 0.02), insecticides (p trend <0.01), fungicides (p trend =0.04) and phenoxy herbicides (p trend =0.01) and organophosphates (p trend <0.01). Odds ratios increased further when only "potentially carcinogenic" pesticides were considered (OR[1 used] 1.30, CI 0.90–1.88; OR[2-4 used] 1.54, CI 1.11–2.12; OR[5 + used] 1.94, CI 1.17–3.23) with ORs at the top end of exposure being between 1.5 and 2.1. Elevated risks were also found among those reporting use of malathion in combination with several other pesticides (2,4-D OR 2.06 CI 1.45-2.93, Carbaryl OR 3.34 CI 1.77-6.31, DDT OR 2.11 CI 1.17-3.80, glyphosate OR 2.10 CI 1.31-3.37, mecoprop OR 3.04 CI 1.80-5.15) and mecoprop alone (OR 2.09 CI 1.23-3.54).	
Hossain J	Case-	357 cases and	Self-reported	Longest held job	STS	No significant association between being a farmer and	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Occup Enviro Med 2007 (209)	control	1474 controls aged 19 years and up from 6 Canadian provinces between 1991 and 1994	occupational pesticide exposure			STS. An analysis of specific types of farming found that chicken farmers had an increased risk of STS (OR 1.63 CI 1.11-2.38) compared to farmers of grain, mixed, beef, hogs, sheep, small animal, market garden, orchards, dairy, egg production, seed cleaning plant, nurseryman, gardener, greenhouse operator or landscaper. Doing ground maintenance at apartment complexes was also associated with an increased risk of STS (OR 2.18 CI 1.12-4.24) compared to at a government building or school. Forestry works or manufacturing of pesticides was not associated with STS.	
Jones Enviro Research 2014(194)	Cohort	37,099 Iowa women aged 55-65 at enrollment in 1986, 7262 living on a farm and 2744 in a rural area (not on a farm).	GIS residence addresses and crop acreage/pasture land within 750m of residence		Lymphohematopoietic cancers by cancer registry linkage	We observed no association between farm or rural residence and non-Hodgkin lymphoma (NHL; overall or for major subtypes), multiple myeloma.	
Kachuri Int J Cancer 2013 (204)	Case-control	342 Multiple Myeloma (MM) cases and 1,357 frequency-matched population controls in 6 Canadian provinces	Self-reported use of multiple pesticides, as a proxy for exposure, was classified in two different ways: total number of pesticides used and the self-reported days per year (days/year) of pesticide use.	Multiple pesticides	Multiple myeloma in Canadian men	Increased risks were observed for fungicides (Ptrend=0.04) and pesticides classified as probably carcinogenic or higher (Ptrend=0.03). Excess risks of MM were observed among men who reported using at least one carbamate pesticide (OR 1.94, CI 1.16–3.25), one phenoxy herbicide (OR 1.56, CI 1.09–2.25) and 3 or more organochlorines (OR 2.21, CI 1.05–4.66). Significantly higher odds of MM were seen for exposure to carbaryl (OR 2.71 CI 1.47–5.00), lindane (OR 2.37 CI 1.08-5.16) and captan (OR 2.96 CI 1.40–6.24). Use of mecoprop and carbaryl for >2 days per year was also significantly associated with MM and showed greater risk than the use of these products for less than 2 days per year (Mecoprop: OR 2.56 CI 1.17–5.64, Carbaryl: OR 3.33 CI 1.24-8.97).	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Karunanayake J Agromedicine 2012 (205)	Case-control	316 Hodgkin lymphoma cases diagnosed 1991-1994 and 1506 controls in 6 Canadian provinces	Lifetime exposure to more than 10 hours of pesticide use	Multiple pesticides	Hodgkin lymphoma	Increased risk of Hodgkin lymphoma with exposure to the insecticide chlorpyrifos (OR 1.19 CI 1.09-1.37), no associations with other insecticides were reported. These results are based on 6 exposed cases and 6 exposed controls only. No associations between Hodgkin lymphoma and herbicide exposure, fungicides and fumigants.	
Kokouva BMC Public Health 2011 (196)	Case-control	354 cases and 455 sex- and age-matched hospital based controls.	Exposure to pesticides via self-report from farming applications	Any	lymphohaematopoietic cancers (LHC)	Pesticide exposure was independently associated with total LHC cases (OR 1.41 CI 1.00 - 2.00, p trend=0.004) and leukemia (OR 2.05 CI 1.02-4.12, p trend=0.002) after controlling for age, smoking and family history (cancers, LHC and immunological disorders). Smoking during pesticide application increased to risk of LHC, myelodysplastic syndrome and leukemia and eating during pesticide application increased the risk of leukemia. No significant associations between LHC and the insecticide, fungicide or herbicide categories and the carbamates, organophosphates and organochlorine categories.	
Lope Can Epi Biomarkers 2008(223)	Retropective cohort	2,992,166 workers in which 3,127 men and 1,282 women were diagnosed from 1971-1989 in Sweden	Occupational exposure based on job exposure matrices	Any	Multiple Myeloma (MM)	Working in agriculture was associated with an increased risk of MM (RR 1.22 CI 1.09-1.37) in men but not significantly so in women (RR 1.70 CI 0.98-2.93). Increased risk of MM with occupations associated with pesticide use, primarily farming (RR 1.20 CI 1.07-1.34). Probable pesticide exposure was associated with an increased risk of MM in men (RR 1.20 CI 1.07-1.34) but not women although the results for women were based on only 8 cases (RR 1.29 CI (0.83-2.00).	
McDuffie BMC Cancer 2009(201)	Case-control	1528 cases (HL (n = 316), MM (n = 342), NHL (n = 513), STS (n = 357))	Self-reported pesticide exposure	More than 10 hours per year of pesticide exposure combined	Hodgkin lymphoma (HL), Multiple Myeloma (MM), non-Hodgkin's	A positive family history of cancer combined with more than 10 hours annually increased the risk of MM (OR 1.69 CI 1.14-2.51) and NHL (OR 1.72 CI 1.21-2.45) but not HL or STS.	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		and 1506 controls in 6 Canadian provinces			Lymphoma (NHL), and Soft Tissue Sarcoma (STS)		
McDuffie J Occup Enviro Med 2005 (208)	Case-Control	513 cases and 1506 controls aged 19 years and up from 6 Canadian provinces between 1991 and 1994 (a farmer subset analysis of 235 cases and 673 controls also used)	Self-reported insect repellent or herbicide use	Insect repellents containing DEET, phenoxy herbicides (2,4-D, mecoprop, and MCPA), dicamba and the use of gloves by the 235 cases and 673 controls who lived/worked on a farm	NHL	For the entire study, NHL risk was increased with the simultaneous use of DEET and either mecoprop (OR 2.05 CI 1.30-3.21) or dicamba (OR 1.81 CI 1.23-2.75). Information about PPE use by farmers, limited PPE use other than gloves. In farmers, exposure to any phenoxy herbicide with the use of DEET and rubber gloves increased the risk of NHL (OR 1.99 CI 1.06-3.74). In farmers, exposure to mecoprop with the use of DEET and rubber gloves increased the risk of NHL (OR 3.86 CI 1.57-9.49). Exposure to dicamba with the use of DEET and rubber gloves increased the risk of NHL (OR 2.04 CI 1.02-4.06). No significant increase in NHL risk with the use of herbicides alone or the use of DEET alone.	
Merhi Cancer Causes Control 2007(192)	Meta-analysis	13 case-control studies published 1990 to 2005	Occupational pesticide exposure	Any	Non-Hodgkin lymphoma (NHL), leukemia and multiple myeloma	A significant increase in risk of NHL (OR 1.35 CI 1.2-1.5) but not multiple myeloma (OR 1.16 CI 0.99-1.36). Long periods of pesticide exposure increased the OR for NHL to 1.65 (CI 1.08-2.51). Increased odds of combined hematopoietic cancers (OR 1.3 CI 1.2-1.5) with occupational pesticide exposure.	
Miligi Annl NY Acad Scien 2006 (195)	Case-control	1925 cases and 1232 controls (random population sample)	Pesticide exposure by self-report	Any	Incident hematolym phopoietic malignancies	Non-Hodgkin's lymphoma (NHL) was significantly associated with the use of 2,4-D without protective equipment (OR 4.4 CI 1.1-29.1). No significant associations between NHL, leukemia, CLL and any pesticides use (including herbicides, fungicides, fumigants, insecticides, phenoxy herbicides, MCPA, 2,4-D (with protective equip)). Also in leukemia.	
Mills et al. Cancer Causes and Control	Nested case-control within a	131 cases of lymphohemato poeitic cancers (LHC) and 5	Linking county and month and crop of job history from	Methyl bromide, Diazinon, malathion, dchloro-propane, captan,	LHC, including non-Hodkins lymphoma	Elevated LHC risk in workers cultivating vegetables (OR 1.67 (CI 1.12-2.48)), NHL risk increased with 2,4-D exposure (OR 3.80 (CI 1.85-7.81)). No associations for multiple myeloma (n=20 only). Increased risk in	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
2005 (197)	cohort study	age-matched controls for each case from the cohort of 139,000 Hispanic farm workers in California	union records with pesticide use reports from California Department of Pesticide Regulation	simazine, **chlorothalonil**, mancozeb, methyl parathion, bitrofen, propyzamide, toxaphene, trifluralin, 2,4-D, Maneb	(NHL) and lymphocytic and granulocytic leukemia	women for NHL with exposure to methyl bromide (OR 3.78 (CI 1.11-12.82)). Note increased risks for female farm workers. Also in leukemia.	
Navaranjan Cancer Causes Control 2013(203)	Case-control	316 male cases and 1,506 male age-matched population controls in Cross-Canada Study of Pesticides and Health	Self-reported use	Any	Hodgkin Lymphoma (HL)	Increase in HL risk with use of 3+ probably carcinogenic pesticides (OR 2.47 CI 1.06-5.75, work-related OR 3.36 CI 1.33-8.52). Increased HL risk with those less than 40 years reporting use of 2 acetylcholinesterase inhibitors (OR 3.16 CI 1.02-9.29,), work-related only (OR 11.15 CI 1.15-108.2). No association between the use of herbicides or phenoxy or urea herbicides. There was an increased risk of HL in those less than 40 years with the occupational use of 2 to 4 fungicides (OR 4.72 CI 1.08-20.6, p trend 0.02) and 2 to 4 (but not 5+ where there were small numbers (OR 2.27 CI 0.54-9.61)) insecticides (OR 1.98 CI 1.10-3.56, p trend 0.02).	
Orsi Occup Enviro Med 2009(199)	Case-control	491 cases (244 cases of non-Hodgkin's lymphoma (NHL), 87 of Hodgkin's lymphoma (HL), 104 of lymphoproliferative syndromes (LPS) and 56 of multiple myeloma (MM) cases) and 456	Occupational and non-occupational pesticide exposure by questionnaire		Non-Hodgkin's lymphoma (NHL),Hodgkin's lymphoma (HL), lymphoproliferative syndromes (LPS) and multiple myeloma (MM)	Significant associations between HL and occupational exposure to triazole fungicides (OR 8.4 CI 2.2–32.4), and urea herbicides (OR10.8 CI 2.4–48.1). Exposure to insecticides, fungicides and herbicides were linked to a three-fold increase in risk of MM (ORs 2.8 [1.2–6.5], 3.2 [1.4–7.2], 2.9 [1.3– 6.5] respectively). For LPS subtypes, associations restricted to hairy-cell leukaemia (HCL) were evidenced for exposure to organochlorine insecticides (OR 4.9 CI 1.1–21.2), phenoxy herbicides (OR 4.1 CI 1.1–15.5), and triazine herbicides (OR 5.1 CI 1.4–19.3), although these findings were based on small numbers. No association between non-occupational pesticides exposure and NHL, HL, LPS or MM. Difficulty due to crossover between types and classes of pesticides for farmers. One of the only studies where the power was calculated.	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		controls in France between 2000 and 2004					
Pahwa BMC Cancer 2009 (207)	Case-control	316 newly diagnosed HL cases and 1,506 frequency age and sex matched controls in 6 Canadian provinces	Lifetime exposure to more than 10 hours of pesticide use	Multiple pesticides	Hodgkin Lymphoma (HL) and ethnicity	Exposure to the herbicide dichlorprop showed an increased risk of HL (OR 6.35CI 1.56– 25.92).	
Pahwa et al. J Occup Environ Health 2006 (202)	Case-control	Males over age 19 with Hodgkin lymphoma (n=316) , multiple myeloma (n=342) and soft tissue sarcoma (n=357) and age matched provincial controls (n=1506)	Telephone interview-exposure to home/garden pesticides and commercial pesticide use by days per year of use and average acres sprayed per year.	Any phenoxyherbicide exposure and specifically for: 2,4-D, mecoprop and **MCPA** (included an analysis of the use of DEET and rubber gloves (i.e. the DEET repellent making the gloves less effective))	Hodgkin lymphoma, multiple myeloma and soft tissue sarcoma	Exposure to **MCPA** significantly increased risk of multiple myeloma (OR 1.66 (CI 1.02-2.71). No significant associations between Hodgkin lymphoma and soft tissue sarcoma and any specific pesticide use. See also in lymphoma. Recall bias with ill cases and general population controls	
Pahwa J Agromedicine 2012(211)	Case-control	342 male cases and 1506 male controls aged 19 years and up from 6 Canadian provinces	Self-reported pesticide exposure	Pesticide exposure more than 10 hours per year	MM	Exposure to carbamate insecticides was associated with an increased risk of MM (OR 1.90 CI 1.11-3.27). Exposure to fungicide captan (OR 2.35 CI 1.03-5.35), insecticides carbaryl (OR 2.43 CI 1.31-4.49) and herbicide mecoprop (OR 1.89 CI 1.15-3.12) was also associated with an increased risk of MM. Exposure to herbicides, including phenoxys (2,4-D, MCPA, diclopmethyl), phosphonic acid (glyphosphate),	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		between 1991 and 1994				thiocarbamates (diallate, phenols), dicamba, dinitroanilines (trifluralin) was not associated with MM. Exposure to insecticides, including carbamates (carbofuran, methomyl), organochlorines (chlordane,lindane, aldrin, methoxychlor) and organophosphates (malathion, dimethoate, diazinon) was not associated with MM. Exposure to fungicides, including amide (vitavax), aldehyde (formaldehyde), mercury containing (mercury dust, mercury liquid, sulphur compunds) and fumigants (carbon tetrachloride and malathion) was not associated with MM. The OR for carbaryl increased with more than 2 days per year of use (OR 3.26 CI 1.2508.48) whereas the OR for captan decreased (OR 2.22 CI 0.66-7.44).	
Pahwa Occup Enviro Med 2011 (210)	Case-control	357 male cases and 1474 male controls aged 19 years and up from 6 Canadian provinces between 1991 and 1994	Self-reported pesticide exposure	Participants with pesticide exposure more than 10 hours per year and a 15% sample of the remainder of participants	STS	Exposure to organochlorine aldrin (OR 3.71 CI 1.00-13.76) and organophosphate diazinon (OR 3.31 CI 1.78-6.23) were significantly associated with STS. Exposure to herbicides, including phenoxys (2,4-D, MCPA, mecoprop, diclopmethyl), phosphonic acid (glyphosphate), thiocarbamates (diallate, phenols), dicamba, dinitroanilines (trifluralin) was not associated with STS. Exposure to insecticides, including carbamates (carbaryl, carbofuran, methomyl), organochlorines (chlordane, lindane, methoxychlor) and organophosphates (malathion, dimethoate, diazinon) was not associated with STS. Exposure to fungicides, including amide (captan, vitavax), aldehyde (formaldehyde), mercury containing (mercury dust, mercury liquid, sulphur compounds) was not associated with STS. For diazinon exposure, use 0 to 2 days a year was associated with great odds of STS (OR 4.28 CI 1.70-10.79) than use more than 2 days a year (OR 2.68 CI 1.15-6.27).	
Schinasi Int J Enviro Res	Meta-analysis	44 studies	Occupational pesticide exposure	21 pesticide groups and 80 individual pesticides	Non-Hodgkin lymphoma (NHL)	Random effects meta-analyses showed that phenoxy herbicides (Meta-RR (mRR) 1.4 CI 1.2-1.6), carbamate /thiocarbamate herbicides (mRR 1.4 CI 1.1-2.0),	

Lymphoma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Public Health 2014 (212)						organophosphorus insecticides (mRR 1.6 CI 1.4-1.0), triazine herbicides (mRR 1.5 CI 1.0-2.1), carbamate insecticides (mRR 1.7 CI 1.3-2.3), organochlorine insecticides (mRR 1.3 CI 1.0-1.5) were positively associated with NHL The pesticides lindane (mRR 1.6 CI 1.2-2.2), dicamba (mRR 1.4 CI 1.0-2.1), 2,4-D (mRR 1.4 CI 1.0-1.9), carbaryl (mRR 1.7 CI 1.3-2.3), carbofuran (mRR 1.6 CI 1.2-2.3), glyphosphate (mRR 1.5 CI 1.1-2.0), diazinon (mRR 1.6 CI 1.2-2.2), malathion (mRR 1.8 CI 1.4-2.2) were positively associated with NHL. B cell lymphoma was positively associated with phenoxy herbicides (mRR 1.8 CI 1.2-2.8) and the organophosphorus herbicide glyphosate (mRR 2.0 CI 1.1-3.6). Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide (mRR 2.0 CI 1.1-3.7) exposure.	
Viel Environment International 2011(215)	Case-control	34 newly diagnosed cases and 34 controls who are neighbours to a municipal solid waste incinerator	Serum concentration of pesticides	Organochlorine pesticides (hexachlorobenzene [HCB], β- and γ-hexachlorocyclohexane [HCCH], oxychlordane, trans-nonachlor, cis-nonachlor, p,p'-dichloro-diphenyl-dichloroethylene [DDE], o,p'-dichloro-diphenyl-trichloroethane [DDT], p,p'-DDT, and mirex),	Non-Hodgkin Lymphoma	Increased ß-hexachlorocyclohexane levels were associated with increased NHL risk (OR 1.05 CI 1.00-1.12).	

16.19 Adult brain cancer

Adult brain cancer and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Carréon Enviro Health Persp 2005(154)	Case-control	342 cases and 528 controls, all females aged 18-80 living in non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin from 1995 to 1997	Self-reported exposures prior to Jan 1, 1993	arsenicals, benzoic acids, carbamates, chloroacetanilides, dinitroanilines, inorganics, organochlorines, organophosphates, phenoxys, triazines, carbamates, urea-based and estrogenic pesticides	Glioma	No significant associations between pesticide exposure in women and gliomas.	
Lee Occup Enviro Med 2005 (155)	Case-control	251 cases and 498 controls age, sex and frequency matched marital states diagnosed or selected between 1988 and 1993 in Nebraska, US	Self-reported use prior to 1985 (Cases were 76% proxy interviews and controls were 60% proxies, all close relatives)	Any pesticides, pesticides by class and individual pesticides (multiple pesticides)	Glioma	Brain cancer risk was increased among adult male farmers when insecticides (OR 1.8 CI 1.0-3.0), herbicides (OR 1.7 CI 1.0-3.0), or nitrosatable pesticides (OR 1.9 CI 1.1-3.4) were used on the farm on where they lived or worked. Associations were also reported for the organochlorine, organophosphate, dinitroaniline, phenoxy and triazine classes but these were only significant for proxy respondents. ORs for glioma were significantly increased for the herbicides metribuzin (OR 3.4 CI 1.2-9.7) and paraquat (OR 11.1 CI 1.2-101), and for the insecticides bufencarb (OR = 18.9CI 1.9-187), chlorpyrifos (OR = 22.6 CI 2.7-191), and coumaphos (OR = 5.9CI 1.1-32), but these estimates were imprecise and based	

Adult brain cancer and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						on small numbers of exposed participants.	
Provost Occup Enviro Med 2007 (156)	Case-control	221 cases and 442 individually matched controls between 1999 and 2001 in southwestern France	Occupational pesticide exposure	Cumulative index based on lifelong jobs and tasks	Glioma and meningioma	In the highest quartile of the cumulative index, a significant association was found for brain tumors (OR 2.16 CI 1.10-4.23) and for gliomas (OR 3.21 CI 1.13-9.11), but not for meningiomas. A significant increase in risk for all brain tumors was also seen for the treatment of home plants (OR = 2.24, 95% CI 1.16 to 4.30).	
Ruder AJE 2009 (157)	Case-Control	288 cases and 474 controls aged 18-80 living in non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin from 1995 to 1997	Exposure to crops livestock and farm tasks		Glioma	There was an increased risk of glioma in farmers who never immediately washed up (OR 3.08 CI 1.78-5.74) or changing clothes (OR 2.84 CI 1.04-7.78) after applying pesticides. The use of pentachlorophenol as a wood preservative was significant (OR 4.55 CI 1.14-18.1) when proxy respondents were excluded and was based on small numbers (6 cases and 11 controls).	
Ruder Arch Enviro Health 2004 (158)	Case-control	457 cases and 648 controls males aged 18-80 living in non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin from 1995 to 1997	Self-reported exposure	12 specific pesticides	Histologically confirmed primary intracranial glioma	No positive significant associations found between glioma and the 12 specific pesticides. There were significant inverse relationships with several pesticides.	
Samanic AJE 2008 (159)	Case-control	462 glioma cases, 195 meningioma	Self-reported occupational pesticide	Herbicides, insecticides	Glioma and meningioma	No association between insecticide and herbicide exposures and risk for glioma for men and women and	

Adult brain cancer and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		cases and 765 controls with non-malignant conditions admitted to 2 US hospital	exposure			meningioma for men. Women who reported ever using herbicides had a significantly increased risk of meningioma (OR 2.4 CI 1.4-4.3) with significant trends for increase years of exposure and increasing cumulative exposure (both p=0.01).	
Yiin Enviro Health 2012 (160)	Case-control	798 cases and 1,175 controls aged 18-80 living in non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin from 1995 to 1997	Quantitative estimates of lifetime occupational pesticide exposure	Individual pesticides	Histologically confirmed primary intracranial glioma	No positive significant associations between glioma and cumulative years or estimated lifetime cumulative exposure of farm pesticide use. There were significant inverse relationships with several pesticides.	
Ruder J Agri Safety and Healthy 2006 (161)	Case-control	798 cases and 1,175 controls aged 18-80 living in non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin from 1995 to 1997	Quantitative estimates of lifetime occupational pesticide exposure	Individual pesticides	Histologically confirmed primary intracranial glioma	No positive significant associations with living on a farm or ever use of pesticides, insecticides, herbicides or fungicides.	

16.20 Kidney cancer

Kidney cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Karami Cacinogenesis 2008 (190)	Case-control	1097 cases and 1476 control from Central and	Self-reported and job matrix occupational	Any	Renal Cell Carcinoma (RCC)	A significant increase in risk of RCC for participants ever exposed to pesticides (OR 1.60 CI 1.00-2.55)	

Kidney cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		Eastern Europe between 1999 and 2003	pesticide exposure information on all jobs held for at least 12 months			with significant trends for increasing years (p=0.01), hours (p=0.03) and cumulative exposure index (p=0.04). Using only high confidence exposures strengthened the association between pesticides exposure and RCC (OR 1.82 CI 1.10-3.00).	

16.21 Childhood leukemia

Child leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Alderton AJE 2006(288)	Case-control	158 cases with leukemia and Down's syndrome and 173 controls with Down's syndrome	History of maternal or child exposure to pest extermination or any pesticides	Any	Childhood ALL or AML in the presence of Down's syndrome	Increased risk of ALL with maternal exposure to professional pest extermination (OR 2.25 CI 1.13-4.19) or any pesticide (OR 2.18 CI 1.08-4.39). Associations with AML were non-significant. No association between childhood pesticide exposures and AML of ALL.	
Bailey Int J Cancer 2014(286)	Meta-analysis	13 case-control studies participating in the Childhood Leukemia International Consortium conducted over 30 years prior to 2012 in North America, Europe and Austalasia	Maternal, paternal occupational pesticide exposure	Any (ALL Maternal data for 8,236 cases and 14,850 controls and paternal data for 8,169 cases and 14,201 controls & AML Maternal data for 1,329 cases and 12,141 controls and paternal data for 1,231 cases and 11,383 controls)	ALL and AML	No association between maternal pesticide exposure during pregnancy and ALL (OR 1.01 CI 0.78-1.30). Increased risk of ALL with paternal exposure around conception (OR 1.20 CI 1.06-1.38). Increased risk of AML with maternal exposure during pregnancy (OR 1.94 CI 1.19-3.18) but not with paternal exposure around conception (OR 0.91 CI 0.66-1.24).	
Cooper Enviro Health Persp 2008(200)	Review	15 adult case control studies (11 of pentachlorophenol and 4 of chlrorophenol), 2 occupational cohort groups and 2 childhood cancer studies	Occupational or parental occupational exposure	Pentachlorophenol (fungicide) and chlorophenols	childhood leukemia, brain cancer and lymphoma	Leukemia and pentachlorophenol: 1 cohort study found no association, 1 case-control found significant associations for leukemia risk but they were based on very small numbers (upper end of CI over 100 for all estimates). Also in lymphoma.	

Child leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Glass Occup Enviro Med 2012 (294)	Case-control	Occupational information from 378 mothers and 327 fathers of ALL cases and 854 mothers and 748 fathers of controls 2003-2006	Occupational maternal and paternal pesticide exposure before and around time of conception, during pregnancy and for 1 year post-partum	Any	ALL	No association between paternal pesticide exposure and ALL. Insufficient sample size to make conclusions about maternal exposures.	
McNally Leukemia & Lymphoma 2006(289)	Review	4 case-control studies		Any	Childhood leukemia	Three of 4 case-control studies report increased risk of childhood leukemia with exposure to pesticides. Specifically, increased risks of leukemia were reported with domestic use of insecticides (OR 2.6 CI 1.2-5.7), pesticide use on farms (OR 1.5 CI 1.0 2.2), agricultural use of metam sodium (OR 2.05 CI 1.01-4.17) and diocofol (OR 1.83 CI 1.05-3.22). One new study (Reynolds et al. 2005) identified.	
Menegaux Occup Enviro Med 2006 (290)	Case-control	280 incident cases of acute leukemia and 288 controls matched on gender, age, hospital and ethnic origin	Parental occupational history, home and garden insecticide use and insecticidal treatment of pediculosis.		Acute leukemia	Acute leukemia was significantly associated with maternal home insecticide use during pregnancy (OR 1.8 CI 1.2-2.8) and during childhood (OR 1.7 CI 1.1-2.4), and with garden insecticide use (OR 2.4 CI 1.3-4.3) and fungicide use (OR 2.5 CI 1.0-6.2) and insecticidal treatment of more than one episode of pediculosis (OR 1.9 CI 1.2-3.3) during childhood. No associations with garden herbicide exposure, No analysis of occupational exposure due to small numbers. Sample size calculation reported.	

Child leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Metayer et al. H Exposure Science and Evnviro Epi 2013 (287)	Case-control	269 acute lymphoblastic leukemia (ALL) cases and 333 healthy controls less than 8 years of age and living in the same residence since diagnosis or study entry in California	Dust samples from homes collected using high volume surface samplers or household vacuum bags.	Commercial (alachlor, metolachor, bromoxynil, bromoxynil octanoate, pebulate, butylate, prometryn, simazine, ethalfluralin and pendimethalin) and residential (cyanazine, trifluralin, 2-methyl-4-chlorophenoxyacetic acid (**MCPA**), mecoprop, 2,4-dichlorophenoxyacetic acid (2,4-D), chlorthal and dicamba)	Childhood ALL	Significant trend of increased risk of ALL with dust levels of chlorthal (p=0.05). No individual ORs were significant. No other herbicides were significant for an association with childhood ALL.	Marginal significance of findings. Does eliminate recall bias with dust sampling.
Reynolds Epidemiology 2005 (279)	Case-control	2189 cases and 4335 controls matched for birth date and sex	Mother's residential proximity to agricultural applications of pesticides at the time of child's birth	Specific chemicals and chemical groups used within 0.5 miles of maternal residence divided in low (0 to 49th percentile) and high (50th percentile and up) and when numbers allowed very high (90th percentile and up) exposure	Early childhood cancer and leukemia risk	90% of residences had less than 1lb per square mile applied of specific chemicals and 70% had less than 1lb per square mile of chemical groups. High use of metam sodium increased ALL risk (OR 3.28 CI 1.37-7.86), leukemia risk (OR 2.05 CI 1.01-4.17). High use of dicofol increased leukemia risk (OR 1.83 CI 1.05-3.22). Low use of carbamates increased leukemia risk (OR 1.39 CI 1.04-1.86) but not high use (OR 1.08 CI 0.80-1.47). In childhood brain cancer and general cancer.	

Child leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Rull Enviro Res 2009(291)	Case-control	213 ALL cases and 268 matched controls	Child's residential proximity to agricultural applications of pesticides during the first year and to the date of diagnosis	Specific chemicals and chemical groups used within 0.5 miles of maternal residence	ALL	Sample size too small to estimate specific pesticides and many estimates lacked precision. Increased risk of ALL for moderate lifetime fumigant (OR 1.7 CI 1.0-3.1), chlorinated phenols (OR 2.0 CI 1.0-3.8), organophosphates (OR 1.6 CI 1.0-2.7), triazines (OR 1.9 CI 1.0-3.7) and urea pesticides (OR 2.3 CI 1.0-5.3) exposure but not high exposure. Lifetime exposure to moderate but not high levels of pesticides classified as probable carcinogen, possible carginogens, probable or possible carcinogens, cholinesterase inhibitors and suspected genotoxins was associated with slightly increased risk of ALL (ORs 1.5 to 1.6 CIs 1.0 to 2.3-2.7). Only probable carcinogens were associated with ALL in the first year of life (OR 1.9 CI 1.0-3.4). After adjustment for other chemicals, only moderate triazine exposure (OR 4.1 CI 1.5-11.1) and high azoles exposure (OR 3.9 CI 1.0-15.7) remained associated with ALL.	
Soldin Ther Drug Monit 2009(292)		41 cases of ALL 2005-2008 and 77 age, sex and county of residence matched controls	Questionnaire and urine metabolites	Organophosphates	ALL	ALL cases were more likely to report maternal insecticide use at home ($p<0.05$). Cases had higher levels of diethylthiophosphate ($p<0.03$) and diethyldithiophosphate ($p<0.05$). Small sample size.	

Child leukemia and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Turner Enviro Health Perspectives 2010 (284)	Meta-analysis	15 case-control studies 1950-2009	Residential pesticide exposure in pregnancy or in childhood	Any	Childhood leukemia	Exposures during pregnancy to overall residential pesticides (summary OR = 1.54 CI 1.13–2.11), insecticides (OR = 2.0 CI 1.80–2.32), and herbicides (OR = 1.61 CI 1.20–2.16) were significantly associated with childhood leukemia. Exposures during childhood to overall residential pesticides (OR = 1.38 CI 1.12–1.70) and insecticides (OR = 1.61 CI, 1.33–1.95) were also significantly associated with childhood leukemia, although when lower quality studies were excluded the association with insecticides was no longer significant. There was no association with childhood herbicide exposure and leukemia.	
Ward Enviro Health Persp 2009(293)	Case-control	184 ALL cases and 212 controls matched using birth certificate data on birth date, sex, race and Hispanic ethnicity	Carpet dust samples from the room the child spent the most time in	Organochlorines (α- and γ-chlordane, methoxychlor, and pentachlorophenol)	ALL	There were no significant positive associations for chlordane, DDT, DDE, methoxychlor, or pentachlorophenol.	
Wigle Enviro Health Perspectives 2009 (284)	Meta-analysis	31 studies (26 case-control and 5 cohort)	Parental occupational pesticide exposure	Any	Childhood leukemia	There was no overall association between childhood leukemia and any paternal occupational pesticide exposure (Summary (s)OR = 1.09 CI 0.88–1.34). There were elevated childhood leukemia risks for paternal occupational exposure to insecticides (sOR = 1.43 CI 1.06–1.92), herbicides (sOR = 1.25 CI 0.94–1.66), and fungicides (sOR = 1.66 CI 0.87–3.17). Childhood leukemia was associated with prenatal maternal occupational pesticide exposure (OR = 2.09 CI 1.51–2.88). Childhood leukemia risk was also elevated for prenatal maternal occupational exposure to insecticides (OR = 2.72 CI 1.47–5.04) and herbicides (OR = 3.62 95% CI 1.28–10.3).	

16.22 Childhood Wilms' tumor

Child Wilms' tumor and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Cooney Enviro Health Persp 2007 (295)	Case-control	523 cases and 517 controls frequency matched on age and residence area from the US and Canada	Exposure to residential pesticides from the month before pregnancy through the diagnosis reference date	Any and by type of pesticide and use	Wilms' tumor	Slight but significant increase in Wilms' tumor in children of mothers who reported pesticide use in the home (OR 1.3 CI 1.0-1.7) or insecticide use in the home (OR 1.4 CI 1.0-1.8).	
Fear Pedia Blood Can 2009 (297)	Case-control	2,568 cases and 2,568 age, sex and residence matched in Great Britain 1962 to 1999	Paternal occupation at birth	Any	Wilms' tumor	No significant associations between paternal occupation and associated exposures (Agriculture and agrochemical) and Wilms' tumor.	
Tsai Int J Hyg Enviro Health 2006(296)	Case-control	303 cases and 575 frequency matched controls between 1992 and 1995 in 6 US states	Parental occupational exposures during pregnancy and in the 2 years prior to birth through self-report	Any	Wilms' tumor	No significant association between Wilms' tumor and parental occupational exposure to pesticides during pregnancy or in the two years prior to birth.	

16.23 Childhood brain cancer

Child brain cancer and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Greenop Cancer Causes Control 2013(281)	Case-control	568 cases (374 consented to participate) and 1,467 age- and sex- matched controls recruited between 2005 and 2010 in Australia	Exposure to pesticides before and during pregnancy and during childhood	Occupational and residential pesticide exposure	Childhood Brain Tumor (CBT)	Significant increase in the risk of CBT with professional pest control treatment in the home in the year before the pregnancy (OR 1.54 CI 1.07-2.22) and if the only treatment happened in the year before pregnancy (OR 1.90 CI 1.08-3.36). Elevated risk of CBT with any termite treatment (OR 2.17 CI 1.12-4.19), treatment of bedroom (OR 1.56 CI 1.01-3.43) in the year before pregnancy or the child being home for treatment after birth (OR 1.63 CI 1.02-2.60). No significant association between professional pest control treatments and CBT during pregnancy or after birth. No association with paternal presence during pest treatments or paternal occupational exposure in the year prior to conception. Estimates for low-grade gliomas for pesticide exposure before and during pregnancy were similar to CBT overall, whereas they were increased from high-grade gliomas (OR 2.99 CI 0.99-9.02 and OR 4.58 CI 1.39-15.14 respectively).	
Moore Cancer Causes and Control 2011 (280)	Meta-analysis	7 case-control and 2 cohort studies published to October 2009 for 1,426 total cases	Paternal occupational pesticide exposure	Any	Neuroblastoma	No association (Summary RR 1.07 (CI 0.79-1.46)) between paternal pesticide exposure and neuroblastoma.	

Child brain cancer and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Reynolds Epidemiology 2005 (279)	Case-control	2189 cases and 4335 controls matched for birth date and sex	Mother's residential proximity to agricultural applications of pesticides at the time of child's birth	Specific chemicals and chemical groups used within 0.5 miles of maternal residence divided in low (0 to 49th percentile) and high (50th percentile and up) and when numbers allowed very high (90th percentile and up) exposure	Early childhood cancer (including CNS)	90% of residences had less than 1lb per square mile applied of specific chemicals and 70% had less than 1lb per square mile of chemical groups. No associations with CNS tumors. In leukemia and general cancer.	
Rosso Cancer Causes Control 2008 (282)	Case-control	318 cases under 6 years of age at diagnosis between 1991-1997 and 318 individually matched population controls in the US and Canada	Self reported paternal hobbies	Any	Medulloblastoma (MB) and primitive neuroectodermal tumor (PNET)	There was a significant association between MB and PNET when the father engaged in lawn care with pesticides during pregnancy (OR 1.6 CI 1.0-2.5) and after birth (OR 1.8 CI 1.2-2.8). The median age in the study was 23 months and the authors stratified the results to investigate effects in older and younger children. The increase in risk of CBT was greater for children over age 23 months at diagnosis for exposures both during pregnancy (OR 1.9 CI 1.0-3.7) and after birth (OR 2.0 CI 1.1-3.8). The estimates from children less than 23 months were non-significant. There was evidence of recall bias for lawn care.	
Shim Enviro Health Persp 2009 (283)	Case-control	526 one-to-one matched case-control pairs less than 10 years of	Residential pesticides use and parental occupational	Insecticides, herbicides and fungicides	Childhood Brain Tumor (CBT), primitive neuroectodermal	Residential exposure to herbicides was associated with an increased risk of astrocytoma (OR 1.9 CI 1.2-3.0) but the risk was significantly reduced	

Child brain cancer and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		age from 4 UC Atlantic Coast States	pesticide use in the 2 years prior to birth		tumors (PNET), astrocytoma, other tumor types	if the father washed immediately afterwards (OR 0.4 CI 0.1-1.0) or wore protective clothing (OR 0.4 CI 0.2-0.6). A combination of residential and paternal occupational exposure to herbicides was also associated with an increased risk of astrocytoma (OR 1.8 CI 1.1-3.1). The father's application or occupational exposure to insecticides was associated with an increased risk of other CBT (non-astrocytoma, non-PNET) (OR 2.9 CI 1.4-6.2). There were no associations between insecticide application and PNET or astrocytoma. There were no significant associations with PNET .	

16.24 Breast cancer

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Ashley-Martin Int J Enviro Res Pub Health 2012(182)	Case-control	207 cases and 621 age, family history and menopausal status matched controls in Prince Edward Island	Fungicide exposure based on geocoding of participant postal codes	Fungicides	Breast Cancer	No significant association between breast cancer and fungicide exposure.	
Boada Enviro Health 2012 (173)	Case-control	121 cases and 103 controls in Gran Canaria Island, Spain	Serum biomarker levels	Organochlorines	Breast Cancer	Cases presented more frequently a combination of aldrin, dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD), and this mixture was not found in any of the controls. Controls had a combination of lindane and endrin. Breast cancer was associated with DDD levels (OR 1.008 CI 1.001-1.015) only.	
Brody Enviro Health 2006 (184)	Case-control	824 cases diagnosed from 1988-1995 and 745 controls interviewed 1997-1998 all of whom lived in homes served by public drinking water supplies in Cape Cod, Massachusetts	Nitrate-N levels in public drinking water supplies. Fraction of recharge zones in residential, commercial and pesticide land use areas.	Nitrates as a wastewater contamination indicator.	Breast Cancer	No significant association between breast cancer and average annual nitrate-N, sum of annual nitrate-N concentrations or number of years exposure to nitrate-N over 1 mg/L. No significant association between breast cancer and fraction of land use in recharge zones.	
Charlier Bull Enviro Contam	Cohort	125 women with breast cancer	Serum organochlorine	p,p'-dichlorodiphenyldichlo-	Breast cancer relapse	Mean organochlorine concentration was significant higher in the 14	

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Toxicol 2007 (174)			levels on first day of radiation therapy	roethylene (DDE) and hexachlorobenzene (HCB)		patients who relapsed (7.8 ± 6.2 vs 3.6 ± 4.7 ppb; $p < 0.005$) than the nonrelapsing patients. No information about the length of follow-up for relapse or what year the study was initiated.	
El-Zaemey Int J Enviro Health Res 2014 (166)	Case-control	1,205 cases and 1,789 controls in Western Australia	Self-reported occupational and household pesticide exposure		Breast Cancer	No significant association between household or occupational pesticide use and breast cancer. Stratified by belief as to whether pesticides cause breast cancer to estimate recall bias with no change in results.	
Engel AJE 2005 (162)	Cohort	30,454 women with no history of breast cancer at enrollment 1993-1997 followed to 2000 for 309 cases participating in the Agricultural Health Study	Self-reported pesticide use	Multiple pesticides	Incident breast cancer	No significant associations between incident breast cancer and ever applying pesticides, farm size or washing of clothes worn during pesticide application. There was an increased risk of breast cancer among the wives who never used pesticides whose husbands used aldrin (RR1.9 CI 1.3-2.7), Carbaryl (RR 1.4 CI 1.0-2.0), Chlordane (RR 1.7 CI 1.2-2.5), dieldrin (RR 2.0 CI 1.1-3.3), heptachlor (RR 1.6 CI 1.1-2.4), lindane (RR 1.7 CI 1.1-2.5), malathion (RR 1.4 CI 1.0-2.0), 2,4,5-TP (RR 2.0 CI 1.2-3.2), captan (RR 2.7 CI 1.7-4.3), with between 18 and 101 exposed cases for each one. The husbands' increasing use of dieldrin, 2,4,5-TP, 2,4,5-T showed a significant trend of increasing risk of breast cancer with high cumulative use (p trend <0.01). In women with a family history of breast cancer, their use of diazinon and their husbands'	

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						use of parathion and paraquat showed a significantly increase in risk of breast cancer.	
Farooq Enviro Health 2010 (165)	Case-control	447 cases and 758 controls with benign breast disease or undergoing non-breast related surgery in New York City	Self-reported residential pesticide use	Any residential pesticide	Breast cancer	No significant association between breast cancer and residential pesticide application by the participant or professionally.	
Fredslund Int J Circumpolar Health 2012 (175)	Review					Suggests that high organochlorine levels in Artic populations may be related to high breast cancer rates.	
Khanjani Arch Enviro Comtan Toxico 2006 (176)	Ecological	11 statistical zone within the state of Vicotria from 1983-2002 where 47,250 breast cancer cases occurred among 2,147,409 women	Organochlorine contamination data from a 1993 breastmilk study based in Victoria	Organochlorines	Breast Cancer	Three regions with high organochlorine contamination levels showed increased SIR for breast cancer (Loddon-Campaspe SIR 1.14 CI 1.09-1.19, Gippsland SIR 1.09 CI 1.04-1.14 and Ovens-Murry SIR 1.10 CI 1.03-1.17, with a highly contaminated subsection of ovens-Murra y, Ovens and King Valley being higher SIR 1.15 CI 1.07-1.23). No evidence of dose-response relationship.	
Khanjani J Enviro Sci Health Part C 2007 (170)	Meta-analysis	21 case-control studies from 1966 to July 2006	Cyclodiene organochlorines	Aldrin, Dieldrin, Oxychlordane and Chlordane, Heptachlor and Heptachlor Epoxide	Breast Cancer	No significant associations breast cancer and cyclodienes organochlorine except for heptachlor (2 studies, pooled geometric means ratio 5.32 CI 3.79-7.48).	
McElroy J Exp Sci Enviro Epi 2007 (183)	Case-control	3,275 cases age 20-79 from 1987 to 2000 and 3,669 population controls	Atrazine levels in well water in 3 statewide random studies	Atrazone	Breast Cancer	No significant associations between breast cancer and atrazine well water levels. High level (>3ppb) exposure could not be ruled out due to small	

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		of similar age from rural Wisconsin	from 1994, 1996 and 2001			exposure numbers in this category.	
Mills Int J Occup Enviro Health 2005 (360)	Case-control	128 cases diagnosed 1988-2001 and 640 cancer-free controls in California Hispanics	Monthly job histories combined with California's comprehensive state wide pesticide use reporting data		Breast Cancer	No significant association of breast cancer with quartiles of pesticide use. Use of chlordane, malathion and 2,4-D was associated with increased risk in either cases diagnosed 1988 to 1994 or 1995-2001 but not in both time periods.	
Mills J Enviro Health 2006 (168)	Ecological	23,513 Hispanic women diagnosed with breast cancer 1988 to 1999	County level specific pesticide use data for organochlorine and triazine herbicides	Organochlorine and triazine herbicides	Breast Cancer Incidence	No control group. Increased breast cancer incidence with highest quartile of organochlorines methoxychlor (IRR 1.18 CI 1.03-1.35) and toxaphene (IRR 1.16 CI 1.01-1.34). No significant association between breast cancer incidence rates and triazines atrazine and simazine, except for the second quarter of simazine use in 1994-1999 (IRR 1.40 CI 1.1401.72).	
Ociepa-Zawal J Enviro Sci Health Pt B 2010 (172)	Case-control	54 cases and 23 controls	Adipose tissue biomarker levels	Organochlorine levels	Breast cancer	Significantly higher levels of ß-hexachlorocyclohexane levels in breast cancer patients (p=0.049). No difference in γ-hexachlorocyclohexane or hexachlorobenzene levels.	
Reynolds Enviro Health Persp 2005 (169)	Ecological	176,302 invasive breast cancer cases and 70,968,598 person-years in California	Pesticide use reporting data and proximity to residence at diagnosis	Classes: probable or likely carcinogens, possible or suggestive carcinogens, mammary carcinogens, xeno-estrogens, cholinesterase inhibitors, and organo-chlorines. Individual pesticides: simazine, diuron,	Breast Cancer	No association between breast cancer rates and high agricultural pesticide use.	

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
				oryzalin, propargite, and methyl bromide			
Rubin J Circumpolar Health 2006 (177)	Case-control	63 cases and 63 age-matched controls	Serum biomarkers	13 organochlorine pesticides	Breast Cancer	No association between organochlorines and breast cancer.	
Salehi J Toxi Enviro Health Pt B 2008 (181)	Review					No clear evidence to support exposure to organochlorine pesticides as having a causal role in breast cancer.	
Shakeel Asian Pacific J Cancer Prev 2010 (179)	Review	Articles between 1990 and 2009 on pesticides, organochlorines, organophosphates and breast cancer		Organochlorines and organophosphates	Breast Cancer	No significant consistent association found between pesticides and breast cancer, except for DDT.	
Smith-Bindman Arch Intern Med 2012 (180)	Review					No studies showing conclusive associations between organochlorines and breast cancer.	
St-Hilaire Int J Health Geographics 2011 (163)	Ecological	Age-adjusted county level average ER+ and ER- breast cancer rate in 439 counties and 11 US states between 2000 and 2003		Proportion of agricultural land as a proxy for pesticide use	Estrogen Receptor (ER) Positive (+) and Negative (-) Breast Cancers County level incidence	ER+ breast cancers were significantly associated with the proportion of agricultural land (p=0.009) in a county, with the association strengthening as the annual precipitation decreased (p interaction=0.045). No association between ER- breast cancers and proportion of agricultural land in a county.	
Teitelbaum AJE 2006 (164)	Case-control	1,508 newly diagnosed cases and 1,556 age-matched controls in Long Island, New York between 1996 and 1997	Self-reported residential pesticide use		Breast cancer	Ever lifetime residential pesticide use was associated with breast cancer (OR 1.39 CI 1.15-1.68) but no increase in risk with increasing number of applications. Lawn and garden pesticide ever use was associated with breast cancer risk	

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						(OR 1.34 CI 1.11-1.63), but there was no dose response. Specific use of lawn and garden pesticides to control weeds, insects or diseases of lawns, trees and indoor or outdoor plants were all associated with ORs of about 1.5. There were slightly higher odds ratios reported for professional pest control applications and for liquid or other/combined product types. No association was found for nuisance-pest pesticides, insect repellants, or products to control lice or fleas and ticks on pets.	
Waliszewski Bull Enviro Contam Toxico 2005 (171)	Case-control	127 cases with malignant breast tumors and 127 cases benign breast tumors and 127 controls from motor vehicle accidents in Mexico	Breast adipose tissue organochlorine levels from cases and abdominal adipose organochlorine levels from controls	Hexachlorobenzene and hexachlorocyclohexane	Malignant breast tumors	Hexachlorobenzene was associated with an increased risk of benign (RR 2.11 CI 1.98-2.25) and malignant (RR 2.01 CI 1.94-2.07) breast cancer. Hexachlorocyclohexane was associated with an increased risk of benign (RR 1.96 CI 1.90-2.01) and malignant (RR 1.58 CI 1.54-1.62) breast cancer. Not clear what groups were used in the RR calculations.	
Xu Enviro Health Persp 2010 (178)	Cross-sectional	4,753 participants in 3 cycles of the National Health and Nutrition Examination Survey	Serum organochlorine levels	hexachlorobenzene, β-hexachlorocyclohexane (HCH), G-HCH, oxychlordane, *trans*-nonachlor, heptachlor epoxide, and mirex Also aldrin, dieldrin, and endrin measured in approximately 2/3 of particiapant.	Breast cancer and prostate cancer	No association between serum organochlorine levels and breast cancer. Also in prostate cancer.	

Breast cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Zota Enviro Health 2010 (167)	Case-control	787 women diagnosed with breast cancer between 1988 and 1995 and 721 controls from Cape Cod, Massachusetts	Self-reported pesticide exposure	Residential pesticides categorized into combined pesticide use, insect or bug control, termites/carpenter ants, mosquito control, mothball control, lawn care, outdoor/indoor plant care, insect repellent, lice control, flea collar for pets and flea control for pets	Breast cancer	There were no associations between pesticide use and breast cancer, except for often/very often insect repellent use versus never use (OR 1.5 CI 1.0-2.3).	

16.25 Prostate cancer

Prostate cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Aronson J Exp Sci Enviro Epi 2010 (235)	Case-control	79 cases and 329 age frequency matched controls aged 50-80 in Kingston, Ontario	Serum organochlorine levels	13 organochlorine pesticides (aldrin, b-hexachlorocyclo-hexane, a-chlordane, g-chlordane, cis-nonachlor, p,p'-DDE, p,p'-DDT, dieldrin, heptachlorepoxide, hexachlorobenzene, mirex, oxychlordane, and trans-nonachlor)	Prostate cancer	No association between serum organochlorine levels and prostate cancer risk.	
Band T Prostate 2011 (241)	Case-control	1,153 cases and 3,999 age-matched controls with other cancers, including 113 case farmers and 316 control farmers	Self-reported and job matrix lifetime exposure to 180 pesticides compounds	180 pesticides	Prostate cancer	A significant association between prostate cancer and ever exposure to azinphis-methyl (OR 1.70 CI 1.11-2.60), carbaryl (OR 1.54 CI 1.08-2.18), DDT (OR 1.47 CI 1.02-2.12), endosulfan (OR 1.52 CI 1.00-2.29), malathion (OR 1.34 CI 1.01-1.78), mercury (OR 2.41 CI 1.02-5.74). A significant association between prostate cancer and high exposure to copper sulfate (OR 1.74 CI 1.04-2.91), dichlone (OR 1.88 CI 1.01-3.52), ferbam (OR 1.90 CI 1.09-3.30), maneb (OR 1.90 CI 1.09-3.30), sulfur (OR 1.81 CI 1.12-2.92), ziram (OR 1.83 CI 1.08-3.10), 2,4-DB (OR 2.19 CI 1.06-4.50), MCPA (OR 2.31 CI 1.09-4.88), simazine (OR 1.89 CI 1.08-3.33), 3,5-Dinitro-cresol (OR 1.80 CI 1.05-3.08), azinphos-methyl (OR 1.88 CI 1.06-3.32), carbaryl (OR 1.73 CI 1.09-2.74), DDT (OR 1.68 CI 1.04-2.70),	

Prostate cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						diazinon (OR 1.93 CI 1.21-3.08), lindane (OR 2.02 CI 1.15-3.55), malathion (OR 1.49 CI 1.02-2.18). A significant association between prostate cancer and low (but not high) exposure tocaptan (OR 1.76 CI 1.12-2.78), hydrogen sulfide (OR 1.66 CI 1.02-2.72).	
Barranco Cancer Causes Control 2007 (238)	Ecological	Prostate cancer incidence and mortality from the Texas Cancer Registry	Groundwater selenium and boron concentrations		Prostate cancer incidence and mortality	Areas with higher boron concentrations had lower prostate cancer incidence (r= 0.6) and mortality (r=0.6) (linear regression p<0.002).	
Barry Enviro Health Persp 2011 (244)	Case-control within a cohort	776 cases and 1,444 male controls in a subset of white Agricultural Health Study pesticide users	Self-reported occupational use	Multiple pesticides	Prostate cancer	Several pesticides were inversely associated (p trend <0.05 for ORs less than 1) with prostate cancer, including carbaryl, cyanazine, 2,4,5-T, metolachlor and imazethapyr.	
Boers Occup Enviro Med 2005 (246)	Case-control within a Cohort	58,279 men aged 55 to 69 years in the Netherlands followed from Sept 1986 to Dec 1995 (subset included 1,386 cases and 2,335 controls)	Self-reported occupational history		Prostate cancer	A significant negative association for the highest tertile of pesticide exposure (RR 0.6 CI 0.37-0.95) and prostate cancer compared to no exposure.	
Budnik Enviro Health 2012 (237)	Systematic review	91 studies from 1990-2011, 5 epidemiological studies contributed to meta-analysis.		Methyl bromide	Prostate cancer	No significant association between methyl bromide exposure and prostate cancer (OR 1.21 CI 0.98-1.4).	
Cockburn AJE 2011 (233)	Case-control	173 cases and 162 population	Ambient past pesticide		Prostate cancer	Increased risk of prostate cancer with exposure to methyl bromide (OR 1.62 CI	

Prostate cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		controls from California's Central Valley	exposure based on residential history and independently recorded pesticide and land use data			1.02-2.59), to organochlorines as a group (dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene) (OR 1.64 CI 1.02-2.63) and to high levels of captan (OR 1.74 CI 1.01-3.13). No association with other compounds including simazine, maneb and paraquat.	
Doolan Asian Pac J Can Prev 2014 (248)	Review				Prostate cancer	No proven association between overall pesticide exposure and prostate cancer. More research needed to determine if specific pesticides are associated with an increased risk of prostate cancer.	
Fritschi Occup Enviro Med 2007 (245)	Case-control	606 cases of prostate cancer, 400 cases of BPH and 471 male population based controls in Western Australia	Self-reported occupational pesticide exposure	Any	Prostate cancer and benign prostatic hyperplasia (BPH)	No significant association between pesticide exposure, including organophosphate, organochlorine, phenoxy herbicides, other herbicides and other pesticides, and prostate cancer or BPH. Also in other outcomes.	
Koutros AJE 2013 (240)	Cohort	1,962 cases (919 aggressive prostate cancer cases) among 54,412 pesticide applicators in the Agricultural Health Study	Self-reported occupational pesticide exposure	Chlorpyrifos, coumaphos, dichlorvos, diazinon, fonofos, malathion, parathion, phorate, terbufos, aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene, atrazine, cyanazine	Prostate cancer and aggressive prostate cancer	Three organophosphate insecticides were significantly associated with aggressive prostate cancer: fonofos (RR for the highest quartile of exposure (Q4) vs. nonexposed 1.63 CI 1.22-2.17; Ptrend < 0.001), malathion (RR 1.43 CI 1.08-1.88; Ptrend = 0.04) and terbufos (RR 1.29 CI 1.02-1.64; Ptrend = 0.03). The organochlorine insecticide aldrin was also associated with increased risk of ag- gressive prostate cancer (RR1.49 CI 1.03-2.18; Ptrend = 0.02). No associations seen for incident prostate cancer.	
Meyer Occup Enviro Med 2007 (243)	Case-control	405 cases and 392 controls matched for age, race and region in South	Farming or applying pesticides	Any	Prostate cancer	Increased risk of prostate cancer in Caucasian farmers (OR 1.8 CI 1.3-2.7) but not African-American farmers (OR 1.0 CI 0.6-1.6). Increased risk of prostate cancer in	

Prostate cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		Carolina from 1999 to 2001				farmers who mixed or applied pesticides (OR 1.6 CI 1.2-2.2).	
Mink Euro J Cancer Prev 2008 (247)	Review	8 cohort studies and 5 case-control studies				No consistently increased risks to support a causal association between agricultural pesticide use and prostate cancer.	
Mullins Urologic Oncology 2012 (234)	Review				Prostate Cancer	Conflicting results in the literature on the association between prostate cancer and pesticide exposure.	
Prins Endocr Relat Cancer 2008 (239)	Review				Prostate Cancer	Describes the possible role of pesticides as endocrine disruptors in the development of prostate cancer.	
Ragin Am J Mens Health 2013 (242)	Meta-analysis	12 studies adding to 3,978 cases and 7,393 controls	Exposure to pesticide or farming	Any	Prostate cancer	Prostate cancer cases were almost four times more likely to be farmers compared with controls with benign prostate hyperplasia (BPH; meta OR = 3.83, CI 1.96–7.48, two studies). There were similar results were obtained when non-BPH controls were considered, but with moderate heterogeneity between studies (meta OR = 1.38, CI 1.16–1.64, five studies). Pesticide exposure was inversely associated with prostate cancer (meta OR crude = 0.68, CI = 0.49–0.96, four studies), whereas no association with exposure to fertilizers was observed.	
Sawada Enviro Health Persp 2010 (236)	Case-control within a cohort	201 cases and 402 matched controls from the cohort of 14,203 Japanese men aged 40 to 69 years followed from 1990-2005	Serum organochlorine levels	dichlorodiphe-nyltrichloroethane (DDT), hexachlorobenzene (HCB), β-hexachlorocyclohex ane (β-HCH), *trans*- and *cis*-nonachlor, oxychlordane, and mirex	Prostate Cancer	No association between serum organochlorine levels and prostate cancer.	

Prostate cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Xu Enviro Health Persp 2010 (178)	Cross-sectional	4,753 participants in 3 cycles of the National Health and Nutrition Examination Survey	Serum organochlorine levels	hexachlorobenzene, β-hexachlorocyclohexane (HCH), G-HCH, oxychlordane, *trans*-nonachlor, heptachlor epoxide, and mirex Also aldrin, dieldrin, and endrin measured in approximately 2/3 of particiapant.	Breast cancer and prostate cancer	After adjustment for other covariates, serum concentrations of β-hexachlorocyclohexane (HCH) (*p* trend = 0.02), *trans*-nonachlor (*p* trend = 0.002), and dieldrin (*p* trend = 0.04) were significantly associated with the risk of prevalent prostate cancer. ORs for the second and third tertiles of detectable values were 1.46 (CI 0.52–4.13) and 3.36 (CI 1.24–9.10) for β-HCH; 5.84 (CI 1.06–32.2) and 14.1 (CI 2.55–77.9) for *trans*-nonachlor; and 1.06 (95% CI, 0.30–3.73) and 2.74 (95% CI, 1.01–7.49) for dieldrin compared with concentrations in the lowest tertile or below the limit of detection**.** Also in breast cancer.	

16.26 Pancreatic cancer

Pancreatic cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Andreotti Int J Cancer 2009 (226)	Case-control within a cohort	93 cases and 82,503 cancer-free controls in the Agricultural Health Study	Self-reported occupational exposure	24 pesticides	Incident pancreatic cancer	Association between pendimethalin (OR 3.0 CI 1.3-7.2) and EPTC (OR 2.56 CI 1.1-5.4) for pancreatic cancer in the top half of lifetime users compared to never users.	
Andreotti Molec Carcinogenesis 2012 (227)	Review	Studies published 1998-2010				Some evidence of an association between pancreatic cancer and organochlorine exposure but further research is needed. May be an association between pancreatic cancer and other pesticides but more research is needed to determine which specific pesticides or pesticide classes elevate risk.	
de Basea Occup Enviro Med 2011 (230)	Cross-sectional	135 cases in Finland	Serum OC concentration and occupational exposure	p,p'-DDT, p,p'-DDE, hexachlorobenzene or ß-hexachlorocyclohexane	Incident exocrine pancreatic cancer	Examined links between OC serum levels and occupational history.	
Hardell Biomed & Physiotherpy 2007 (361)	Case-control	21 cases and 59 controls in Sweden	Adipose tissue concentration of OCs	Organochlorines	Exocrine pancreatic cancer	Significantly higher concentrations of hexachlorobenzene (HCB) were found in cases. ORs were 53 (CI 4.64-605) and 18.4 (CI 2.71-124) for HCB and sum of chlordanes respectively. Significantly longer survival in cases with sum of chlordane concentrations below the median (142 versus 294 days). All analyses based on small numbers.	

Pancreatic cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Ojajarvi Scand J Work Enviro Health 2007 (229)	Meta-analysis(Bayesian)	77 studies published 1969 to 1998	Occupational exposure to pesticide based on job title	Any	Pancreatic cancer	Increased risk of pancreatic cancer with chlorinated hydrocarbon exposure (meta RR 2.21 CI 1.31-3.68) to which laundry and dry cleaning workers, metal-plating workers, and printers and pressmen are typically exposed. No excess risk found for fungicide or insecticide exposure or for farmers.	
Porta Enviro Int 2007 (231)	Cross-sectional	144 cases		Organochlorines (OC)	Exocrine pancreatic cancer	Examined association between OC concentration and risk factors for pancreatic cancer.	
Porta Enviro Res 2008 (232)	Cross-sectional	135 cases		Organochlorines (OC)	Exocrine pancreatic cancer	Examined association between OC concentration and occupational social class for pancreatic cancer.	
Santibañez Eur J Epi 2010 (228)	Case-control	161 cases and 455 age, sex and residence matched controls in Spain	Occupational exposures by job matrix	Any	Incident exocrine pancreatic cancer	No significant increase in pancreatic cancer for agricultural workers. Other results are outside the inclusion criteria for this review.	

16.27 Liver cancer

Liver cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Schmeisser Cancer Causes Control 2010(198)	Case-control	104 male cases aged 35-70 diagnosed 1995-1997 and 1,401 male population controls in Europe (multi-center)	Occupational job matrix exposure by history and self-report		Extrahepatic biliary tract carcinoma	No association with pesticide exposure.	
Su Asian Pac J Can Prev 2013(362)	Review				Liver cancer	No new information or relevant references in review.	

16.28 Respiratory tract cancers

Respiratory tract cancers and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Alavanja AJE 2004 (251)	Cohort	57,284 pesticide applicators and 32,333 spouses followed from enrollment in 1993-1997 to 2001	Self-reported occupational exposure	50 pesticides	Lung cancer	Very low overall standardized incidence ratio (SIR 0.44 CI 0.39-0.49) due to low smoking prevalence. There were significant associations with lung cancer and the use of two herbicides: metolachlor and pendimenthalin (Q4 ORs 5.0 CI 1.7-14.9 p trend 0.0002; and OR 4.4 CI 1.2-15.4 p trend 0.003, respectively) and two insecticides: chlorpyrifos and diazinon (OR not significant p trend 0.03; and OR 3.2 CI 1.1-8.9 p trend 0.04, respectively). Risks related to spousal exposure were not explored due to small numbers of cases.	
Aozasa Sci World J 2011 (249)	Review			Any	Nasal NK/T-cell lymphoma	Reported results from one study of 88 cases and 305 controls in Japan, Korea and China showed significant increases in risk with ever pesticide use (OR 2.01 CI 1.99-8.09), use of herbicides (OR 3.17 CI 1.36-7.38), insecticides (OR 3.45 CI 1.67-7.13) or fungicide (OR 6.05 CI 1.98-18.46) with slight drops in ORs with the use of protective measures although they remained significant.	
Greiser BMC Cancer 2012 (250)	Case-control	427 cases and 2,401 male population based controls in Germany		Insecticide use in the home	Nasal cancer	Use of insecticides in the significantly increase the risk of nasal cancer (OR 1.48 CI 1.04-2.11).	
McHugh Cancer Causes & Control 2010	Case-control	212 Mexican-American cases and 328 age, sex	Self-report and job history of environmental	Any	Lung cancer	Conventional pesticides were associated with an increased risk of lung cancer (OR 2.05 CI 1.23-2.39).	

Respiratory tract cancers and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
(252)		and ethnicity matched population controls between 1991 and 2005 near Houston, Texas	and occupation exposures			Controls recruited from a US group practice, may not be representative.	

16.29 Gastrointestinal cancer

Gastrointestinal cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Jansson Occup Enviro Med 2006(185)	Case-control	189 cases of esophageal carcinoma, 262 cases of cardia adenocarcinoma and 167 cases of esophageal squamous cell carcinoma and 820 frequency matched controls	Self-reported and job history based occupational exposure	Airborne exposures	Esophageal, esophageal squamous cell and cardia adenocarcinoma	Association between cardia adenocarcinoma and high exposure to pesticides (OR 2.1 CI 1.0-4.6). No significant association between esophageal or esophageal squamous cell carcinoma and high pesticide exposure.	
Lee Int J Cancer 2007(187)	Case-control nested within a cohort	305 cases from 1993-1997 to 2002 and 56,813 controls in the Agricultural Health Study	Self-reported occupational exposure	50 pesticides	Colorectal cancer	Chlorpyrifos showed a significant does-response and elevated OR at the highest exposure level (OR 2.7 CI 1.2-6.4, p trend=0.008) for rectal cancer. Aldicarb was associated with an increased risk of colon cancer at the highest exposure level (OR 4.1 CI 1.3-12.8, p trend 0.001). Two insecticides also showed a significant increase in risk of rectal cancer, carbaryl (OR 2.0 CI 1.1-3.5) and toxaphene (OR 2.1 CI 1.2-3.6). Several pesticides were also inversely associated with colorectal cancers.	
Mills Enviro Res 2007(188)	Case-control within a cohort	100 new cases and 210 age, sex and ethnicity matched controls recruited between 1988 to 2003 in			Gastric cancer	There were increased risks of gastric cancer with the use of 2,4-D (OR 1.85 CI 1.05-3.25), chlordane (OR 2.86 CI 1.56-5.23) and propargite (OR 2.86 CI 1.56-5.23). Also associated with work with citrus	

Gastrointestinal cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		the United Farm Workers cohort				crops (OR 2.88 CI 1.02-8.12). There were significant associations with gastric cancer for different levels of 2,4-D (low exp), chlordane (low and mid exp),propargite (mid and high exp), and triflurin (high exp).	
Santibañez Occup Enviro Med 2012 (186)	Case-control	399 cases and 455 sex, age and province of residence matched controls in Spain	Occupational exposure by job exposure matrix		Stomach cancer (241 intestinal cases and 109 diffuse adenocarcinomas)	Significant increase in risk for diffuse adenocarcinomas and the highest level of exposure to 'pesticides' (OR 10.39 CI 2.51-43.02, p trend 0.02). Men employed in agricultural had a higher risk of diffuse adenocarcinoma (OR 6.16 CI 1.10-34.60). No significiant findings for intestinal gastric carcinoma.	
Sritharan Global J Health Sciences 2014(189)	Cross-sectional	114 participants from communities of Timiskaming and Peel			None	There was more use of insecticides in the current home/residence in Timiskaming residents (P=0.008), an areas of high colorectal cancer incidence compared to Peel residents, an area with the lowest colorectal cancer incidence in Canada. Questionable comparability between groups on many other possible confounders.	

16.30 Ovarian cancer

Ovarian cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Salehi J Toxico Enviro Health Part B 2008 (225)	Review	4 studies including Young et al. 2005 (3 case-control and		Triazine herbicides		Weak evidence for an association between triazine herbicide use and ovarian cancer. Further studies needed.	

Ovarian cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		1 ecological)					
Young J Occup Enviro Med 2005(224)	Case-control	256 incident cases and 1,122 random digit-dialed controls	Agricultural pesticide exposure via self-reported work history	Triazine herbicides	Ovarian epithelial cancer	No association between exposure to triazine herbicides and ovarian cancer.	

16.31 Skin cancer

Skin cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Burkart Int J Dermatology 2009 (363)	Comment on Fortes Int J Dermatology 2008 (253)					Discussed physiological hypotheses behind the findings of an association between pesticide use and cutaneous melanoma.	
Dennis Enviro Health persp 2010 (257)	Cohort	150 cases and 24,554 non cases among the Agricultural Health Study participants from Iowa and North Carolina	Self-reported occupational pesticide exposure	50 pesticides	Cutaneous melanoma	Increased risk of cutaneous melanoma with the use of maneb/mancozeb (≥ 63 exposure days: OR 2.4 CI 1.2–4.9 trend p = 0.006), parathion (≥ 56 exposure days: OR 2.4 CI 1.3–4.4 trend p = 0.003), and carbaryl (≥ 56 exposure days: OR 1.7 CI 1.1–2.5 trend p = 0.013).Concomitant exposure to lead arsenate increased the risk of cutaneous melanoma with exposure to benomyl (OR 6.7 CI 1.6-27.0) and maneb/mancozeb (OR 10.8 CI 2.3-51.3).	
Fortes Eur J Cancer 2007 (255)	Case-control	287 cases and 299 hospital based controls	Occupational and residential self-reported pesticide exposure	Any	Cutaneous melanoma	Increased risk of melanoma with indoor pesticide use greater than 4 times annually (OR 2.18 CI 1.07-4.43) compared to low use (<1 time annually), with exposure greater than 10 years (OR 2.46 CI 1.23-4.94) compared to less than 10 years exposure. A trend for increased risk of melanoma with increasing intensity of pesticide use (p trend=0.027).	
Fortes Int J Dermatology 2008 (253)	Review	10 studies			Cutaneous melanoma	Eight of the 10 studies found a significant increase in risk of cutaneous melanoma with occupational pesticide exposure. Nice box plot of study outcomes.	
Gallagher Int J Cancer 2011	Case-control	80 cases and 310 controls in	Serum biomarker levels	Organochlorines	Cutaneous Malignant	Increased risk of CMM with exposure to (ORs provided are for the highest	

Skin cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
(256)		British Columbia			Melanoma (CMM)	level exposure) cis-nonachlor (OR 2.27 CI 1.11-4.62 p trend 0.025), HCB (OR 3.11 CI 1.05-9.18 p trend 0.009), mirex (OR 2.71 CI 1.35-5.41 p trend 0.004) and trans-nonachlor (OR 4.26 CI 1.37-13.26 p trend 0.006).	
MacKie Ann Oncology 2009 (254)	Review				Cutaneous melanoma	Pesticide use appears to be a possible contributors to cutaneous melanoma and should be added to consideration in future studies.	
Morales-Suárez-Varela Cancer Causes Control 2005 (258)	Case-control	118 cases age 35 to 69 years diagnosed 1995-1997 across Europe, and 833 controls with colon cancer and 2071 population controls	Job Exposure Matrix	Any	Mycosis Fungoides (MF)	Exposure to occupational pesticides for greater than 10 years was associated with a significantly increased risk of MF in men (OR 6.8 CI 1.3-35.2, p trend=0.005) but not women (only 5 pesticides exposed cases for women)	

16.32 Testicular cancer

Testicular cancer and pesticide exposure (Adult and Child)

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Béranger PlosONE 2013 (263)	Systematic review	72 articles 1990 to 2012	Occupational and environmental pesticide exposures	Any	Testicular germ cell tumors (TGCT)	Occupational association of TGCT with agricultural workers, construction workers, firemen, policemen, military personnel, as well as workers in paper, plastic or metal industries. Electromagnetic fields, PCBs and pesticides were also suggested but evidence is inconsistent and studies with significant associations tended to be of lower quality.	
Biggs Cancer Epi Bio 2008(264)	Case-control	246 cases diagnosed 1999-2003 and 630 controls aged 18 to 44 years in Washington State	Serum organochlorine biomarkers	β-hexachlorocyclohexane [β-HCH], γ-hexachlorocyclohexane [γ-HCH or lindane], dieldrin, hexachlorobenzene (HCB), heptachlor epoxide, mirex, oxychlordane, and trans-nonachlor)	Testicular Germ Cell Carcinoma (TGCC)	No association between organochlorine serum levels and TGCC.	
Giannandrea J Enviro Sci Health Pt B 2011 (259)	Case-control	50 cases and 48 hospital based controls in Italy	Serum organochlorine biomarkers and self-reported pesticide exposure	Organochlorine pesticides (HCB and DDE)	Testicular cancer	Testicular cancer was significantly associated with household insecticide use (OR 3.23 CI 1.15-9.11) and total organochlorine (DDE + HCB) levels (OR 3.34 (CI 1.09-10.17).	
Guo Cancer Causes Control 2005 (260)	Cohort	All economically active Finnish men born 1906 to 1945 followed for 19.7million person-years	Census occupations in 1970 converted to chemical exposures via a job exposure		Testicular cancer	With a lag of 20 years, exposure to insecticides was associated with an elevated risk of testicular cancer (SIR 4.26 CI 1.16-10.9). No increased risk with overall pesticide, herbicide or fungicide	

		from 1971 to 1995 to identify 387 cases	matrix			exposure.
McGlynn J Natl Can Inst 2008 (262)	Case-control	754 cases and 928 controls enrolled in the Servicemen's Testicular Tumor Environmental and Endocrine Study	Serum biomarkers	*cis*-nonachlor, *trans*-nonachlor, oxychlordane, total chlordanes, ß-hexachlorocyclohexane, mirex,	Testicular Germ Cell Tumors (TGCT)	TGCT risk was statistically significantly associated with higher serum levels of two chlordane components, *cis*-nonachlor (Q4 vs Q1, OR 1.56 CI 1.11-2.18, *P*trend = .009) and *trans*-nonachlor (Q4 vs Q1, OR 1.46 CI 1.07-2.00, *P*trend = .026). Seminoma risk was statistically significantly associated with *cis*-nonachlor (Q4 vs Q1, OR 1.93 CI 1.27-2.93, *P*trend = .0045), *trans*-nonachlor (Q4 vs Q1, OR 1.72 CI 1.11-2.67, *P*trend = .033), and oxychlordane (Q4 vs Q1, OR 1.64 CI 1.04-2.60, *P*trend = .048). There were no statistically significant associations between serum levels of oxychlordane,ß-HCH, or Mirex and the risk of TGCT.
McGlynn Nat Rev Urol 2012 (261)	Review				Testicular cancer	Exposure to organochlorine pesticides is likely associated with the development of testicular cancer. Agricultural pesticide exposure in general has not been linked to testicular cancer.
Purdue Enviro Health Persp 2009 (265)	Case-control nested within a cohort	49 cases aged 27-62 years diagnosed before 1999 and 51 age, region and year of blood draw matched controls participating in the Norwegian Janus Serum	Serum blood sample drawn at study entry between 1972 and 1978	11 Organochlorine pesticides	Testicular Germ Cell Tumors (TGCT)	No significant association between TGCT and organochlorine serum levels.

	Bank cohort				

16.33 General cancer and general pesticide exposure

Cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Alavanja Med Work Pesticide-related illnesses 2007 (121)	Review					Provides a general overview of the state of cancer research and pesticide exposure.	
Bassil Can Fam Phy 2007 (119)	Systematic review	Studies published between 1992 and 2003 on NHL, leukemia and 8 solid tumor cancers		Any	Non-Hodgkin lymphoma, leukemia and brain, breast, kidney, lung, ovarian, pancreatic, prostate, and stomach cancer.	NHL: Positive results in 10/12 studies, significant results in 4/12 studies. Leukemia: 14/16 studies found positive significant associations, childhood leukemia studies found most important exposures occurred during pregnancy. Brain cancer: 11/11 studies found positive associations. Breast cancer: 5/6 found positive association All studies on pancreatic (3), brain (11), prostate (8) and kidney cancer (6) found positive associations. The study on ovarian cancer failed to find an association. Not clear whether "positive association" is equivalent to "significant positive association" in this review.	
Bradbury Brit J Cancer 2014 (118)	Cohort	1.3 million British women	Organic food consumption (Never, sometimes, usually and always)	Introduction indicates that only difference between conventional and organic food is the pesticide residue	Cancer incidence, soft tissue sarcoma, breast cancer and Non-Hodgkin Lymphoma, oral cavity and pharynx,	A significant increase in the risk of breast cancer for women who usually or always ate organic food (RR 1.09 CI 1.02-1.15), this increase in risk remained after adjustment for hormone replacement therapy. A significant decrease in risk of NHL in women who usually or always ate organic	

Cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
					esophagus, stomach, colorectum, pancreas, lung, malignant melanoma, endometrium, ovary, kidney, bladder, bran, multiple myeloma and leukemia	food (RR 0.79 CI 0.64-0.99). No association with other cancer sites or all cancers.	
Frost Occup Med 2011 (116)	Cohort	65,910 participants in the British Pesticide Users Health Study followed from 1987 to 2004 (incidence) or 2005 (mortality)	Status as a registered pesticide user	Any	Mortality and cancer incidence	SIR for all cause mortality in men and women and for all cancers and cancers of the lip, oral cavity and pharynx, digestive organs and respiratory system were lower than expected. SIR of testicular cancer (SIR 1.26 CI 1.04-1.53), non-melanoma skin cancer (SIR 1.11 CI 1.00-1.23) and MM (SIR 1.49 CI 1.05-2.13) were above expected. Mortality from injury significantly above expected (SMR 4.21 CI 2.11-8.42).	
Kourtos J Occup Enviro Med 2010 (364)	Cohort	52,394 participants in the Agricultural Health Study and 32,346 spouses of the participants recruited 1993-1997 and followed to 2006 for outcomes	Self-reported occupational exposure		Cancer incidence	Not relevant, no pesticide exposures considered.	

Cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Ljunggren Enviro Int 2014 (153)	Case-control	7 controls, 8 subjects with cancer and 13 subjects with cardiovascular disease living in a contaminated area in Sweden	Serum POP levels	Hexachlorobenzene, cis-chlordane and trans-nonachlor	Cancer and cardiovascular disease	Trans-nonachlor was significantly higher in the LDL/VLDL of individuals with CVD than controls. No significant differences between cancer patients and controls. Also in other outcomes	
MacFarlane Ann Epidemiology 2010 (120)	Cohort	12,050 men and 1,084 women from a cohort recruited from government bio monitoring offered 1960 to 1980,	Occupational pesticide exposure starting	Any, most common were organophosphates or carbamates	Incident cancer from 1983 onwards	No association between occupational pesticide exposure and cancer (SMR 0.76 CI 0.69-0.84) or non-injury related mortality.	
Weichenthal Enviro Health Persp 2010(117)	Review	28 studies of the AHS cohort and the relationship between cancer and pesticide use	Self-reported lifetime use days or intensity weighed lifetime days of pesticides exposure	32 pesticides, with positive associations reported for: alachlor, aldicarb, carbaryl, chlorpyrifos, diazinon, dicamba, *S*-ethyl- *N*,*N*-dipropylthiocarbamate, imazethapyr, metolachlor, pendimethalin, permethrin, trifluralin	Cancer	The highest quintile of Diazinon (OP) use was associated with increased all cause cancers (OR 1.58 CI 1.10-2.28). The highest quartile of EPTC (Thiocarbamate) was associated with increased all-cause cancers (OR 1.28 CI 1.09-1.50).	

16.34 Childhood cancer and general or multiple pesticide exposures

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Carozza Enviro Health Persp 2008 (272)	Ecological	All children aged 0 to 14 years from 25 US states	Percent cropland for each of 1,078 counties used to classify countries as low, medium or high agricultural activity	Any	All incident childhood cancer	No significant association with all cancers (OR 1.0 CI 1.0-1.1). Residence in a county of high agricultural activity was associated with an increased risk of: Leukemias (OR 1.2 CI 1.1-1.3), lymphoid leukemia (OR 1.3 CI 1.1-1.4) & acute myeloid leukemia (OR 1.8 CI 1.4-2.3) Lymphomas and reticuloendothelial (OR 1.4 CI 1.2-1.7), HL (OR 2.1 CI 1.6-2.7) & NHL (OR 2.1 CI 1.6-2.8) CNS tumors (OR 1.3 CI 1.1-1.4), astrocytomas (OR 1.5 CI 1.3-1.7) & PNET (OR 1.9 CI 1.5-2.4) Sympathetic nervous system tumors (OR 1.7 CI 1.4-2.1), neuroblastoma (OR 1.8 CI 1.5-2.1) & retinoblastoma (OR 2.6 CI 1.9-3.5) Renal tumors (OR 2.1 CI 1.7-2.6), Wilms' tumor (OR 2.1 CI 1.7-2.7) & Renal carcinoma (OR 3.3 CI 1.3-8.3) Hepatic tumor (OR 3.3 CI 2.1-5.0) & hepatoblastoma (OR 4.0 CI 2.5-6.3) Malignant bone tumors (OR 2.3 CI 1.8-2.9), osteosarcoma (OR 2.7 CI 2.0-3.6)	

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						& Ewing's sarcoma (OR 4.3 CI 3.0-6.2) Soft-tissue sarcoma (OR 1.7 CI 1.4-2.0), rhabdomyosarcomas (OR 2.5 CI 1.9-3.3), germ cell, trophoblastic and other gonadal neoplasm (OR 2.3 CI 1.8-2.8) Carcinoma and other (OR 2.2 CI 1.8-2.8), thyroid carcinoma (OR 3.0 CI 2.0-4.6), malignant melanoma (OR 4.6 (CI 3.0-7.0) Other and unspecified (OR 11.2 CI 5.1-24.4) Risks were generally somewhere between 1.0 and the OR for each cancer category for the medium level of agricultural intensity.	
Carozza Int H Hyg Enviro Med 2009 (278)	Case-control	1778 cases and 1802 controls born in Texas from 1990 to 1998	Probable agricultural pesticide exposure based on proximity of birth residence within 1000m to crop fields	Any	All childhood cancer	No significant associations found between agricultural land within 1km of birth residence and incidence of all cancers or any specific cancer considered, including leukemia, lymphoma and reticuloendothelial neoplasms, brain cancers, sympathetic nervous system tumors, retinoblastoma, renal tumors, hepatic tumors, malignant bone tumors, soft tissue sarcoma. germ-cell, trophoblastic & other gonadal neoplasms, carcinomas & other malignant epithelial neoplasms, other & unspecified malignant neoplasms.	
Flower Enviro Health Persp	Cohort	Children of 17,357 Iowa	Self-reported parental	50 pesticides	Childhood cancer	Risk of all childhood cancers combined was increased [SIR 1.36 CI 1.03–1.79].	

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
2004 (271)		pesticide applicators in the Agricultural Health Study identified in 1993-1997 followed from 1975 to 1998	pesticide exposure			Risk of all lymphomas combined was also increased (SIR 2.18 CI 1.13–4.19), as was risk of Hodgkin's lymphoma (SIR 2.56 CI 1.06–6.14). No association was detected between frequency of parental pesticide application and childhood cancer risk. No association between maternal pesticide mixing or application and childhood cancer. An increased risk of cancer was detected among children whose fathers did not use chemically resistant gloves (OR 1.98 CI 1.05–3.76) compared with children whose fathers used gloves. Of 16 specific pesticides used by fathers prenatally, ORs were increased for aldrin (OR 2.66 CI 1.08-6.59).	
Infante-Rivard J Toxico and Enviro Health Pt B 2007 (274)	Review	15 case-control, 4 cohort and 2 ecological studies published 1999-2004		Any	Childhood cancer	15 of 21 studies reported significant increase in childhood cancer risks with either childhood pesticide exposure or parental occupational exposure. No definitive unambiguous causal relationship. Critical exposure window not defined, role of genetic susceptibility not fully defined. A review of the state of the evidence based on Bradford Hill criteria.	
Jurewicz Int J Occup Med Enviro Health 2006 (270)	Review	Studies from 1998 to 2005		Any	Childhood cancer	Leukemia, brain cancer, non-Hodgkin's lymphoma and neuroblastoma are potentially associated with pesticide exposure among children. Epidemiological study limitations: exposure assessment, small number of exposed subjects, limited studies	

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						focused on each type of cancer and difficulties with estimating critical exposure windows.	
Nasterlack Int Arch Occup Enviro Health 2006 (275)	Review	18 studies from 1998 to 2004		Any	Childhood cancer	The studies suggest an increase in the risk of different cancer types associated with exposure to pesticides subject to many limitations. Many of the risk estimates have Cis that include the null. Formula for Population Attributable Risk (PAR).	
Nasterlack Int J Hyg Enviro Health 2007 (276)	Review	36 studies from 1998 to 2006			Childhood cancer	The studies suggest an increase in the risk of different cancer types associated with exposure to pesticides, subject to many limitations. Many of the risk estimates have Cis that include the null.	
Pearce Arch Enviro Occup Health 2006 (273)	Case-control	4,723 cases under age 25 matched on sex and year of birth to controls from 2 sources: 1) all other patients on the registry with a different cancer 2) 100 cancer-free individual from a Birth Registry in the North of England	Paternal occupational exposure to pesticides or herbicides based on a JEM	Any	Childhood and young adult cancer	No significant positive association between paternal occupational pesticide or herbicide exposure except for male neuroblastoma and ganglioneuroblastoma (OR 2.38 CI 1.01-5.57) and male fibrosarcoma, neurofibroscarcoma and other fibromatous neoplasm (OR 3.89 CI 1.48-10.20). These associations were present when the registry patients were used as controls but not when using the Birth Registry controls. Multiple negative associations when Birth Registry controls were used.	
Reynolds Epidemiology 2005 (279)	Case-control	2189 cases and 4335 controls matched for	Mother's residential proximity to	Specific chemicals and chemical groups used within 0.5 miles	Early childhood cancer and leukemia risk	90% of residences had less than 1lb per square mile applied of specific chemicals and 70% had less than 1lb	

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		birth date and sex	agricultural applications of pesticides at the time of child's birth	of maternal residence divided in low (0 to 49th percentile) and high (50th percentile and up) and when numbers allowed very high (90th percentile and up) exposure		per square mile of chemical groups. No associations with leukemia or CNS tumors combined. In leukemia and childhood brain cancer.	
Vinson Occup Enviro Med 2011 (269)	Meta-analysis	2 cohort and 38 case-control studies published 1985 to 2008			Childhood cancer	No association between parental pesticide exposure and childhood cancer incidence (leukemia, lymphoma or brain cancer) when only the cohort studies considered. When all 40 studies considered, there were significant positive associations between: • Any childhood pesticide exposure and lymphoma (OR 1.37 CI 1.22-1.54), leukemia (OR 1.23 CI 1.14-1.32), brain tumor (OR 1.22 CI 1.13-1.31), Ewing's sarcoma (OR 2.01 CI 1.45-2.79) and neuroblastoma (OR 1.70 CI 1.14-1.51). No association with germ cell tumors or renal tumors. • Maternal prenatal pesticide exposure and lymphoma (OR 1.53 CI 1.22-1.91) and leukemia (OR 1.48 CI 1.26-1.75) • Brain cancer and paternal pesticide exposure before birth (OR 1.49 CI 1.23-1.79) or after birth (OR 1.66 CI 1.11-2.49) • Leukemia and maternal postnatal (OR 2.12 CI 1.17-3.84) or paternal postnatal exposure (OR 1.33 CI 1.07-1.66) or paternal and maternal prenatal exposure (OR 1.84 CI	

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						1.39-2.44) • No increased cancer risk with living in an agricultural area • Brain cancer and paternal occupational (OR 1.40 CI 1.20-1.62) and residential exposure (OR 1.48 CI 1.22-1.80) • Leukemia and paternal occupational exposure (OR 1.37 CI 1.23-1.52) • Ewing's sarcoma and paternal occupational exposure (OR 2.34 CI 1.33-4.12) • Maternal home and garden pesticide use and lymphoma (OR 1.48 CI 1.23-1.80) and leukemia (1.56 CI 1.21-2.02) • Lymphoma and herbicide (OR 1.31 CI 1.02-1.67), insecticide (OR 1.46 CI 1.20-1.78) or fungicide (OR 1.45 CI 1.06-1.99) exposure • Leukemia and herbicide (OR 1.26 CI 1.14-1.39) or insecticide (OR 1.17 CI 1.03-1.33) exposure • Brain cancer and herbicide (OR 1.31 CI 1.08-1.60), insecticide (OR 1.18 CI 1.06-1.33) or fungicide (OR 1.32 CI 1.06-1.65) exposure.	
Walker J Agri Safety and Health 2007 (277)	Case-control	6,974 cases and 6,974 controls aged 0 to 14 identified through the Texas Cancer Registry and the Texas Birth	Percent cropland in county of birth and total county-specific pesticide exposure based carcinogenicity	Any	Childhood cancer (all cancers, leukemia, lymphoma, CNS tumors and subsites)	No significant associations found.	

Childhood cancer and general or multiple pesticide exposures

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
		Registry	classification				

16.35 Cancer and specific pesticide exposure

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
Barry Cancer Causes Control 2012 (128)	Cohort	53,588 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2007	Self-reported occupational exposure	Methyl bromide (soil fumigant)	All cancers	High use of methyl bromide was associated with stomach cancer (RR 3.13 CI 1.25-7.80, p trend 0.02 versus no use). No dose-response relationship with all cancers, prostate cancer, stomach cancer, LHC, NHL, leukemia, oral cavity cancers, colon cancer, rectal cancer, lung cancer, bladder cancer, kidney cancer or melanoma.
Bonner AJE 2007 (140)	Cohort	19,717 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Malathion (organophosphate insecticide)	All Cancers	No significant associations with all cancer, LHC, leukemia, NHL, lung cancer, prostate cancer, colorectal cancer, kidney cancer, bladder cancer or melanoma.
Bonner Enviro Health Persp 2005 (142)	Cohort	48,877 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Carbofuran (carbamate insecticide)	All Cancers	No significant associations with all cancer, LHC, lung cancer, prostate cancer, colon cancer.
Christensen Enviro Health Persp 2010 (132)	Cohort	47,822 male Agricultural Health Study participants from Iowa and North Carolina	Self-reported occupational exposure		Incident cancer in men	No association with all cancers, prostate cancer, lung cancer, colorectal cancer or LHC. Significant interaction between ever use of coumaphos and prostate cancer only in men

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
		followed from 1993 to 2005				with a family history of prostate cancer (RR 1.65 CI 1.13-2.38, p interaction 0.004).
DeLancey Ann Epidemiology 2009 (135)	Cohort	23,072 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2005	Self-reported occupational exposure	Metribuzin (triazinone herbicide)	Incident cancer	No significant dose-response associations for all cancer, LHC, leukemia, NHL, prostate cancer, lung cancer or colon cancer. There was a significant trend of increasing risk of leukemia with increasing exposure ($p<0.04$) but the individual RRs were not significant.
DeRoos Enviro Health Persp 2004(151)	Cohort	57,311 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2001	Self-reported occupational exposure	Glyphosphate (herbicide)	Incident cancer	No association between glyphosphate exposure and the incidence of all cancer, all LHC, NHL, leukemia, MM, or lung, oral cavity, colon, rectal, pancreatic, kidney, bladder, prostate or melanoma cancer.
Freeman AJE 2005 (123)	Cohort	23,206 male Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2005	Self-reported occupational exposure	Diazinon (Organophosphate insecticide)	Incident cancer	There were significantly increased risks for the highest tertile of lifetime days of exposure to diazinon for all cancer (RR 1.06 CI 1.09-1.78, p trend 0.009), lung cancer (RR 2.41 CI 1.31-4.43, p trend 0.005) and leukemia (RR 3.36 CI 1.08-10.49, p trend 0.026) and for the lowest tertile of lifetime exposure days for prostate cancer (RR 1.41 CI 1.05-1.88, p trend 0.34). Using intensity-weighed diazinon exposure showed an additional

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
						significant association with the highest tertile LHC (RR 2.01 CI 1.02-3.94, p trend 0.049). No association with colorectal cancer, melanoma, or NHL.
Freeman Enviro Health Persp 2011 (145)	Cohort	57,310 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2007	Self-reported occupational exposure	Atrazine (Triazine herbicide)	Incident cancer	No strong association between atrazine use and any cancer (prostate, lung, colon, rectum, bladder, oral cavity, esophagus, pancreas, larynx, cutaneous melanoma, kidney, brain, thyroid, liver, LHC, leukemia, NHL, MM and other lymphomas) or overall cancer incidence. Limited evidence for an association between atrazine use and thyroid (Intensity weighted lifetime days Q2 RR 4.55 (CI 1.27-16.24), Q4 RR 4.84 CI 1.31-17.93, p trend 0.08).
Greenburg Cancer Causes Control 2008 (143)	Cohort	48,986 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2004	Self-reported occupational exposure	Captan (Thiophthalimide fungicide)	Incident cancer	No significant association between captan exposure and overall cancer or cancers of the prostate, lung, colon, colorectal or blood-related (NHL, leukemia, MM and Hodgkins) cancers.
Hou Epidemiology 2006 (148)	Cohort	9,089 exposed and 15,285 unexposed Agricultural Health Study participants from Iowa and North Carolina	Self-reported occupational exposure	Pendimethalin (dinitroanilines herbicide)	Incident cancer	No significant association between pendimethalin exposure and overall cancer incidence or lung, colorectal, colon, prostate, melanoma, LHC and NHL. There is a significant association between pendimethalin exposure and

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
		followed from 1993 to 2002				rectal cancer (Highest tertile RR 4.3 CI 1.5-12.7, p trend 0.007) with no exposure as baseline but the association was attenuated to non-significant when the lowest exposure level was used as baseline (p trend 0.08). There were some significant associations with lung cancer but they were inconsistent across exposure levels with no significant trend.
Kang Enviro Res 2008 (130)	Cohort	50,127 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Trifluralin (2,6-dinitro herbicide)	Incident cancer	No significant association between trifluralin exposure and all cancer or prostate, lung, LHC, NHL, leukemia, rectum, bladder and kidney) A significant association was found between intensity weighed but not lifetime exposure days trifluralin exposure and colon cancer (Highest tertile non-exposed referent RR 1.76 CI 1.05-2.95, lowest tertile referent RR 1.76 CI 1.05-2.95, p trend <0.04).
Kourtos Int J Cancer 2009 (127)	Cohort	29,398 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2004	Self-reported occupational exposure	Imazethapyr (aromatic amine)	Incident cancer	A significantly increased risk of bladder cancer (RR top half highest tertile 2.37 CI 1.20-4.68 p trend 0.01) and colon cancer (RR top half highest tertile 1.78 CI 1.08-2.93 p trend 0.02) and lifetime imazethapyr exposure. The significant colon cancer finding was limited to proximal colon cancers (RR 2.73 CI 1.42-5.25 p trend 0.001). No

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
						significant associations for prostate, lung, rectum, kidney, oral, pancreas, LHC or melanoma.
Koutros Cancer causes control 2008 (141)	Cohort	49,762 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2004	Self-reported occupational exposure	Dichlorvos (organophosphate insecticide)	Incident cancer	No significant association between dichlorvos exposure and all cancers or prostate,, colon, lung or LHCs.
Lee AJE 2004 (126)	Cohort	49,980 participants (26,510 exposed) Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2000	Self-reported occupational exposure	Alachlor (chloroacetanilide herbicide)	Incident cancer	A significant trend for all lymphohematopoietic cancers for lifetime exposure days (p trend 0.03) and intensity-weighed exposure days (p 0.03). No individually significant rate ratios or other trends that were significant with both lifetime exposure and intensity weighed exposure days. A significant 3rd quarter RR for all cancers in lifetime exposure (RR 1.34 CI 1.04-1.73) and intensity weighed exposure (RR 1.42 CI 1.11-1.82), which the authors state, is potentially due to chance. No significant associations for buccal cavity and pharynx cancers, esophageal cancer, stomach cancer, colorectal cancer, lever, pancreas, larynx, lung, melanoma, prostate, testis, bladder, kidney, brain or thyroid or individual LHC

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
						(NHL, MM or leukemia).
Lee J Natl Cancer Inst 2004 (137)	Cohort	54,383 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2001	Self-reported occupational exposure	Chlorpyrifos (organophosphate insecticide)	Incident cancer	The incidence of lung cancer was statistically significantly associated with both chlorpyrifos lifetime exposure-days (*P*trend 0.002) and chlorpyrifos intensity-weighted exposure- days (*P*trend 0.036) with the highest lifetime days exposure category having a significant OR (OR 2.18 CI 1.31-3.64). No consistent association with all cancers or cancers of the buccal cavity and pharynx, esophagus, stomach, colorectal, pancreas, melanoma, prostate, bladder, kidney or brain or all LHC, NHL, MM or leukemia. Bladder cancer, rectal cancer, all LHC and leukemia did show an association with either lifetime day or intensity weighed exposure but not both.
Lerro Int J Cancer 2015 (129)	Cohort	33,484 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2010-2011	Self-reported occupational exposure	Acetochlor (chloracetanilide herbicide)	Incident cancer	Increased risk of lung cancer was observed among acetochlor users (RR 1.74 CI 1.07–2.84) compared to nonusers, and among individuals who reported using acetochlor/atrazine product mixtures (RR 2.33 CI 1.30–4.17), compared to nonusers of acetochlor. Colorectal cancer risk was significantly elevated among the highest category of acetochlor users (RR 1.75 CI 1.08–2.83) compared to never

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
						users. Borderline association were seen for melanoma (RR 1.61 CI 0.98-2.66) and pancreatic (RR 2.36 CI 0.98-5.65) cancer. No association for all site, bladder, LHC, colon, kidney, NHL, prostate or aggressive prostate cancer.
Lo Connecticut Medicine 2011 (152)	Ecological	Cancer incidence in North Stamford (high contamination area) compared to New Canaan, Wilton, Weston and Darien (low contamination areas) from 1998 to 2007	Well water contamination	Chlordane and dieldrin (organochlorines)	Cancer incidence	No significant difference between cancer incidence in North Stamford and the low contamination areas.
Lynch Enviro Health Persp 2006 (147)	Cohort	50,317 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2002	Self-reported occupational exposure	Cyanazine (triazine herbicide)	Incident cancer	No significant associations found between cyanazine usage and the risk all cancers, all LHC, NHL, prostate, colon and lung cancer (minimum of 30 exposed cases).
Lynch Enviro Res 2009 (125)	Cohort	19,655 (5,297 exposed) Agricultural Health Study participants from Iowa and North Carolina	Self-reported occupational exposure	Butylate (thiocarbamates herbicide)	Incident cancer	Significant associations were found between the highest level of butylate lifetime days and all cancer (RR 1.70 CI 1.20-2.40, p trend 0.01), prostate cancer (RR 2.09 CI 1.27-3.44, p trend 0.004), all LHC (RR 2.27 CI

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
		followed from 1993 to 2004				1.18-4.37, p trend 0.003) and NHL (RR 3.44 CI 1.29-9.21, p trend 0002) using the low exposed group as a referent. No significant associations for lung, leukemia, melanoma, bladder, kidney and oral cavity cancers.
Mahajan Enviro Health Persp 2006 (133)	Cohort	45,372 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Fonofos (Organophosphate insecticide)	Incident cancer	No significant associations for all cancer, prostate, lung, colon, LHC, or melanoma skin cancer. Significant increase in leukemia for highest tertile exposure when no exposure used as referent (RR 2.67 CI 1.06-6.70, p trend 0.04) but not when low exposure used as referent. Prostate cancer risk was elevated in those with a family history of prostate cancer only (RR 1.67 CI 1.35-2.07 for ever exposure, p trend 0.02). There was a significant interaction between family history of prostate cancer and Fonofos exposure with the joint effect being RR 2.63 (CI 1.96-3.53).
Mahajan Enviro Health Persp 2006 (134)	Cohort	5,903 exposed and 15,113 unexposed Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Phorate (organophosphate pesticide)	Incident cancer	No significant associations for all cancer, LHC, colon cancer, lung cancer or prostate cancer. Increased risk of prostate cancer in those with a family history of prostate cancer and ever phorate exposure (RR 1.53 CI 1.09-2.14).

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
Mahajan Int J Cancer 2007 (131)	Cohort	21,416 (1,291 cases) Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2003	Self-reported occupational exposure	Carbaryl (carbamate insecticide)	Incident cancer	No significant positive associations between carbaryl use and all cancers, lung, prostate, colon, LHC, leukemia and bladder cancer. A significant increase in melanoma risk with more than 175 days of use (RR 4.11 CI 1.33-112.75 p trend 0.07), more than 10 years of use (RR 3.19 CI 1.28-7.92 p trend 0.04) or more than 10 days or use per year (RR 5.50 CI 2.19-13.84 p trend <0.01).
Mozzachio Enviro Res 2008 (144)	Cohort	47,625 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2004	Self-reported occupational exposure	Chlorothalonil (fungicide)	Incident cancer	No association between chlorothalonil exposure and all cancers, colon, lung and prostate cancer. There was a significant 2nd tertile association for lung cancer in intensity weighed and lifetime exposure days but no significant trend or increase in the 3rd tertile.
Park Int J Occup Enviro Health 2009 (150)	Cohort	56,222 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2004	Self-reported occupational exposure	Paraquat (herbicide)	Incident cancer	No significant positive associations between paraquat and all cancers, leukemia, pancreatic cancer, lung, kidney, bladder, female breast cancer or skin melanoma. A significant increase in NHL among ever users versus non users (RR 1.51 CI 1.01-2.26), intensity weighed measures failed to show a significant trend.

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
Purdue Int J Cancer 2007 (122)	Cohort	22,409 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Organochlorine insecticides (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene)	Incident cancer	No overall associations between ever use of OCs and all cancers, prostate, lung, rectal, bladder, NHL,and melanoma except leukemia (RR 2.0 CI 1.0-4.1) and colon cancer (RR 0.6 CI 0.5-0.9). Significantly increased risks of some cancers were observed for some chemicals (rectal cancer and high chlordane use (LD RR 2.7 CI 1.1-7.2), lung cancer and high dieldrin use (LD RR 2.8 CI 1.1-7.2), non-Hodgkin lymphoma (NHL) and high lindane (IW RR 2.6 CI 1.1-6.4), melanoma and high toxaphene use (LD RR 2.9 CI 1.1-8.1), leukemia and high chlordane/heptachlor use (LD RR 2.6 CI 1.2-6.0). Negative associations between colon cancer and high aldrin use (IW RR 0.4 CI 0.2-1.0) and all cancers and high hepatachlor use (LD RR 0.7 CI 0.5-1.0). All p trends mentioned significant.
Rusiecki Enviro Health Persp 2009 (136)	Cohort	49,093 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2004	Self-reported occupational exposure	Permethrin and other pyrethroid products (pyrethroid insecticides)	Incident cancer	No association between permethrin exposure and all cancers, melanoma, NHL, leukemia, colon, rectal, lung or prostate cancer. Significant increase (p trend <0.01 for both) in risk of MM for highest tertile of LD (RR 5.72 CI 2.76-11.87) and IW (RR 5.01 CI 2.41-10.42) use but these estimates are based on small

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
						numbers (n=15 cases).
Rusiecki Int J Cancer 2006 (149)	Cohort	50,194 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Metolachlor (chloroacetanilide herbicide)	Incident cancer	No significant positive assocaitions between metolachlor use and all cancers, oral cavity, colon, lung, prostate, LHC and NHL. A significantly decreased risk of prostate cancer in two different tertile for each exposure metric but there was no significant trend.
Rusiecki J Natl Can Inst 2004 (146)	Cohort	53,943 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2001	Self-reported occupational exposure	Atrazine (triazine herbicide)	Incident cancer	No significant associations between lifetime exposure or intensity weighed exposure days to atrazine for all cancers, oral cavity, esophageal, colorectal, pancreatic, prostate, kidney, lung, or bladder cancer, melanoma, NHL, leukemia or multiple myeloma.
Samanic Enviro Health Persp 2006 (138)	Cohort	41,969 Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	Dicamba (Benzoic acid herbicide)	Incident cancer	No significant positive associations between dicambia use and all cancers. A significant trend for lung cancer but no individual RR was significant (p trend= 0.02). A significant association with colon cancer only when the low exposure group was used as referent (highest tertile LD RR 3.29 CI 1.40-7.73, p trend 0.02, IW RR 2.57 CI 1.28-5.17, p trend 0.002).
Sathiakumar Crit Rev in Toxico	Review	36 studies		Triazine herbicides	Cancer	NHL, prostate and breast cancer most frequently investigated.

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
2011 (139)						Few studies on other cancers. As a group the studies had significant limitations including exposure measurement precision, limited follow-up, few subjects with high exposure. Agricultural worker and community based exposure studies did not provide convincing evidence of an association between triazine exposure and cancers. No consistent convincing evidence of a causal association between triazine herbicides and cancer. Article sponsored by triazine manufacturing company.
van Bemmel Enviro Health Persp 2008 (124)	Cohort	48,378 male Agricultural Health Study participants from Iowa and North Carolina followed from 1993 to 2002	Self-reported occupational exposure	EPTC (*S*-ethyl-*N*,*N*-dipropylthiocarbamate) (a thiocarbamate herbicide)	Incident cancer	EPTC was significant associated with all cancers in the highest tertile of use (LD RR 1.28 CI 1.09-1.50, p trend <0.01 IW days RR 1.16 CI 1.01-1.35 p trend 0.02). EPTC was associated with leukemia only in the highest tertile of use for LD (RR 2.36 CI 1.16-4.84, p trend 0.02) but not IW days (RR 1.87 CI 0.97-3.59, p trend 0.05). EPTC was associated with the middle but not highest tertile of use for LD melanoma (RR 2.53 CI 1.32-4.87, p trend 0.89) but not IW days (RR 1.27 CI 0.51-3.18, p trend 0.35). EPTC was also associated with prostate cancer for the lowest tertile of LD (RR 1.31 CI 1.06-

Cancer and specific pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result
						1.63) and the middle tertile of IW days (RR 1.61 CI 1.24-2.11) without significant trend. EPTC was associated with colon cancer in the highest tertile of both lifetime exposure days and intensity-weighted lifetime days (RR 2.09 CI 1.26–3.47 and RR 2.05 CI 1.34–3.14, respectively) and the trend test was < 0.01 for both, the pattern of RRs was not monotonic with increasing use.

16.36 Other adult cancers

Other adult cancers and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Behrens Cancer Causes Control 2012 (266)	Case-control	293 cases and 3,198 controls matched on country, 5-year age group and sex between 1994 and 1997	Self-reported pesticide exposure (duration and application method and use of PPE)	Any	Uveal melanoma of the eye	No significant positive association between pesticide application or mixing in farming. Application of chemicals in forestry was associated with uveal melanoma (OR 8.93 CI 1.73-42.13).	
Merletti Int J Cancer 2006 (268)	Case-control	96 cases aged 35 to 69 years and 2,632 population controls (68% healthy, 32% colon cancer) in 1995-7 in 7 European countries	Occupational pesticide exposure	Any pesticide, fungicide, insecticide and herbicide	Bone sarcoma (68 chondrosarcoma, 28 osteosarcoma)	A significant increase in risk of bone cancer for ever use of pesticides (OR 2.3 CI 1.31-4.13), herbicides (OR 2.70 CI 1.30-5.57) and insecticides (OR 2.64 CI 1.37-5.10). This relationship lacked a dose-response relationship, with the lowest (OR 1.03 CI 0.23-4.57), middle (OR 3.13 CI 1.26-7.76) and highest (OR 1.44 CI 0.43-4.85) tertiles not showing a significant trend. No significant association between being a farmer and bone sarcoma. Ever use of pesticides showed a lower odds of bone cancer with protective equipment (i.e. 1 of mask, gloves, glasses, overalls and handkerchief) (OR 2.01 CI 0.75-5.43) then without (OR 2.47 CI 1.29-4.70).	
Nordby et al. Scan J Work Environ Health 2005(36)	Retrospective cohort	105403 female and 131243 male farmers born 1925-1971 and their 300805 children born 1952-1991	Farm production and fungal forecasts (humid and temperate condition) served as a proxy for mancozeb exposure	**Mancozeb**	Thyroid cancer	No association with thyroid cancer (n=141 female and 79 male and 99 children) Also in birth defects.	
Tarvainen Int	Cohort	46.8 million	JEM to	Any	Mouth and	No positive association between farming and	

Other adult cancers and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
J Cancer 2008 (267)		person-years of follow-up of a cohort of Finns born 1906-1945	estimate occupational exposure		pharynx cancer	mouth and pharynx cancer in men (SIR 0.67 CI 0.58-0.77) or women (SIR 0.80 CI 0.64-0.98) with evidence of a healthy worker effect. Evidence of an increase incidence of mouth and pharynx cancer in men and women with the lowest tertile of fungicide exposure (SIR 1.48 CI 1.05-2.04). No significant increase in incidence with exposure the middle and highest tertile of fungicide exposure. No increased SIR with exposure to pesticides, herbicides or insecticides, however there was an elevated risk of mouth and pharynx cancer with cumulative highest tertile pesticide exposure (RR 1.92 CI 1.00-3.68).	

16.37 Other childhood cancers

Other childhood cancers and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Abdolahi Occup Enviro Med 2013 (298)	Case-control	198 cases and 245 controls referred by cases	Paternal occupational exposures	Exposures assigned by occupational hygenists (probability, intensity and frequency)	Retinoblastoma	An elevated risk of retinoblastoma associated with paternal pesticide exposure in the 10 years prior to conception (OR= 1.64; 95% CI: 1.08-2.50) as well as in the year before conception (OR= 2.12; 95% CI: 1.25-3.61). Exposure-response trends were observed for pesticides in the full sample (p for trend < 0.0001).	
Chen AJE 2005 (301)	Case-control	253 cases and 394 controls in the US	Parental occupational exposure	Assessed by occupational hygienist for exposure to any pesticide	Childhood germ cell tumors	No significant association between maternal pre-conceptual, prenatal and childhood pesticide exposure,. No significant association between paternal pre-conceptual, prenatal or childhood pesticide exposure and germ-cell tumors.	
Chen Int J Hyg and Eviro Health 2006 (299)	Case-control	253 cases and 394 controls matched on sex, age and geographic area	Parental pesticide exposure from 6 month before pregnancy to breastfeeding and childhood exposures	Residential pesticides	Germ cell tumors	No significant association between maternal, paternal or childhood residential pesticide exposure and germ-cell tumors except for maternal herbicide exposure in girls (OR 1.4 CI 1.0-2.0).	
Moore Int J Cancer 2005 (300)	Case-control	196 cases aged 1.6 to 22.8 years and 196 population controls matched on geographical region, sex, ethnic origin and birth date within 2 years in the US	Occupational pesticide exposure	Possible and probable pesticide exposure	Ewing's sarcoma	No significant association between probable or possible parental occupational pesticide exposure and Ewing's sarcoma. In boys younger than 15 years, a household extermination during childhood was associated with Ewing's sarcoma (OR 3.0 CI 1.1-8.1). No other associations were apparent for household exterminations during	

Other childhood cancers and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
						childhood.	

16.38 Asthma

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Baldi Int J Hygiene Enviro Health 2014(313)	Cross-sectional	15,494 AGRICAN (France) farmers, 1,246 with self-reported asthma	Occupational ever pesticide use on specific crops	Any	Self-reported asthma (Allergic asthma is asthma with hay fever or eczema, non-allergic asthma is without hay fever or eczema)	Allergic asthma was associated with the use of pesticides on grassland (OR 1.35 CI 1.03-1.76), vineyards (OR 1.35 CI 1.02-1.80) and fruit-growing crops (OR 1.56 CI 1.01-2.40). Non-allergic asthma was associated with the use of pesticides on beets (OR 1.47 CI 1.03-2.10).	

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Chatzi Occup Environ Med 2007 (314)	Cross-sectional	120 grape farmers and 100 controls in Northern Crete	Number of working hours per day, the number of years working in grape cultivations, the preventive measures used, the use of pesticides and work-related symptoms. At the end of the questionnaire, there was a list of 50 commonly used pesticides (brand names) for participants to identify those currently used.	50 commonly used pesticides	The definition of current asthma according to the questionnaire was based on asthma symptoms or medication. A second definition for asthma included the previous definition, followed by a positive bronchodilatation test.	No significant relationship between asthma and pesticide use.	Also in respiratory symptoms table

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Doust Euro Resp Review 2014 (308)	Review	23 studies published after 1990 (12 asthma studies in adults, 5 studies of asthma in children, 12 studies of wheeze in adults, 4 studies of wheeze in children and 7 of COPD in adults)		Any	Asthma and COPD	Pesticides may be associated with prevalent asthma subject to methodological limitations on study design, exposure measurement and adjustment for confounders. Asthma more consistently associated with pesticide exposure in children (4/5 studies) than adults (7/12 studies). Only 4 of 12 studies found an association with adult wheeze. In children 3 of 4 studies found a positive association. Possible association with COPD but evidence is even weaker than for asthma. In COPD also.	

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Duramad Environ Health Perspec 2006 (302)	Prospective cohort	36 12-month olds and 239 24 month olds (22 of which were sampled at 12 and 24 months) in the subjects of CHAMA-COS (Center for the Health Assessment of Mothers and Children of Salinas), a longitudinal birth cohort in Salinas Valley, California.	Maternal and paternal work in agriculture	**organophosphate** (OP) pesticides	T-helper 1 (Th1) and T-helper 2 (Th2) cytokines, biomarkers of allergic asthma blood samples collected at 12 and 24 months of age	Children who were diagnosed with asthma had significantly higher Th2 (1.0%; 95% CI, 0.7–1.2%) than those without asthma (0.7%; 95 % CI, 0.6–0.7%; $p < 0.05$) at 2 years of age. Children who lived with agricultural workers had higher levels of Th2 (0.8%; 95% CI, 0.7–0.9%) than children who did not (0.6%; 95% CI, 0.5–0.7%; $p = 0.02$). Specifically, children of women who worked in the fields had significantly higher Th2 (0.9%; 95% CI, 0.7–1.0%) than children of mothers who did not work in agriculture (0.6%; 95% CI, 0.6–0.7%; $p = 0.001$). A mother working in the fields was associated with a 25.9% (95% CI, 0.8–57.3%; $p = 0.04$) increase in children's Th2 levels in the adjusted model.	Exposure index not well defined: parental work status only.

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Henneberger Int Arch Occup Enviro Health 2014 (312)	Cross-sectional	926 AHS pesticide applicators with active asthma, 202 with exacerbations in the past 12 months	Occupational pesticide use in the last 12 months	36 specific pesticides	Asthma exacerbation in the last 12 months requiring a doctor or emergency room visit. Allergic asthma was defined as asthma with hay fever or eczema.	Inverse associations with exacerbation were observed for two herbicides (glyphosate OR 0.5 CI 0.3–0.8, and paraquat, OR 0.3 CI 0.1–0.9). Allergic asthma cases had positive exacerbation-pesticide associations with the herbicide pendimethalin (OR 2.1 CI 1.1–4.1) and for the insecticide aldicarb (OR 10.2 CI 1.9–55). Evidence of asthma patients prone to exacerbations avoiding triggers.Applicators with allergic asthma were more likely to use PPE when handling insecticides (OR 1.8 CI 1.1-3.0).	

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hoppin et al. Amer J Respir Crit Cre Med 2008 (309)	Case-control	25,814 farm women in the Agricultural Health Study	Personal use of 50 specific pesticides, lifetime total years of pesticide use, and frequency of application. Total lifetime days of pesticide application was calculated as the product of the total years of use and the frequency of use.	**Herbicides:** 2,4-D Alachlor Atrazine Butylate Chlorimuron-ethyl Cyanazine Dicamba Glyphosate Imazethapyr Metolachlor Metribuzin Paraquat Pendimethalin Petroleum oil Trifluralin **Insecticides:** *Carbamates* Carbaryl Carbofuran *Organophosphates* Chlorpyrifos Coumaphos Dichlorvos Diazinon Fonofos Malathion Parathion Phorate Terbufos *Organochlorines* Aldrin Chlordane DDT Heptachlor Lindane Pyrethroids Permethrin (animals) Permethrin (crops) **Fungicides**: Captan **Chlorothalonil** Maneb Metalaxyl **Fumigants:** 80/20 mix Methyl bromide	Self-reported history of doctor-diagnosed asthma with or without eczema and/or hay fever to create two case groups: patients with atopic asthma and those with non-atopic asthma	Any use of pesticides on the farm was associated only with atopic asthma (OR, 1.46; 95% CI, 1.14–1.87). A total of 7 of 16 insecticides (Any insecticide OR 1.43 (CI 1.12-1.81), Any carbamate OR 1.46 (CI 1.14-1.86), Carbaryl OR 1.41 (CI 1.1.10-1.80), Any organophosphate OR 1.45 (CI 1.12-1.87), Coumaphos OR 2.19 (CI 1.02-4.69), Malathion OR 1.60 (CI 1.22-2.10), Parathion OR 2.88 (CI 1.34-6.20), Phorate OR 2.04 (CI 1.07-2.31), Any organochlorine OR 1.57 (CI 1.07-2.31), DDT OR 1.79 (CI 1.06-3.03), Permethrin (Animals) OR 1.71 (CI 1.01-2.91)) , 2 of 11 herbicides (Any herbicide OR 1.43 (CI 1.12-1.83), 2,4-D OR 1.53 (CI 1.12-210), Glyphosate OR 1.31 (CI 1.02-1.67)), and 1 of 4 fungicides (Metalaxyl OR 2.61 (CI 1.35-5.04)) were significantly associated with atopic asthma; only permethrin use on crops (OR 2.19 (CI 1.33-3.61) was associated with nonatopic asthma.	Growing up on a farm confounded all the models.

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hoppin et al. Annals NY Acad Sci 2006 (310)	Prospective cohort	~89,000 liscensed pesticide applicators and spouses in Iowa and North Carolina who had all variables present (n=17,920), 97% male	Never use, use of pesticide but not in past year (former use) and current use in past year	40 individual pesticides: 2,4-D, Alachlor, Atrazine, Butylate Chlorimuron-ethyl Cyanazine, Dicambia, EPTC, Glyphosate, Imazethapyr,, Metolachlor. Metribuzin, Paraquat, Pandimethalin, Petroleum oil, Trifluralin, Aldicarb, Carbaryl, Carbofuran, Chlorpyrifos, Coumaphos, Diazinon, Dichlorvos, Fonofos, Malathion, **Phorate**, Terbufos, Triclorfon, Lindane, Permethrin (crops and animals), Benomyl, Captan, **Chlorothalonil**, Maneb/,**Mancozeb**, Metalaxyl, Ziram, Alumiium phosphide, Methyl bromide	Self reported wheeze in the last year, adult asthma, Farmer's Lung Chronic Bronchitis	Use of organophosphates in farmers, alachlor (OR 1.23 (CI 1.06-1.41)), atrazine (OR 1.18 (CI 1.05-1.32)), EPTC (OR 1.37 (CI 1.08-1.73), petroleum oil (OR 1.26 (1.09-1.47)), trifluralin (OR 1.15 (CI 1.02-1.30)), malathion (OR 1.13 (CI 1.00-1.27)), permethrin (animals) (OR 1.28 (CI 1.06-1.55)) were significantly associated with wheeze. Increasing odds of wheeze with increased days of chlorimuron-ethyl ($p<0.01$) and chlorpyrifos ($p=0.01$).	Interesting point in discussion about the 'healthy worker effect' and farmer who self-select to stay in farming or to contract out pesticide application

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hoppin Eur Resp J 2009 (311)	Case-control	19,704 male farmers in the Agricultural Health Study	Lifetime use of 48 pesticides	Herbicides: 2,4,5-TP, EPTC, paraquat and petroleum oil Insecticides: Organochlorines: chlordane, heptachlor, and lindane, DDT Organophosphates: diazinon, parathion, and coumaphos, **phorate** and malathion Fungicide: captan Fumigants: ethylene dibromide and 80/20 mix (carbon tetrachloride and carbon disulfide) Captan-treated seed Metalaxyl-treated seed	Doctor-diagnosed asthma cases categorized as allergic (N=127) and non-allergic (N=314) based on their history of eczema or hayfever	For allergic asthma, three herbicides (2,4,5-TP (OR 1.91 (CI 1.06-3.44), EPTC (OR 1.61(CI 1.06-2.43)), and paraquat (OR 1.67 (CI 1.05-2.65)), six insecticides (organochlorines: chlordane (OR 1.77 (CI 1.19-2.63)), heptachlor (OR 2.01 (CI 1.30-3.11)), and lindane (OR 1.57 (CI 1.01-2.41)); and organophosphates: diazinon (OR 1.57 (CI 1.05-2.35)), parathion (OR 2.05 (CI1.21-3.46)), and coumaphos (OR 2.34 (CI 1.49-3.70))), one fungicide (captan (OR 1.83 (CI 1.15-2.94))), and two fumigants (ethylene dibromide (OR 2.07(CI 1.02-4.20)) and 80/20 mix (OR 2.15(CI 1.23-3.76))) were positively associated. For non-allergic asthma, one herbicide (petroleum oil (OR 1.35 (CI 1.04-1.74))) and three insecticides (organochlorine: DDT (OR 1.41 (CI 1.09-1.84)) and organophosphates; phorate (OR 1.29 (CI 1.01-1.65)) and malathion (OR 1.35 (CI 1.04-1.75))) were associated. Allergic asthma was associated with captan-treated seed (OR=2.49 (CI=1.42-4.36) and metalaxyl-treated seed (OR=5.18, CI =2.48-10.8).	

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
O'Sullivan Amer J Emerg Medicine 2005 (315)	Cross-sectional	All patients presenting to Lincoln Hospital in New York for asthma during the 4 days of spraying of malathion and resmethrin in Sept 1999	Spraying of Malathion and Resmethrin occurred in the hospital's geographic area over 4 days in September 1999.	Malathion and Resmethrin	Emergency department visits for asthma-related symptoms	Findings showed that the spraying of insecticides did not increase the rate or severity of asthma presentations as measured by the Lincoln Hospital's ED asthma census or hospital admissions for asthma compared to the same 4 days 1 year and 2 years earlier and other days of the same month when no spraying occurred, including an analysis that considered the 5 days after spraying to account for delayed effects.	No comparison group.

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Reardon J Allergy Clin Immuno 2009 (306)	Prospective birth cohort	Nonsmoking African American and Dominican mothers recruited during pregnancy	Personal air samples collected from monitors worn by women for 2 days during the last trimester of pregnancy	Organophosphates: chlorpyrifos and diazinon and pyrethroids:*cis*-permethrin and *trans*-permethrin	German cockroach allergen (Bla g 2) in house dust collected prenatally and serum IgE levels at ages 2, 3, and 5 years. Parent-reported asthma and respiratory symptoms (cough and wheeze) in prior 12 at 2, 3, and 5 years	Diazinon was significantly inversely associated with cough (OR 0.78 (CI 0.67-0.91)), wheeze (OR 0.83 (CI 0.72-0.95)) or specific IgE (OR 0.64 (0.50-0.82)), by 5 yearswhereas *cis*-permethrin was positively associated with cough by 5 years (OR 1.3 (CI 1.03-1.56)).	Not clear how many women/child pairs were included in study, pesticide specific ORs calculated based on 323 to 338 children but source document indicates only 72 women wore the air monitors to measure pesticide residue of the 316 in the initial cohort. I suspect that each outcome measurement was entered separately because GEE equations were used.

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Salam Enviro Health Perspec 2004 (304)	Case-control	4244 school age children in 12 southern California communities, controls frequency matched on age, sex and community and exposure to maternal in-utero smoking	Telephone interviews to assess exposure history	Any herbicide or pesticide exposure	Case: physician diagnosed asthma by age 5 (n=338, 279 participated) Control: asthma-free at study entry (n=570, 412 participated)	Asthma-diagnosis in the first 5 years of life was associated with exposure to herbicides (OR4.58; CI, 1.36-15.43), pesticides(OR 2.39; CI, 1.17-4.89) in the first year and later. Risk of early persistant asthma was increased with exposure to herbicides (OR 10.08; CI, 2.46-41.33), pesticides(OR 3.58; CI, 1.59-8.06) in the first year and later.	Recall bias a possibility, although unlikely to be a differential misclassification problem.
Tagiyeva Eur Resp J 2010 (303)	Birth cohort	11,193 mothers and 9,473 fathers antenatally, and for 4,631 mothers and 5,315 fathers postnatally.	Maternal and parental occupation	Fungicide/biocide exposures	Parent report of wheezing at 81 months and doctor diagnosed asthma	Medium/high maternal levels of biocide/fungicide exposure were associated with a antenatal OR 1.23 (CI 1.07-1.40) and post-natal OR (95% CI) of 1.22 (1.02–2.05), respectively, for wheezing up to 81 months. Medium/high maternal biocide/fungicide exposure during the post-natal period was associated with asthma (OR (95% CI) 1.47 (1.14–1.88)).	Exposure index not very specific.

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Weselak Enviro Research 2007 (307)	Retrospective cohort	3405 children of farmers who were on the farm in utero and after birth	Self-reported present and former pesticide use (crop name, chemical name, reason for use, total area sprayed or dusted, total quantity used, method of application, months of application, and the number of years of use were requested) from month of conception to month of delivery	Any Pesticide Fungicides Insecticides Herbicides Phenoxy Triazine Thiocarbamate **Organo-phosphates** Dicamba Glyphosate 2,4-DB 2,4-D **MCPA** Atrazine Cyanazine Carbaryl Captan	Self-reported asthma, allergies, hay fever, persistent cough/bronchitis	All adjusted for significant confounders. No significant association between asthma and pesticide exposure.	Restropective nature may have caused significant recall bias but unlikely differential

Asthma and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Xu et al. JOEM 2012 (305)	Cross-sectional	14,065 children younger than 18 years in the 1999 to 2004 National Health and Nutrition Examination Survey	Pesticide application in (what room: entire home, kitchen/dining room or other rooms) and around the home and applicator (professional or non-professional)	Any pesticide use	Wheezing and dry cough	Pesticide use in the home was not associated with wheezing, chronic cough and chronic phlegm. Pesticide use in the kitchen or dining rooms was significantly associated with increased odds of wheezing (OR, 1.39; CI 1.08 to 1.78) and dry cough (OR, 2.38; CI 1.40 to 4.06) after controlling for covariates.	No specific pesticides; may have obscured significant association. Only major confounders accounted for. All variables based on self-report. Exposure index lacked variability.

16.39 Chronic Obstructive Pulmonary Disease

COPD and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Doust Euro Resp Review 2014 (308)	Review	23 studies published after 1990 (12 asthma studies in adults, 5 studies of asthma in children, 12 studies of wheeze in adults, 4 studies of wheeze in children and 7 of COPD in adults)		Any	Asthma and COPD	Pesticides may be associated with prevalent asthma subject to methodological limitations on study design, exposure measurement and adjustment for confounders. Asthma more consistently associated with pesticide exposure in children (4/5 studies) than adults (7/12 studies). Only 4 of 12 studies found an association with adult wheeze. In children 3 of 4 studies found a positive association. Possible association with COPD but evidence is even weaker than for asthma. In asthma also.	

COPD and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hoppin Amer J of Ind Med 2007 (318)	Cross-sectional	20,908 private pesticide applicators, primarily farmers enrolling in the Agricultural Health Study	Lifetime self-reported pesticide use of 50 specific pesticides	Aldicarb, Carbaryl, Carbofuran, Aldrin, Chlordane, Dieldrin, DDT, Heptachlor, Lindane, Toxaphene, Chlorpyrifos, Coumaphos, Diazinon, Dichlorvos, Fonofos, Malathion, Parathion, **Phorate**, Terbufos, Permethrin (animals), Permethrin (crop), 2,4-D, 2,4,5-T, 2,4,5-TP, Alachlor , Atrazine, Butylate, Chlorimuron-ethyl, Cyanazine, Dicamba, EPTC, Glyphosate, Imazethapyr, Metolachlor, Metribuzin, Paraquat, Pendimethalin, Petroleum oil, Trifluralin, Ethylene dibromide, Methyl bromide, 80/20 mix, Aluminum phosphide, Benomyl, Captan, **Chlorothalonil, Maneb/mancozeb**, Metalaxyl, Ziram	Self-report of doctor-diagnosed chronic bronchitis after age 20	After adjustment for correlated pesticides as well as confounders, 11 pesticides were significantly associated with chronic bronchitis. Heptachlor use had the highest odds ratio (OR = 1.50, 95% Confidence Interval (CI) 1.19, 1.89).Four other organochlorine insecticides also had elevated odds ratios (chlordane (OR 1.37 (CI 1.14-1.65)), DDT (OR 1.43 (CI 1.19-1.73)), lindane (OR 1.40 (CI 1.13-1.73)), toxaphene (OR 1.40 (CI 1.13-1.75)), heptachlor (OR 1.71 (CI 1.37-2.13))). Specific organophosphates (coumaphos (OR 1.42 (CI 1.11-1.83)), diazinon (OR 1.47 (CI 1.22-1.76)), dichlorvos (OR 1.36 (CI 1.06-1.73)), malathion (OR 1.66 (CI1.38-1.99)), parathion (OR 1.33 (CI 1.03-1.73))), carbamates (carbaryl (OR 1.43 (CI 1.20-1.70)) and carbofuran (OR 1.41 (CI 1.19-1.67))), and permethrin (animals)(OR 1.37 (CI 1.07-1.75)) permethrin (crops) (OR 1.26 (CI1.00-1.59))) were associated with chronic bronchitis. Two chlorophenoxy herbicides (2,4,5-T (OR 1.51 (CI 1.25-1.81)) and 2,4,5-TP (OR 1.69 (CI 1.26-2.25))) and two other herbicides (chlorimuron-ethyl (OR 1.21 (CI 1.02-1.44)) and petroleum oil (OR 1.25 (CI 1.04-1.52))) were associated with chronic bronchitis as well.No association between chronic bronchitis and any fungicides or fumigants was found.	

COPD and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Tual et al. Annals of Epi 2013 (319)	Cross-sectional	Random 10% sample of the French agricultural cohort AGRICAN (AGRIculture and CANcer) collected from 2005 to 2007 (n=14,441)	Questionnaire (Use of pesticides on crops (including seeds), on animals, and in the farmyard and on embankments)	Any pesticide use (not specific)	Self report of physician diagnosed chronic bronchitis after age 20	Exposure to pesticides in potato farmers was significantly associated with CB risk (OR 1.63 (No CI provided)).	

COPD and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Valcin et al. Occup Enviro Med 2007(317)	Cross-sectional	21,541 non-smoking women in the Agricultural Health Study	Lifetime self-reported pesticide use: 1) ever use of any pesticide, 2) ever use of each pesticide functional group (herbicides, insecticides, fungicides, and fumigants), 3) ever use of each insecticide class (carbamates, organochlorines, organophosphates, and pyrethroids), and 4) ever use of each of 50 individual chemicals	Carbaryl, Carbofuran, Aldrin,Chlordane, Dieldrin, DDT, Heptachlor, Lindane Chlorpyrifos, Coumaphos, Diazinon, Dichlorvos, Fonofos, Malathion, Parathion,**Phorate**, Terbufos, Pyrethroids, Permethrin (crop), Permethrin (animals),**2,4-D**, 2,4,5-T, Alachlor, Atrazine, Butylate, Cyanazine, Chlorimuron-ethyl, Dicamba, EPTC, Glyphosate, Imazethapyr, Metolachlor, Metribuzin, Paraquat, Pendimethalin, Petroleum oil, Trifluralin, Benomyl, Captan,**Chlorothalonil, Maneb/Mancozeb**, Metalaxyl, Methylbromide	Self-report of doctor-diagnosed chronic bronchitis	Five pesticides were associated with chronic bronchitis after multivariate adjustment and sensitivity analyses: dichlorvos (OR=1.63, 95%CI=1.01,2.61), DDT (OR=1.67, 95% CI=1.13,2.47), cyanazine (OR=1.88, 95%CI=1.00,3.54), paraquat (OR=1.91, 95%CI=1.02,3.55), and methyl bromide (OR=1.82, 95%CI=1.02,3.24). The risk of chronic bronchitis was increased among women who applied pesticides 120 days or more in their lifetimes, OR=1.50 (95% CI=1.17, 1.91). Women who used three or more agricultural pesticides in addition to the most commonly used pesticides (glyphosate, 2,4-D, malathion, diazinon, carbaryl) had an increased risk of chronic bronchitis, OR= 1.58 (95% CI= 1.19, 2.09); however, those who used fewer agricultural pesticides showed no elevated risk. There was no association between overall use of pesticides and chronic bronchitis (OR= 1.14, 95% CI= 0.97, 1.35). Among the insecticides, three organochlorines (dieldrin, DDT, and lindane), four organophosphates (diazinon, dichlorvos, malathion, and parathion), and two carbamates (carbaryl and carbofuran) were significantly associated with chronic bronchitis. Herbicides that were statistically significant in the single pesticide base models were **2,4-D**, alachlor, atrazine, cyanazine, metribuzin, paraquat, and petroleum oil. The fungicide **chlorothalonil** and the fumigant methyl bromide were also statistically significant after base-model adjustment.	

16.40 Lung function

Lung function and respiratory symptoms and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Chatzi Occup Environ Med 2007 (314)	Cross-sectional	120 grape farmers and 100 controls in Northern Crete	Number of working hours per day, the number of years working in grape cultivations, the preventive measures used, the use of pesticides and work-related symptoms. At the end of the questionnaire, there was a list of 50 commonly used pesticides (brand names) for participants to identify those currently used.	50 commonly used pesticides	Allergic Rhinitis (AR) based on the questionnaire was defined as the occurrence of two or more nasal symptoms (eg, rhinorrhoea, sneezing, nasal obstruction and nasal itching) during the last 12 months, apart from a cold. AR with atopy defined as AR with a positive skin prick test (SPT) and/or a positive enzyme immunoassay test	Grape farmers who used pesticides had higher prevalence rates of allergic rhinitis symptoms (OR, 3.0; 95% CI, 1.4 to 6.2) compared with grape farmers who reported no current use of pesticides, and control subjects. Logistic regression models controlling for age, sex and smoking status showed that the highest risks were observed for paraquat and other **bipyridyl herbicides** (AR alone OR, 2.2; 95% CI, 1.0 to 4.8, AR with atopy OR, 4.0; 95% CI, 1.4 to 11.2)), **dithiocarbamate fungicides** (AR alone OR, 2.5; 95% CI, 1.1 to 5.3, AR with atopy AR with atopy: OR, 3.5; 95% CI, 1.2 to 10.2) and carbamate insecticides (AR alone OR, 3.0; 95% CI, 1.4 to 6.5, AR with atopy OR, 2.4; 95% CI, 1.0 to 6.0). Also significant were herbicides (AR alone OR 2.7 (CI 1.2-6.2), AR with atopy OR 3.2 (CI 1.2-8.6)) glyphosate herbicides (AR alone OR 2.3 CI 1.0-5.0, AR with atopy OR 2.5 (CI 1.0-6.5), fungicides (AR alone OR 2.8 (CI 1.2-6.5) AR with atopy OR 3.1 (CI 1.2-8.1) thiophthalimide (AR alone OR 2.2 (CI 1.0-4.8) AR with atopy OR 3.3 (CI 1.2-8.7)), triazole (AR alone OR 2.2 (CI 1.1-4.6), AR with atopy OR 2.7 (CI 1.0-7.0)), and insecticides (AR with atopy OR 2.4 (CI 1.0-7.0)). Also in asthma table.	

Lung function and respiratory symptoms and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
de Jong et al. BMJ 2014 (320)	Cohort study	11 851 subjects aged 18–89 years from the Netherlands LifeLines cohort study and a second general population cohort (n=2364)	Occupational exposures (No/low/high)	Pesticides in general, herbicides and insecticides specifically	Level of lung function (prebronchodilator FEV1, FEV1/FVC) and mild and moderate/severe airway obstruction	Occupational exposure to pesticides was associated with a lower level of FEV_1 (All pesticides low exposure -51ml (CI -102 to -0) all high pesticide exposure -113ml (CI-201 to -25), all high herbicide -204ml (CI -350 to -58), ever smoker pesticide low exposure -91ml (CI -165 to -17)), every smoker pesticide high -127ml (CI -253 to -1) and every smoker herbicide high -241 (CI -450 to-32) and FEV_1/FVC (all herbicide high exp. -2.8% (CI -4.8 to -0.7), men herbicide high exp. -2.9% (-5.5 to -0.3) and with a higher prevalence of mild (Herbicide high exp. OR 2.11 (CI 1.03-4.30)) and moderate/ severe (Herbicide high exp. OR 3.56 (CI 1.28-9.88)) airway obstruction in the LifeLines cohort. In the general population cohort, occupational exposure to pesticides was associatedwith a higher prevalence of mild (Pesticide high exp. OR 1.48 (CI 1.04-2.10)) and moderate/ severe (Pesticide high exp. OR 1.78 (CI 1.14-2.79), herbicide high exposure OR 1.66 (CI 1.02 to 2.69)) airway obstruction	

Lung function and respiratory symptoms and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Weselak Enviro Research 2007 (307)	Retrospective cohort	3405 children of farmers who were on the farm in utero and after birth	Self-reported present and former pesticide use (crop name, chemical name, reason for use, total area sprayed or dusted, total quantity used, method of application, months of application, and the number of years of use were requested) from month of conception to month of delivery	Any Pesticide Fungicides Insecticides Herbicides Phenoxy Triazine Thiocarbamate **Organo-phosphates** Dicamba Glyphosate 2,4-DB 2,4-D **MCPA** Atrazine Cyanazine Carbaryl Captan	Self-reported allergies, hay fever, persistent cough/bronchitis	All adjusted for significant confounders. No significant association between persistent cough/bronchitis and pesticide exposure. Any pesticide use (OR 1.58 CI 1.19-2.08) and reported use of all three major pesticide classes (herbicides (OR 1.56 CI 1.15-2.11), insecticides (OR 1.48 CI 1.07-2.03) and fungicides (OR 1.69 CI 1.15-2.47)), phenoxy herbicides (OR 1.43 CI: 1.03–1.99) and organophosphates (OR 1.55 CI: 1.02–2.36), and the active ingredient 2,4-D (OR 1.66 CI: 1.11–2.49) during pregnancy showed significant associations with the development of allergies or hayfever in offspring. Male offspring exhibited significant increases in the risk of allergies and hayfever in relation to reported farm use of any pesticide (OR 1.63 CI 1.13-2.34), fungicides (OR 2.12 CI 1.20-3.76), insecticides (OR 1.55 CI 1.02-2.36), herbicides(OR 1.64 CI 1.10-2.46), phenoxy herbicides (OR 1.73 CI 1.12-2.62) and 2,4-D (OR 1.84 CI 1.08-3.14) during the pregnancy period. The odds of developing allergies or hay fever were significantly higher in children over age 12 at the time of the survey when they had been exposed to herbicides, insecticides or any pesticide. Restropective nature may have caused significant recall bias but unlikely differential	

16.41 Interstitial lung disease

Interstitial lung disease and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Hoppin et al. Occup Enviro Med 2007(322)	Cross-sectional	~50 000 farmers and farm spouses in Iowa and North Carolina (21 393 private pesticide applicators (farmers) and 30 242 spouses)	Self-reported pesticide use	50 pesticides including permethrin insecticides, **organochlorine** insecticides**, organophosphate** insecticides, **carbamate** pesticides, phenoxy her-bicides and **triazine** herbicides	Self-reported doctor-diagnosed farmer's lung	Ever use of organochlorine (OR = 1.34, 95% CI 1.04 to 1.74) and carbamate pesticides (OR=1.32, 95% CI 1.03 to 1.68) were associated with farmer's lung in mutually- adjusted models. The insecticide aldicarb (OR 1.65, 95% CI 1.04 to 2.61)were positively associated with farmer's lung among farmers. No association was observed for other chemical classes of pesticides, organophosphate insecticides, permethrin insecti-cides, phenoxy herbicides and triazine herbicides. A dose response relationship was apparent for farmers and spouses based on lifetime days of pesticide application ($p<0.0001$ for farmers and $p=0.0004$ for spouses)	
Newman Am J Respir Crit Care Med 2004(321)	Case-control	706 cases and 706 controls from 10 centers	Self-reported exposures any time before study or in 3 years before diagnosis	No specific pesticides	Sarcoidosis	Significant increase in odds of sarcoidosis with agricultural employment (OR 1.46 (CI 1.13-1.89)) and exposure to insecticides at work OR 1.52 (CI 1.14-2.04)).	

16.42 Diabetes

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Airaksinen Epidem Health services 2011 (323)	Cohort	1,988 participants in the Helsinki birth cohort born between 1934-1944.	Serum values of POPs at the 2003 clinical examination	Oxychlordane, *trans*-nonachlor, 1,1-dichloro-2,2-bis-(p-chlorophenyl)-ethylene (p,p'-DDE)	Type 2 diabetes measured by 2hr 75g GTT	Among the participants with the highest exposure, the risk of type 2 diabetes was 1.64–2.24 times higher than that among individuals with the lowest exposureto oxychlordane(OR 2.08 (CI 1.18-3.69) Plin = 0.003 where Plin is the P value for linear trend across POP categories)., trans- nonachlor (OR 2.24 (CI 1.25-4.03) Plin=0.003), p,p'-DDE (OR 1.75 (CI 0.96-3.19) Plin=0.020). In the stratified analysis, the associations between type 2 diabetes and oxychlordane and *trans*-nonachlor remained significant and were strongest among the overweight participants.	
Arrebola Environ Research 2013(334)	Cross-sectional	386 subjects undergoing non-cancer related surgeries in Southern Spain	Adipose tissue was analyzed for concentrations of 3 organochlorine pesticides and 3 polychlorinated biphenyls (PCBs)	p,p'-dichlorodiphenyldichloroethylene (DDE), Hexachlorobenzene (HCB); ß-hexachlorocyclohexane (b-HCH)	Type 2 diabetes from medical records and interviews	In the models adjusted for adipose tissue origin, sex, age, and body mass index, the 2nd and 3rd tertiles of adipose tissue concentrations of p, p'-DDE were positively associated with the risk of diabetes [odds ratios (95% confidence interval) 3.6 (0.8–17.3) and 4.4 (1.0–21.0), respectively]. A positive association with ß-HCH was also found when body mass index and adipose tissue origin were removed from the models, with odds ratios (95% confidence interval) of 3.3 (1.0–10.4) and 5.5 (1.7–17.3), for the 2nd and 3rd tertiles of exposure, respectively. In addition, a statistically significant interaction was observed between p,p'-DDE and body mass index, such that the risk of diabetes increased with tertiles of exposure in a linear manner in non-obese subjects but not in the obese, in whom an inverted U-shape pattern was observed.	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Codru Environ Health Perspec 2007 (333)	Cross-sectional	352 native American adults	Serum levels	101 PCBs, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), and mirex	Diabetes defined as elevated serum fasting glucose or taking antidiabetic medication	The wet-weight non-lipid adjusted odds ratio (OR) of having diabetes for participants in the highest tertile of DDE (OR 6.4 (CI 2.2-18.4)) and HCB (OR 6.2 (CI 2.3-16.9)). The adjusted OR remained significant for HCB (OR 4.5 (1.4-14.3)) at but not for DDE. Elevated serum mirex was not associated with diabetes, in fact the adjusted OR for mirex was 0.3 (CI 0.1-0.8)).	
Cox et al. Environ Health Pespec 2007 (327)	Cross-sectional	1,303 Mexican Americans aged 20 to 74 years of age	Serum levels	*p*,*p*´-DDT (dichlorodiphenyltrichloroethane), *p*,*p*´-DDE (dichlorodiphenyldichloro- ethylene), dieldrin, oxychlordane, β-hexachlorocyclohexane, hexachlorobenzene, and *trans*- nonachlor	Self-reported diabetes	Self-reported diabetes was significantly associated with serum levels above the detectable limit after adjustment for age and BMI for *trans*-nonachlor (OR 2.9 (CI 1.3-6.4)), oxychlordane (OR 3.1 (CI 1.1-9.1)), and β-hexachlorocyclohexane (OR 2.1 (CI 1.0-4.3)) and among those with the highest level of exposure to *p*,*p*´-DDT (OR 2.9 (CI 1.2-6.8) also adjusted for alcohol) and *p*,*p*´-DDE (OR 2.63 (CI 1.2-5.8) age adjusted only). On adjustment for total serum lipids, the association with *p*,*p*´-DDT remained significant (OR 2.3 CI 1.1-5.0)). Serum glucose levels were elevated ($p<0.05$) among those exposed to *trans*-nonachlor and β-hexachlorocyclohexane. Individuals who reported doing farm work had an increased risk of diabetes (Crude OR 2.4 (CI 1.4-3.6)),	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Everett Environ Internat 2010 (328)	cross-sectional	Between 2341 and 3456 participants from the National Health and Nutrition Examination Survey in the US Survey over the age of 12 years	Serum biomarkers	beta-hexachlorocyclohexane, p,p′- DDE, p,p′-DDT, oxychlordane, *trans*-nonachlor, mirex, dieldrin, and heptachlor epoxide	Self-reported diabetes	Significant evidence for an increased risk of diabetes after adjustment for age, gender, race/ethnicity, education, poverty income ratio, BMI, waist circumference, physical activity and family history, with pesticides was strongest for heptachlor epoxide (≥14.6ng/g lipid adjusted had an OR of 1.70 (95% CI 1.16–2.49) in combined 6 chemical model, OR 2.09 (CI 1.46-3.00) independently)and oxychlordane (≥14.5 ng/g lipid adjusted had an OR of 1.90 (95% CI 1.09–3.32) in combined 6 chemical mode, OR 2.90 (CI 1.78-4.71) independently), intermediate for p,p′-DDT (OR 1.96 (CI 1.29-2.98) independently), and least for ß-hexachlorocyclohexane (OR 2.67 (1.59-4.49 independently), p,p′-DDE (OR 1.90 (CI 1.13-3.18) independently), and *trans*-nonachlor (OR 2.36 (CI 1.48-3.76) independently). Heptachlor epoxide (OR 1.45 (CI 1.04-2.02)) and p,p′-DDT (OR 1.55 (CI 1.03-2.31) were significantly associated with pre-diabetes in separate adjusted logistic regressions. Mirex and dieldrin were not associated with total diabetes or pre-diabetes. The OR of having diabetes increased in a dose-response fashion with each elevated level of pesticide detected from 1.30 (CI 0.47-3.55) with 1 to 8.17 (CI 2.56-26.09) with 6.	
Langer Endocrine Regulation 2014 (57)	Cross-sectional	248 males and 330 females aged 21-40 years (young) and 586 males and 889 females aged 41 to 75 years (old) in Eastern Slovakia	Serum levels	15 PCB congeners, p,p'-DDE and hexachlorobenzene (HCB)	Obesity markers (cholesterol and triglyceride levels and BMI) and diabetes markers (fasting glucose and fasting insulin in serum) and testosterone levels	Increased fasting glucose (DDE young males $p<0.01$, DDE and HCB old males and young and old females $p<0.01$,) and insulin (DDE and HCB old males $p<0.01$, HCB young and old females $p<0.05$). Also in other endocrine	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Lee at al. Diabetes Care 2006 (326)	Cross-sectional	2,016 adult participants in 1999-2002 National Health and Nutrition Examination Survey	Serum concentrations of the selected Persistent Organic Pollutants (POP)	6 persistent organic pollutants 2,2□,4,4',5,5'-hexachlorobiphenyl (PCB153), 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (HpCDD), 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin (OCDD), oxychlordane , *p,p*'-dichlorodiphenyltrichloroethane (DDE), and*trans*-nonachlor Pesticides in this study include the organochlorines oxychlordane, DDE, *trans*-Nonachlor (bioaccumulating component of chlordane).	Diabetes prevalence based on serum blood glucose	A strong dose response relationship between diabetes prevalence and POP concentration even after adjustment for age, sex, race/ethnicity, poverty income ratio, BMI and waist circumference. P value for trend <0.01 for all POP except OCDD. Adjusted ORs ranged from 0.8 (CI 0.3-2.2) at the < 25th percentile to 6.5 (CI 2.0-21.4) at the >=90th percentile for oxychlordane, from 1.5 (CI 0.7-3.1) at the 25th to 50th percentile to 4.3 (CI 1.8-10.2) at the >=90th percentile for DDE and from 1.2 (CI 0.4-3.2) at the < 25th percentile to 11.8 (CI 4.4-31.3) at the >=90th percentile for *trans*-nonachlor.	Obesity, young age and Mexican American ethnicity increased the association between POP concentrations and diabetes.

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Lee Diabetes 2008 (330)	Cross-sectional	246 adults over age 40 with diabetes or impaired fasting glucose using a National Health and Nutrition Examination Survey subset 1999-2002 dataset	Serum biomarkers	BHC: Beta-hexachlorocyclohexane,OXY: Oxychlordane, TNA: *Trans*-Nonachlor, PDE: p,p'-Dichlorodiphenyldichloroethylene; PDT: p,p'-Dichlorodiphenyltrichloroethane HPE: Heptachlor epoxide	Peripheral neuropathy (defined as one or more insensitive sites on a foot) in people with diabetes (defined as with elevated blood sugar or taking insulin/oral antidiabetics)	Organochlorine pesticides showed a strong dose-response relation with prevalence of peripheral neuropathy; adjusted ORs were 1.0, 3.6 (CI 1.1-12.2), and 7.3 (CI 2.1-25.3) (P for trend <0.01), respectively, across three categories of serum concentrations of organochlorine pesticides. Furthermore, when we restricted the analyses to 187 participants with A1C <7%, the adjusted ORs were still 1.0, 3.9, and 6.7 (P for trend <0.01, no individual CIs provided). Organochlorine pesticides were also strongly associated with the prevalence of A1C >=7%; adjusted ORs were 1.0, 2.5 (CI 1.0-6.5), and 5.0 (CI 1.8-13.4) (P for trend <0.01).	
Lee Diabetes Care 2011 (335)	Prospective cohort	1,016 adults over age 70 living in Uppsala Sweden followed for 5 years (725 included in prospective analysis)	Serum biomarkers	p,p'-DDE, *trans*-nonachlor and hexachlorobenzene	Incident diabetes	After adjusting for known type 2 diabetes risk factors, including obesity, odds ratios (ORs) (95% CIs) for type 2 diabetes at age 75 years (n = 36) with exposure to organochlorine pesticides, adjusted ORs across concentrations of *trans*-nonachlor showed that $P_{trend} = 0.03$, but individual ORs only reached significance in the 4^{th} quintile. Adjusted ORs (95% CIs) across quintiles of the sum of three organochlorine pesticides were 1.1, 1.6, 1.5 (Q2 to Q4 ORs not significant), and 3.4 (1.0–11.7) ($P_{trend} = 0.03$).	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Lee Environ Health Perspec 2010 (325)	Case-control within a cohort	90 cases and 90 controls, all African Americans who were free of diabetes at study entry in 1987-1988 whose diabetes status was ascertained by 2005-2006 during a follow-up at years 2,5,7,10,15 or 20.	Serum POP concentrations at study entry (1987-1988)	8 organochlorine pesticides: *trans*-nonachlor, oxychlordane and mirex, hexachlorobenzene, β-hexachlorocyclohexane, γ-hexachlorocyclohexane, p-p'-DDE, p,p'-DDT Other chemicals: 22 polychlorinated biphenyl congeners (PCBs) and 1 polybrominated biphenyl (PBB) PBB153	Incident diabetes defined at every taking antidiabetic medication or having a fasting glucose above 126mg/dL	Increased risk of incident diabetes with exposure to low levels (second quartile) of *trans*-nonachlor (lipid adjusted OR 4.3 (CI 1.5-12.6)), and the highest quartile of exposure to oxychlordane (non-lipid adjusted OR 2.6 (CI 1.0-7.0), lipid adjusted OR NOT significant). Association between incident diabetes and POPs increased with BMI over 30kg/m^2.	U shaped effect curve.
Lee et al. Diabetes Care 2007 (336)	Cross-sectional	749 non-diabetic participants over age 20	Biomarkers	*Trans*-nonaclor, oxyclordane, p,p'-dichlorodiphenyltrichloroethane, ß-hexachlorocyclohexane	Insulin resistance measured by the homeostasis model assessment value for insulin resistance (HOMA-IR)	Organochlorine pesticides strongly associated with HOMA-IR. Adjusted geometric means of HOMA were 3.27, 3.36, 3.48, and 3.85 (*P* for trend <0.01) across quartiles of OC pesticides. Associations with elevated HOMA-IR appeared to be specific to oxychlordane and *trans*-nonachlor and strengthened as waist circumference increased.	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Lee et al. PlosONE 2011 (335)	Controls within a nested case-control study Cohort	90 controls that were diabetes free during a 20 year follow up.	Serum biomarkers	8 organochlorine (OC) pesticides:oxychlordane, *trans*-nonachlor, hexachlorocyclohexane, y-hexachlorocyclohexane, p,p'-DDE, p,p'-DDT, Mirex	Insulin resistance measured by the homeostasis model assessment value for insulin resistance (HOMA-IR)	Parallel to prediction of type 2 diabetes, many statistically significant associations of POPs with dysmetabolic conditions appeared at low dose, forming inverted U-shaped dose-response relations. Among OC pesticides, p,p'-DDE most consistently predicted higher HOMA-IR (P linear trend <0.02) at year 20 after adjusting for baseline values.	
Montgomery AJE 2008 (331)	Cohort	1,176 diabetics and 30,611 diabetes free participants followed from 1993-1997 to 1999-2003 (5 years) in the Agricultural Health Study	Self-reported occupational exposure	50 pesticides	Incident diabetes	Seven pesticides were associated with an increased risk of incident diabetes with either ever use (EU) and/or cumulative days (CD) of use: chlordane (EU OR 1.16 CI 1.02-1.34, CD p trend 0.05), heptachlor (EU OR 1.20 CI 1.01-1.43, CD p trend 0.02), trichlorfon (EU OR 1.85 CI 1.03-3.33, CD p trend 0.02), alachlor (EU OR 1.14 CI 1.00-1.30, CD p trend 0.001), cyanazine (EU OR 1.27 CI 1.09-1.47, CD p trend 0.004), atrazine (CD p trend 0.02). Exposure to organochlorine and organophosphate insecticides may be associated with increased risk of incident diabetes. The significant effects of aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor and cyanazine were limited to participants under 60 years of age. The significant effect of trichlorfon was limited to those who were overweight (BMI 25 to 30 kg/m2) and the significant effects of aldrin, heptachlor, alachlor and cyanazine were limited to participants who were obese (over 30 kg/m2).	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Pal Diabetes and Metabolism 2013(324)	Case-Control	72 individuals, of the 83 originally recruited, adults from Wapekeka and Kasabonika First Nations com-munities in Northern Ontario.	Serum levels	Aroclor 1260, PCB28, PCB52, PCB99, PCB101, PCB105, PCB118, PCB128, PCB138, PCB153, PCB156, PCB163, PCB170, PCB180, PCB183, PCB187, aldrin, α-chlordane, γ-chlordane, β-HCH, *cis*-nonachlor, *trans*-nonachlor, DDE, DDT, hexachlorobenzene, mirex, oxychlordane, PBB153, PBDE47, PBDE99, PBDE100, PBDE153, Parlar26, and Parlar50.	Type 2 Diabetes and insulin resistance (measure by HOMA)	Plasma levels of *trans*-nonachlor, oxychlordane, and DDE were significantly higher ($P < 0.05$) in diabetic individuals after age-adjustment. No association between OC pesticides and insulin resistance.	
Patel et al. Plos ONE 2010 (332)	Meta analysis of 3 cohorts of the general adult population	3 cohorts of National Health and Nutrition Examination Surveys: 1999-2000 n with DM=46, no DM 635), 2003-2004 (n with DM=67, no DM 809), 1999-2004 (n with DM=178, no DM 2367),	Heptachlor Epoxide serum levels	Hepatachlor Epoxide	Type 2 diabetes	Elevated odds ratios for a change in the log exposure level by 1 standard deviation and adjusted for BMI, age, sex, ethnicity and SES in all 3 cohorts of NHANES rounds 1999-2000 (OR 3.2 (CI 2.4-4.4) 2003-2004 (OR 1.9 (CI 1.3-2.6), 1999-2004 OR 3.2 (CI 1.3-2.1). The combined adjusted OR in the three combined cohorts of 1.7 for a 1 SD change in log exposure amount; p=0.001),	

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Saldana et al. Diabetes Care 2007 (329)	Retrospective cohort	11,273 women with a term pregnancy between the ages of 17 and 49 years in the last 25 years in Agricultural Health Study 1993-1997 recruited from pesticide applicators applying for certification to use restricted use pesticides in Iowa and North Carolina.	Agricultural (mixing or applying pesticides or repairing pesticide application equipment) or residential pesticide exposure during the first trimester of the pregnancy	Any exposure and use of specific pesticides: 2,4-D, 2,4,5-TP, 2,4,5-T, Alachor, Atrazine, Butylate, Cyanazine, Dicambia, Glyphosate, Pendimethalin, Petroleum oil, Trifluralin, Diazinon, Malathion, Terbufos, Phorate, Carbaryl, Carbofuran.	Self reported gestational diabetes (GDM) during most recent pregnancy	Increased risk of gestational diabetes (OR 2.2 (CI 1.5-3.3)) in agricultural exposure. No association with indirect (planting, pruning, weeding, picking or harvesting) or residential pesticide use. Increased risk of GDM was specifically associated with the agricultural use of the herbicides 2,4,5-T, 2,4,5-TP, atrazine and butylate and insecticides diazinon, **phorate** and carbofuran (ORs not reported).	No pesticide-specific ORs reported.

Diabetes and pesticide exposure in adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Starling Occup Enviro Med 2014(337)	Cohort	13,637 females spouses of farmers enrolled in the Agricultrual Health Study from 1993-1997 for a mean follow-up of 10 years	Self-reported agricultural pesticide exposure	45 pesticides	Diabetes	Significantly increased risk of incident diabetes with more than 30 years of mixing and applying pesticides (HR 1.60 CI 1.08-2.38). A significantly increased risk of incident diabetes with exposure to dieldrin (HR 1.99 CI 1.12-3.54), fonofos (HR 1.56 CI 1.11-2.19), parathion (HR 1.61 CI 1.05-2.46), phorate (HR 1.57 CI 1.1402.16), 2,4,5-T/2,4,5-TP (HR 1.59 (CI 1.00-2.51). There was a significantly increased risk of gestational diabetes with exposure to dieldrin (HR 1.99 CI 1.12-3.54), fonofos (HR 1.56 CI 1.11-2.19), parathion (HR 1.61 CI 1.05-2.46), phorate (HR 1.57 CI 1.14-2.16), 2,4,5-T/2,4,5-TP (HR 1.59 CI 1.00-2.51).	

16.43 Other endocrine outcomes

Other endocrine outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Alvarez-Pefrerol BMJ 2008 (341)	Prospective cohort	259 from a general birth cohort in Menorca , Spain assessed at age 4	Serum OC concentrations	Dichlorodiphenyl trichloroethane (p,p'-DDT), b-hexachlorocyclohexane (b-HCH) and 6 PCB congers (PCB-138, PCB-153 and PCB-118), hexachlorobenzene, p,p'-DDE	Serum concentrations of free T4 and total T3 and TSH	Dichlorodiphenyl trichloroethane (p,p'-DDT), b-hexachlorocyclohexane (b-HCH) and 6 PCB congers (PCB-138, PCB-153 and PCB-118) levels were related to lower total T3 levels ($p<0.05$), PCB-118 levels was inversely associated with free T4 levels. No association was found between TSH and any measured OCs.	
Goldner et al. Amer J Epidem 2010 (339)	Prospective cohort	Female spouses (n=16,529) in Agricultural Health Study 1993-1997 recruited from pesticide applicators applying for certification to use restricted use pesticides in Iowa and North Carolina.	Ever use of organochlorines. Ever use of herbicides, insecticides, fungicides and fumigants at entry to study	Organochlorines and all pesticide use	Self-reported lifetime prevalence of thyroid disease, hypothyroidism and hyperthyroidism at 5 year follow-up questionnaire	Significant increase in risk of hypothyroidism with ever use of organochlorine insecticides (OR 1.2 (95% CI 1.0-1.6)) and fungicides (OR 1.4 (95% CI 1.1-1.8)). Use of organochlorines chlordane (OR 1.3 (CI 0.99-1.7)), aldrin (OR1.2 (CI 1.0-1.6)), fungicides benomyl (OR 3.1 (CI1.9-5.1)), maneb/**mancozeb** (OR 2.2 (CI 1.5-3.3)), herbicide paraquat (OR1.8 (CI 1.1-2.8)) significantly associated with hypothyroidism. Maneb/**mancozeb** (OR 2.3 (CI 1.2-4.4) significantly associated with hyperthyroidism. Ever use of pesticides or organochlorines showed no association with thyroid disease This study shows how analyses based on overall pesticide exposure can miss associations with specific pesticides.	

Other endocrine outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Lee et al. PlosONE 2011 (338)	Controls within a nested case-control study Cohort	90 controls that were diabetes free during a 20 year follow up.	Serum biomarkers	8 organochlorine (OC) pesticides:oxychlordane, *trans*-nonachlor, hexachlorocyclohexane, y-hexachlorocyclohexane, p,p'-DDE, p,p'-DDT, Mirex	Obesity measured by BMI, dyslipidemia measured by triglycerides, HDL cholesterol, LDL cholesterol and insulin resistance measured by the homeostasis model assessment value for insulin resistance (HOMA-IR)	Parallel to prediction of type 2 diabetes, many statistically significant associations of POPs with dysmetabolic conditions appeared at low dose, forming inverted U-shaped dose-response relations. Among OC pesticides, p,p'-DDE most consistently predicted higher BMI, (P quadratic trend <0.01) triglycerides (P quadratic trend <0.01), and lower HDL-cholesterol (P quadratic trend 0.01) at year 20 after adjusting for baseline values. Oxychlordane (P quadratic trend 0.04), *trans*-nonachlor (P quadratic trend 0.01), and hexachlorobenzene (P linear trend <0.01) also significantly predicted higher triglycerides.	
Smink Acta Pediatr 2008 (340)	Prospectiv e Cohort	482 children followed from the antenatal period until age 6.5 years from the Asthma Multicenter Infants Cohort in Menorca, Spain	Prenatal exposureto hexachlorobenze ne measured in cord blood	Hexacholorobenzene (HCB), p,p'-DDT, p,p'-DDE	BMI (Weight and height) measured at term births and age 6.5 years	Children with HCB levels higher than 1.03 ng/mL in cord blood were 1.14 kg (Standard Error (SE) 0.38) heavier and had a higher BMI ($\beta = 0.80$ kg/m^2(Standard Error (SE) 0.34)) than children with HCB levels lower than 0.46 ng/mL at age 6.5 years. No statistically significant associations were found in height.	Children from normalweight mothers also presented an increased risk of having higher BMI ($\beta = 0.39$ kg/m^2 (Standard Error (SE) 0.19) with increasing concentrations of HCB in cord serum.

16.44 Nutritional and metabolic endocrine disruptors

Nutritional and metabolic endocrine disruptors and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments	Reference
Casal-Casa(365)	Not included, as it is a review article, used for background, confirms epidemiological studies associate organochlorine pesticides with metabolic syndrome and diabetes. Banned in most developed countries in the 1970s and restricted by Stockholm convention in the 2000s. 2 additional references found.							

16.45 Dermatitis

Dermatitis and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Horiuchi et al, Int J Occup environ health 2007 (342)	Descriptive	394 cases of pesticide induced dermatitis	Questionnaires	Dichlorvos, Zineb **Maneb,** Salithion, Calcium polysulfide, Pentaclhoronirobenzene **Chlorothalonil**, Benthiocarb/semethrin, Methomyl, Paraquat**/diquat , Methyl bromide,** Dazomet, Fenitrothion, Anilazine, Triforine, Captan, Leptophos, Chlornitrofen/dymron, Trifluralin, Dazomet, Benomyl, Wattable sulfur, Diazinon, Quinozene, Vamidothion, Copper sulfate, Copper sulfate basic, Glyphosate, Methomyl, Salithion	Pesticide induced dermatitis	Heaviest distribution from April to August with the farming season, exposed mostly while spraying (63%) and during other non-spraying farm work (35%), dermatitis became chronic in 20% of cases. All pesticides implicated in acute or chronic dermatitis except methyl bromide. No analysis completed.	
Ochiai et al. Chemosphere 2014 (343)	Cohort study	81 infants with or without AD who participated in a birth cohort study	Concentrations of pesticides were measured in the umbilical cord tissues collected immediately after birth	15 polychlorinated biphenyl (PCBs) congeners, dichlorodi-phenyltrichloroethane (p,p0-DDT), dichlorodiphenyldichloroethylene (p,p0-DDE), b-hexachlorocyclohex- ane (b-HCH), hexachlorobenzene (HCB), cis-nonachlor, trans-nonachlor, mirex, oxychlordane, and 27 polybrominated diphenyl ether (PBDEs) congeners	Atopic dermatitis	In the relationship between sum PBDE-27 levels and AD, tertile analysis revealed that the risk for developing AD was decreased in middle levels (odds ratio [OR], 0.263; confidence interval [CI], 0.084–0.821) and high levels of sum-PBDE-27 (OR, 0.136; CI, 0.037–0.501) (Table 6). Besides sum PBDE-27,no other associations were found between chemical exposure and the development of AD.	

16.46 Other outcomes

Other outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Blair Ann Epi 2005 (352)	Cohort	52,393 private pesticide applicators and 32,345 spouses of famers followed from 1993-1997 to 2000 in the Agricultural Health Study	Self-reported occupational exposure	Every use	Mortality	Applicators and spouses who had handled pesticides for less than 10 years had significantly lower SMR than the general state population for all causes, all cancers, pancreatic cancer, lung cancer, COPD and cardiovascular disease. Those who had handled pesticides for more than 11 years lower SMR than the general state population for all causes, all cancers, colon cancer, lung cancer, prostate cancer, COPD and cardiovascular disease. Healthy worker effect.	
Blair J Agri Safety and Health 2005 (8)	Review	Article published prior to 2005 using the 89,658 cohort of Agricultural Health Study Participants	Self-reported occupational exposure	Any of 50 specific pesticides	Disease and injury	Significant findings include: • Increased risk of retinal degeneration with orchard farming related to exposure to fungicides (1.7-fold in N. Carolina and 2.0-fold in Iowa) and carbamate insecticides (1.9-fold) and fumigants (1.7-fold) in Iowa • Increased risk of wheeze with exposure to increasing days of pesticide use. Specific pesticides associated with wheeze include herbicides (alachlor, atrazine, cyanazine, EPTC), insecticides (chlorpyrifos, malathion, parathion, and permethrin), and the fungicide metalaxyl	

Other outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Cooper J Rheumatology 2004 (350)	Case-control	265 cases and 355 population controls	Occupational pesticide exposure	Mixing and applying insecticides	Systemic lupus erythematsosus (SLE)	A significant association between SLE and mixing pesticides for agricultural work (OR 7.4 CI 1.4-40.0) but not for applying pesticides. Estimate based on a small number of exposed cases (n=9).	
Crawford J Occup Enviro Med 2008 (345)	Cohort	4,926 cases among 14,229 white male pesticide applicators enrolled in the Agricultural Health Study from 1993-1997 to 1999-2003	Self-reported occupational exposure	50 individual pesticides	Hearing loss	Compared to no exposure, the use of insecticides (OR 1.19 CI 1.04-1.35) and organophosphate insecticides (OR 1.17 CI 1.03-1.31) were significantly associated with hearing loss. No association with carbamates, organochlorines and pyrethroids. Individual pesticides significantly associated with hearing loss include atrazine (OR 1.22 CI 1.07-1.38), heptachlor (OR 1.19 CI 1.04-1.36). Among organophosphates, significant associations (ORs are for highest exposure category) with hearing loss were found for chlorpyrifos (OR 1.15 CI 1.02-1.29) malathion (OR 1.20 CI 1.08-1.34), fonofos (OR 1.19 CI 1.03-1.37), diazinon (OR 1.25 CI 1.07-1.46), phorate (OR 1.25 CI 1.10-1.41), terbufos (OR 1.17 CI 1.04-1.31) and parathion (OR 1.21 CI 1.04-1.40) with significant trends for diazinon, fonofos, phorate and terbufos.	
DeRoos Ann Epi 2005 (351)	Case-control nested within a cohort	135 cases and 675 female controls within the Agricultural Health Study cohort	Self-reported occupational exposure	49 pesticides	Rheumatoid Arthritis (RA)	No association between RA and applying or mixing any pesticides, pesticide type or class or specific pesticide.	

Other outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Fritschi Occup Enviro Med 2007 (245)	Case-control	606 cases of prostate cancer, 400 cases of BPH and 471 male population based controls in Western Australia	Self-reported occupational pesticide exposure	Any	Prostate cancer and benign prostatic hyperplasia (BPH)	No significant association between pesticide exposure, including organophosphate, organochlorine, phenoxy herbicides, other herbicides and other pesticides, and prostate cancer or BPH. Also in prostate cancer.	
Gold Arthritis Rheumatism 2007 (349)	Descriptive	Deaths listed as rheumatoid arthritis (RA) (n=36,178), systemic lupus erythematous (SLE) (n=7,241), systemic sclerosis (SS) (n=5,642) or other systemic autoimmune disease (SAD) (n=4,270) in 26 US states from 1984 to 1998 and 5 controls per case	Occupational exposures based on a JEM from the death certificate	Any	Autoimmune disease as a contributor to cause of death (RA, SLE, SS or SAD)	Farming occupations associated with increased risk of death from any autoimmune disease (OR 1.31 CI 1.22-1.39) and from RA (OR 1.30 (CI 1.22-1.39). Farmers engaged in raising crop (RA OR 1.4 CI 1.3-1.5 & SLE OR 1.3 CI 1.0-1.6) but not in livestock were at a greater risk of autoimmune diseases. No significant associations between farming and SS or SAD.	
Kirrane AJE 2005 (346)	Cross-sectional	31,173 wives of pesticides applicators in the Agricultural Health Study	Self-reported occupational exposure	Class (fungicide, herbicide, insecticide and fumigant) or type (organophosphate, organochlorines and carbamates) and 50 specific pesticides	Retinal degeneration	Wives' own use of fungicide (OR 1.9 CI 1.2-3.1) was significantly associated with retinal degeneration. No specific fungicides were significantly associated with retinal degeneration, possibly due to the small numbers exposed. No association with fumigants, herbicides, insecticides, carbamate, organochlorines or organophosphates	

Other outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Lee Enviro Health Persp 2007 (348)	Cohort	55,071 Agricultural Health Study participants from Iowa and North Carolina followed from 1993-1997 to 2001	Self-reported occupational exposure	Chlorpyrifos (organophosphate insecticide)	Mortality	No significant association between all cause mortality, all malignant neoplasms (colorectal, rancreas, lung and bronchus, prostate, brain, NHl and leukemia), immune and blood disorders, endocrine, nutritional and metabolic disease, cardiovascular disease (ischemic heart diseae, cardiomyopathy, cerebrovascular accident), lower respiratory diseases (COPD) and external causes (motor vehicle collisions, non-motor vehicle collisions and suicide) and chlorpyrifos exposure. There were significant trends and significant RRs in both Intensity Weighed (IW) and Lifetime Days (LD) for the highest exposure category for external causes of mortality (RR IW 1.71 CI 1.13-2.60, p trend 0.005), non-motor vehicle accidents (RR IW 2.09 CI 1.30-3.36, p trend 0.034) and blood and immune disorders (RR IW 12.68 CI 1.88-85.42, p trend 0.003).	
Ljunggren Enviro Int 2014 (153)	Case-control	7 controls, 8 subjects with cancer and 13 subjects with cardiovascular disease living in a contaminated area in Sweden	Serum POP levels	Hexachlorobenzene, cis-chlordane and trans-nonachlor	Cancer and cardiovascular disease	Trans-nonachlor was significantly higher in the LDL/VLDL of individuals with CVD than controls. Also in general cancer.	

Other outcomes and pesticide exposure

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Comments
Mills AJE 2009 (347)	Cohort	476 deaths from myocardial infarction among 54,069 men followed from 1993-1997 to 2006 and 839 nonfatal myocardial infarctions among 32,024 men followed from 1993-1997 to 2003 in the Agricultural Health Study	Self-reported occupational pesticide use	49 individual pesticides	Myocardial infarction	No association with overall pesticide use or by pesticide class (insecticides, herbicide or fungicides) with fatal or nonfatal myocardial infarctions. Ethylene dibromide (HR 1.54CI 1.05-2.27), maneb/mancozeb (HR 1.34 CI 1.01-1.78), and ziram (HR 2.40 CI 1.49-3.86) were associated with myocardial infarction mortality, while aldrin (HR 1.20 CI 1.01-1.43), dichlorodiphenyltri-chloroethane (DDT) (HR 1.24 CI 1.04-1.46), and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (HR 1.21 CI: 1.03-1.43) were associated with nonfatal myocardial infarction incidence. Five pesticides, carbaryl, terbufos, Imazethapyr, pendimethalin and petroleum oil were inversely associated with fatal myocardial infarction.	
Parks Arthritis Case Res 2011 (344)	Cohort	213 cases (178 RA, 27 SLE, 8 both) in a cohort of 76,861 post-menopausal women aged 50 to 79 years enrolled 1993-1998.	Residential or workplace insecticide use	Insecticides	Rheumatoid arthritis (RA) and systemtic lupus erythematosus (SLE)	Personal use of insecticides associated with increased risk of RA/SLE (HR 1.51 CI 1.09-2.09), particularly when used more than 6 times/year (HR 2.04 CI 1.17-3.56) or for more than 20 years (HR 1.97 CI 1.20-3.23). Increased risk of RA/SLE with application of insecticide by others for more than 20 years (HR 1.86 CI 1.07-3.21) and frequent application more than 6 times/year in women with a farm history (HR 2.95 CI 1.16-7.52).	

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