2012 Systematic Review of Pesticide Health Effects

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Table of Contents

Supplement: Summary Tables

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OCFP 2012 Systematic Review of Pesticide Health Effects
Chapter 1: Executive Summary

The second Ontario College of Family Physicians (OCFP) Systematic Review of Pesticide Health Effects reviewed the relevant literature published since 2003. Of this literature, 142 studies met the inclusion criteria, covering three groups of health effects:

1. Reproductive health outcomes and pesticide exposure (update of 2005 review) – 75 studies
2. Neurodevelopmental behavioural health outcomes and pesticide exposure in children (expanded from 2005 review to include all neurodevelopmental outcomes) – 32 studies
3. Respiratory health outcomes and pesticide exposure in children and adults (new outcome area not covered in 2005 review) – 35 studies

Each study was assessed by two independent trained reviewers and scored using criteria adapted from the modified Downs and Black Quality Assessment Tool (see Chapter 2: Methods, Appendix 2B).

Summary: Chapter 3 – Reproductive health outcomes and pesticide exposure

This review provides evidence that non-organochlorine pesticides may cause deleterious reproductive outcomes. The most suggestive evidence is of an association between fetal growth outcomes and pesticide exposure. Of the ten studies that considered fetal growth outcomes, eight reported significant associations. Most of these positive associations were for birth weight, and were from well-designed cohort studies. As low-birth-weight babies are at increased risk of mortality, morbidity, and disability in infancy and childhood and of long-term adverse health outcomes in adult life, reducing low-birth-weight rates should be a public health priority. However, the associations found for a given type of pesticide in one study were not always replicated in other studies of that pesticide. These inconsistencies, which could be due to differences in sample size, methodology, and study design, make it challenging to draw definitive conclusions. While it appears that there is an association between pesticide exposure and birth weight, this relationship varies according to the type of pesticide, with some giving rise to less than consistent findings.

Decreased head circumference, as suggested in several studies, is of particular concern because small head circumference is linked to lower cognitive abilities in older children and adults.

All of the high-quality birth defect studies reported positive associations. However, as a group they considered a diversity of pesticides, which makes comparisons between the studies difficult. Nevertheless, associations were found with hypospadias, neural tube defects, and congenital diaphragmatic hernia. The association with hypospadias is further supported by an earlier systematic review of nine other studies (Rocheleau 2009). Three of four studies of quality <13 out of 20 found a positive association, and both studies ranked >13 had positive findings. The finding of an association between gastroschisis and pesticide exposure is interesting given its largely unknown etiology and warrants further investigation.

Only two studies examined preterm birth as an outcome, and both found positive associations. Both cited biologically plausible explanations for these effects (e.g., organophosphate pesticides can affect enzymes that stimulate contractions of the uterus, thereby decreasing gestational duration). Additional studies with individual-level data would provide further insight into these associations.

In contrast, there is less suggestive evidence in this review that the organochlorine pesticides affect reproductive outcomes. Most of the studies were conducted in countries where DDT and other organochlorine pesticides had been banned for several decades and levels were generally low in the general population. As with the non-organochlorine studies, exposure measurements were almost all by biomarker.

It is possible that associations were not found due to the small sample sizes in most of the studies. Many authors also commented on the low concentrations of the examined organochlorines in maternal and cord blood as well as breast milk. However, some of the studies in which levels were considered high still did not find associations, or if they did, the wide range of exposure levels, lack of dose–response relationships, and other methodological deficiencies make it difficult to draw conclusions. Some of the studies did report a few positive findings that did not attain statistical significance and therefore were reported as negative; however, many of these did not follow a dose–response relationship and therefore could have been spurious.

Certainly, the results of this study would indicate that there are benefits to reducing exposure of pregnant women to commonly used pesticides. The Whyatt (2004) study, which found a significant increase in birth weights of infants born after rather than before a household ban on two frequently used insecticides in New York City, illustrates the possible benefit of pesticide bans within a few years of implementation. In Canada, several provinces and many municipalities have mandated bans and phase-outs of many pesticides in the past several years, and research into reproductive outcomes resulting from these policies is recommended.

Summary: Chapter 4 – Neurodevelopmental/behavioural health outcomes and pesticide exposure in children

The studies in this systematic review show that prenatal pesticide exposure is consistently associated with measurable deficits in child neurodevelopment across a wide age range from birth to adolescence.

Neonates with prenatal organophosphate exposure had absent or hypotonic reflexes and deficits in attentiveness to stimuli. After prenatal organochlorine exposure, neonates displayed irritability on neurological testing. In organophosphate-exposed **children aged 12–36 months**, consistent deficits in the Mental Development Index of the Bayley Scales for Infant Development were found in three large cohort studies. For exposure to the main metabolite of the organochlorine pesticide DDT, there were deficits in both scales but with stronger effects for the Psychomotor Development Index. For these early childhood deficits, the relative risks (RRs) are usually in the 1.5–2.0 range. However, even a small increase in the incidence of such complex childhood

conditions impacts both the healthcare system and the learning and later earning potential of affected individuals.

In **older children aged 3–10 years**, attention problems such as ADHD, reduced overall IQ, and other conditions including autism spectrum disorder and pervasive developmental disorder were more common in children who had higher levels of organophosphate or DDT/DDE exposure during pregnancy. Typically, statistically significant health effects were seen primarily in children in the highest 20–25% of exposure. On the other hand, there are rarely unexposed control groups, which may result in underestimation of the risk of ADHD. Some studies of ADHD and autism associated with prenatal exposure have higher RRs in the 6.0–7.0 range. Knapp (2011) studied 30-year-olds from a birth cohort in the UK and found that both males and females diagnosed with attention deficit at age 10 had "lower employment rates, worse jobs, lower earnings if employed, and lower expected earnings overall." Children diagnosed with ADHD also have a much higher likelihood of engaging in criminal behaviour as adults, with high attendant social costs (Fletcher 2009).

In multi-scale IQ tests, working memory and verbal comprehension appeared to be most consistently affected by pesticide exposure. The effects were modest, with RRs usually less than 2.0. However, the reductions found in total IQ (ranging from –2 to –7 points) have substantial impacts on school performance and later earning potential when viewed from a population perspective. In 2001, Environment Canada scientists (Muir 2001) estimated the cost of the loss of 5 IQ points at CAD 30 billion per year for Canada, and the cost of neurodevelopmental deficits and hypothyroidism at CAD 2 billion per year for Ontario alone. The proportion of those conditions (and costs) considered attributable to environmental exposures was at least 10% and as high as 50%.

Our understanding of the association between pesticide exposure and child neurodevelopment has benefited from several large longitudinal studies of birth cohorts from the USA, Spain, and Mexico. The cohorts were all recruited from groups thought to have higher than average exposure to pesticides. In the future, it will be important to study the associations with health effects in cohorts with typical exposures. This is important, as some endocrine-disrupting pesticides, such as atrazine, appear to have health effects at very low doses (Vandenberg 2012).

Taken as a whole, the results of the systematic review of pesticide exposure and child neurodevelopment suggest that children are experiencing neurodevelopmental problems throughout childhood that are associated with prenatal and childhood pesticide exposures. This suggests that vigilance is required to minimize the pesticide exposures of pregnant women and children from all potential sources, including dietary, indoor and outdoor air, water, and farm and domestic use exposures. The currently used organophosphate insecticides are consistently implicated in neurodevelopmental deficits, as are the organochlorines, such as endosulfan, still heavily used as crop pesticides in agricultural settings.

Summary: Chapter 5 – Respiratory health outcomes and pesticide exposure in children and adults

Overall, there is evidence that exposure to pesticides, and to organophosphate or carbamate insecticides in particular, is associated with the development of respiratory symptoms and a spectrum of obstructive and restrictive lung diseases. Studies of asthma in children reported an association between maternal exposure to organophosphate and organochlorine insecticides, while respiratory tract infections in infants were linked to maternal exposure to organochlorine insecticides in two of three reviewed studies.

Twelve studies investigated the effects of asthma, of which nine studies of medium to high quality found a positive association between organophosphate and carbamate insecticides and atopic asthma, with odds ratios above 2.0. This association was found for occupational, domestic, and environmental exposures, particularly after exposure to the organophosphate insecticides parathion and coumaphos. While the possibility remains that these results could reflect the aggravation of pre-existing asthma, asthma-related respiratory problems are nonetheless associated with pesticide exposure. In children, the evidence is consistent, with all included studies finding a positive association with pesticide exposure, specifically maternal organochlorine insecticide, organophosphate insecticide, biocide (disinfectant), and fungicide exposure. Specifically, in utero and post-natal exposures in the first year of life were associated with asthma and wheeze up to six years of age. Breastfeeding was shown to have a protective effect, despite increased organochlorine pesticide levels in the infants.

The evidence linking chronic bronchitis to pesticide exposure in adults is not as prolific or as robust as that regarding asthma. While three studies did find a positive effect, the resulting odds ratios were below 2.0, with large confidence intervals. In particular, two studies that used data from the Agricultural Health Study found an association between exposure to insecticides and the development of chronic bronchitis. Organochlorine, organophosphate, carbamate, and pyrethroid insecticides all showed an association in farmers, while the herbicide paraquat showed the strongest relationship in their spouses through paraoccupational exposure. In addition, one large retrospective study found that the relationship between insecticide exposure and the development of chronic cough and bronchitis in Ontario farm children did approach significance, but only for girls.

Studies of occupational workers across many industries that use pesticides (e.g., farming, pesticide manufacturing, and pesticide spraying) showed a subtle yet persistent association between decreased lung function and exposure to a broad range of herbicides and insecticides. Exposure to the now-banned organophosphate insecticide chlorpyrifos resulted in a particularly strong association with wheeze, chronic cough, and shortness of breath in many studies. Studies of these occupationally exposed populations linked organophosphate and carbamate insecticides in particular to decreased FEV1/FVC ratios, indicative of obstruction, and to decreased mid-expiratory flow rates (FEF 25–75%). These outcomes may reflect effects of chronic exposures and as well possibly direct toxic effects on the airways due to inhibition of acetyl-cholinesterase and resulting acute bronchoconstriction.

Two studies of exposure to neonicotinoid insecticides and organophosphates also showed associations with restrictive lung function changes. However, a study of chronic, low-level exposures to paraquat found no restrictive lung disease. Finally, sarcoidosis and farmer's lung (hypersensitivity pneumonitis) were both associated with occupational exposure to insecticides. The risk of developing farmer's lung increased after exposure to organochlorine and carbamate insecticides in particular.

The relationship between respiratory tract infections in children and the organochlorine insecticide metabolite dichlorodiphenyldichloroethylene (DDE) was assessed in three high-quality studies with varying results. Two studies showed a positive association between in utero exposure and respiratory tract infections, while a third paradoxically showed that higher levels during pregnancy were in fact protective. In addition, one study found that upper, but not lower, respiratory tract infections in infants were associated with increased exposure to organochlorines.

The sum of the evidence would indicate that reducing or eliminating exposure to all pesticide types, and to organophosphate, carbamate, and organochlorine insecticides in particular, would be prudent in both occupational and domestic settings with respect to preventing negative respiratory health consequences. While the study of agricultural occupational pesticide exposure and negative health outcomes remains challenging, the accumulation of studies showing significant associations between exposure and asthma, chronic obstructive lung diseases, and decreased lung function highlight the importance of reducing exposure when possible and of using proper personal protective equipment when exposure is necessary.

Summary: Chapter 6 – Implications for family practice

Family physicians can counsel to prevent or reduce pesticide exposure in several settings:

1. In preconception and prenatal patient encounters, counsel to reduce pesticide exposure and help reduce negative birth outcomes, neurodevelopment problems, and childhood asthma outcomes associated with prenatal pesticide exposure. Prevention of these effects has an extended benefit in reducing the frequency of adult chronic diseases associated with suboptimal birth outcomes. History taking should focus on occupational exposures and the indoor use of pesticides during pregnancy and early childhood.
2. Advise parents to minimize exposure of older children by reducing use of indoor and home and garden pesticides. Pyrethroids are still approved for many indoor uses, are detected in 100% of Canadian children, and are associated with health effects in children.
3. Alert new parents to the risks of paraoccupational (i.e., take-home) exposures and the protective benefits of wearing personal protective equipment for patients who have unavoidable occupational exposure.
4. Educate patients in occupations at high risk of pesticide exposure about the health effects associated with these exposures.
5. Consider community-based education and action in circumstances in which children are unnecessarily exposed to pesticides. Previous bans on pesticides with high health effect burdens have been shown to reduce health risks to children and reduce detection frequency in children and the environment.

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Chapter 2: Methods

The objective of the current project was to conduct a systematic review of published studies on the association between occupational and non-occupational exposure to pesticides and reproductive, respiratory, and neurobehavioral health outcomes in children and adults.

Phase 1: Literature search

A comprehensive literature search was conducted of peer-reviewed original research pertaining to pesticide exposure and specific reproductive, respiratory, and neurobehavioral health outcomes of interest. The literature search was restricted to human studies published after January 1, 2003 in the English language literature. No restrictions on study type were applied. Specific health outcomes reviewed in each study category (i.e., respiratory, reproductive, and neurobehavioral) were developed by clinicians with experience in environmental health, as well as through discussion and consensus with the review team. Two external librarians were consulted (at the University of Toronto and University of Western Ontario) regarding the development of the search strategy.

The literature search was performed the week of May 2, 2011 using Ovid MEDLINE (1948 to April Week 4, 2011), Ovid MEDLINE database of In-Process and Other Non-indexed Citations (to May 2, 2011), Ovid EMBASE (1980 to 2011 Week 16), and TOXNET (Toxicology Data Network; US National Library of Medicine 2011) (through 5 May 2011). The search terms were organized by health effect and topic area. Searches were performed using both subject headings and keywords compiled from a comprehensive search of MeSH and emtree terms, which were mapped to each topic of interest to ensure the inclusion of all relevant studies. Boolean operators "AND" between exposure and outcome terms, and "OR" between synonymous keywords and MeSH/emtree subject headings, were applied as appropriate. A complete list of subject headings and text words searched is found in Tables 2A.1–2A.4 in Appendix 2A, organized by topic area. MeSH and emtree subject headings were exploded unless otherwise stated.

Phase 2: Abstract screening

After removing duplicate records, all remaining references retrieved from the literature search were screened by one investigator using only the title and abstract (when necessary and available). Primary screening removed records in irrelevant topic areas, many of which were retrieved as a result of the commonly used anticoagulant warfarin also being used as a pesticide (rodenticide). Therefore, many irrelevant references on the topic of stroke, heart disease, and anticoagulant therapy were retrieved, explaining the large number of irrelevant references screened out at this stage. Articles dealing with the acute effects of pesticide poisoning were also eliminated in this screening step.

A secondary screening was done using the remaining abstracts. Two reviewers were assigned to independently review each abstract in each topic area, i.e., neurobehavioral (n = 59 articles), respiratory (n = 49 articles), and reproductive (n = 190 articles), to determine whether it met the

inclusion criteria. Results were compared, and differences were settled by discussion and consensus between reviewers. For records in which it was not clear from the abstract whether the article met the inclusion criteria, the full text was retrieved and reviewed for the necessary information. Where there were multiple publications stemming from the same cohort, all were included providing that either the outcomes or the population analyzed differed. If not, the most recent, relevant publication was used. For the neurobehavioral topic area, articles dealing with the same cohort but at different time points (i.e., ages) were all included.

A study was considered eligible for further review if: (1) it referred to children or adults exposed to pesticides (including both occupational and non-occupational exposure), with the exception of the neurobehavioral topic area, in which only study populations 18 years or younger were included; (2) if the outcome included a relevant respiratory, reproductive, or neurobehavioral health issue; and (3) if the study used a cohort, case-control, or cross-sectional design. Excluded studies were those published in a non-English language, those that did not report original results (i.e., reviews, meta-analyses, case-reports, comments, letters, editorials, cluster investigations, and conference abstracts), and ecological studies. Included studies were required to be original research studies published in the peer-reviewed literature. Grey literature, published theses, and dissertations were excluded. The following sections outline the search and screening process for each topic area.

Neurobehavioral

A total of 1422 references were retrieved using the search strategy (Figure 1); of these, 532 were duplicates and 729 were irrelevant. Of the remaining 161 references, 102 did not meet the inclusion criteria, leaving 59 abstracts to be reviewed. Following the abstract screening, 34 articles were reviewed in full and 32 were included in the final report.

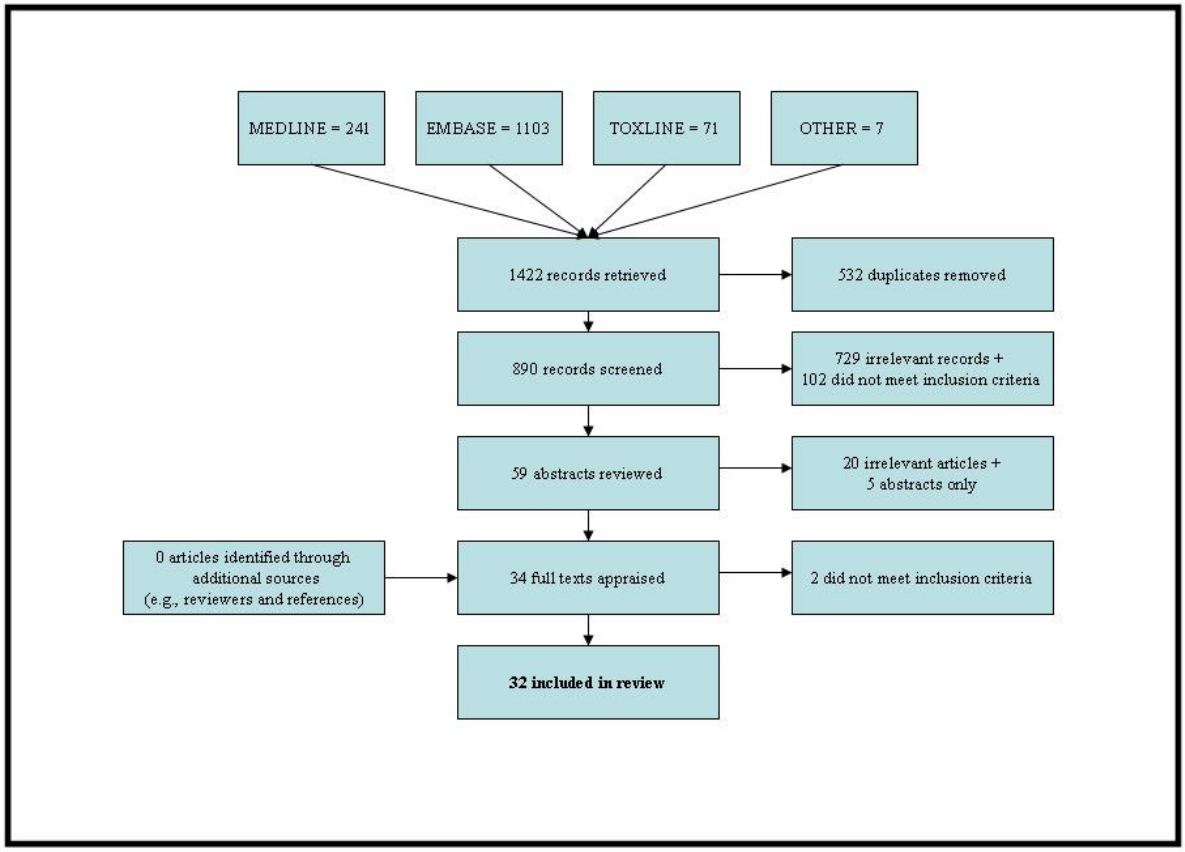

Figure 1. Neurobehavioral search strategy and articles included in review.

Respiratory

The search strategy retrieved a total of 2603 references in the respiratory topic area (Figure 2); of these, 1123 were duplicates and 1256 were irrelevant. Of the remaining 224 articles, 175 did not meet our inclusion criteria, leaving 49 abstracts to review. In total, 40 full texts were appraised and 36 were included in the final report.

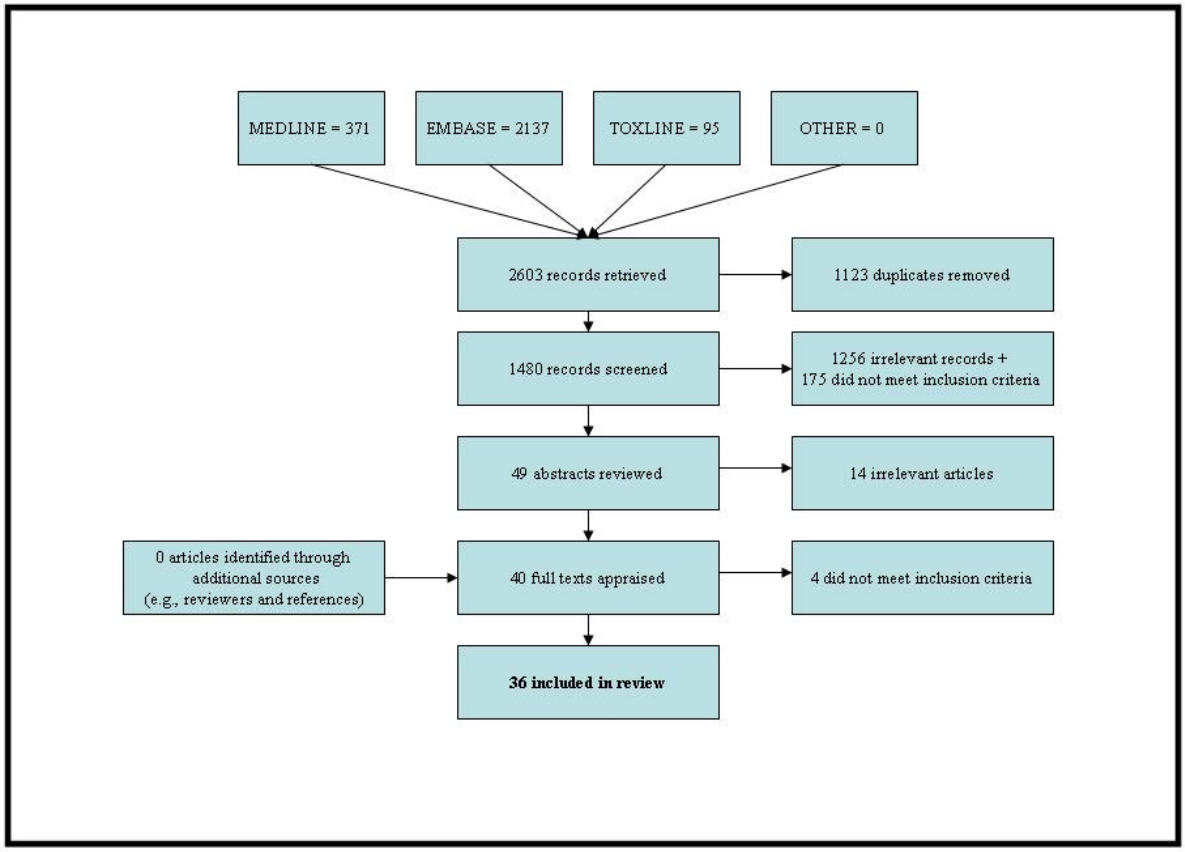

Figure 2. Respiratory search strategy articles included in review.

Reproductive

A total of 1945 references were retrieved using the above search strategy; of these, 1221 were duplicates and 1313 were irrelevant. Of the remaining references, 273 did not meet our inclusion criteria, leaving 190 abstracts to be reviewed. Of these 190 abstracts, 78 remained for full review after removing irrelevant references.

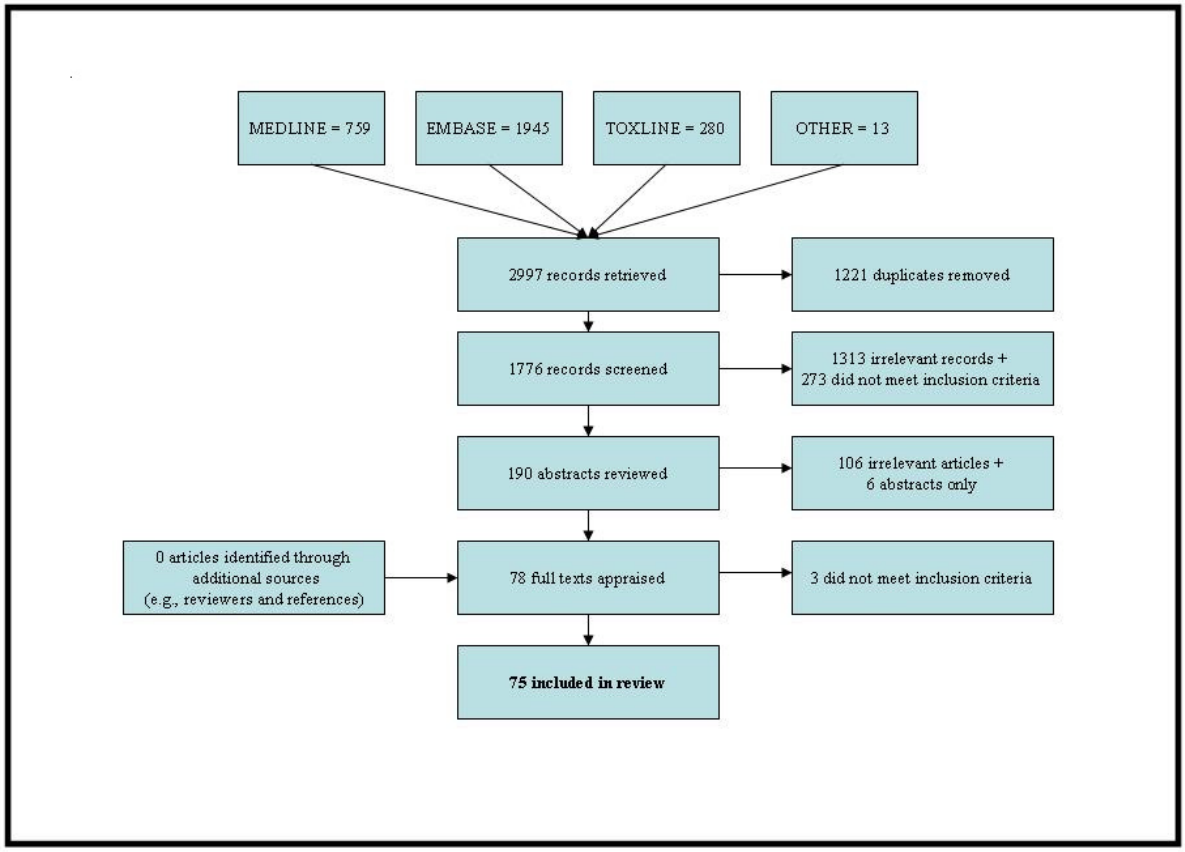

Figure 3. Reproductive search strategy and articles included in review.

Phase 3: Review

Critical appraisal

All articles were reviewed using the Downs and Black (1998) assessment tool as modified by Wigle (2009) to include appraisal of exposure assessment and exposure window identification (see Appendix 2B). The authors of the modified tool were consulted before starting the review process. The same six trained reviewers who performed the abstract screening performed the quality assessment. Prior to assessing articles for inclusion in the review, each reviewer was required to complete a pilot quality assessment exercise in which three studies were appraised using the assessment tool. All reviewers assessed the same three studies. All reviewers scored each article within three points on a 20-point scale. Differences were discussed and the interpretation of assessment tool questions was agreed upon.

The assessment tool informed the development of an electronic appraisal form that each reviewer completed for each reviewed study. Each study eligible for full review was independently scored by two reviewers, discrepancies of more than two points (on a 20-point scale) being resolved through discussion and consensus. In cases in which discrepancies could not be resolved by

consensus, a third party was asked to review the article. The reviewers were not blind to publication information including author and journal.

Data abstraction

A data record containing relevant information was completed for each study identified for inclusion. The following information was collected for each study using a standardized data collection form: ID number, author, year of publication, geographic location, design, population (i.e., age, sex, and sample size), exposure index, type of exposure (i.e., pesticide type), exposure window, outcome index, risk estimate, and confounders (see Appendix 2C). Two reviewers completed the data abstraction form for each identified study.

Appendix 2A: Search terms

Table 2A.1. Pesticide exposure search terms.

MeSH and emtree	Text words
Exp Pesticide	pesticid* OR fungicid* OR herbicid*OR insecticid*OR molluscacid*OR rodenticid*

Table 2A.2. Respiratory outcomes search terms.

MEDLINE – MeSH	Text words
Asthma, Respiratory Sounds	adult onset asthma OR adult-onset asthma OR allergic asthma OR non-allergic asthma OR non allergic asthma OR nonallergic asthma OR wheez* OR nonatopic asthma OR non-atopic asthma OR atopic asthma OR reactive airway disease
Chronic Obstructive Pulmonary Disease, Chronic Bronchitis, Bronchitis, Emphysema, Pulmonary Emphysema Bronchiectasis	COAD OR COPD OR chronic obstructive pulmonary disease OR chronic obstructive airway disease* OR chronic obstructive lung disease* OR chronic airflow obstruction* OR bronchitis OR chronic bronchitis OR emphysema OR pulmonary emphysema
Interstitial Lung Diseases, Pulmonary Eosinophilia, Bronchiolitis Obliterans, Bronchiolitis, Respiratory Hypersensitivity, Extrinsic Allergic Alveolitis	Extrinsic allergic alveolitis OR EAA OR hypersensitivity pneumonitis OR chronic eosinophilic pneumonia OR Carrington Syndrome OR bronchiolitis obliterans OR constrictive bronchiolitis OR interstitial lung disease* OR farmer* lung OR farmer's lung
Pulmonary Fibrosis, Pulmonary Sarcoidosis, Sarcoidosis, Granulomatous Disease, Chronic Granuloma, Respiratory Tract	restrictive lung disease OR sarcoidlike granulomatous pulmonary disease OR sarcoid-like granulomatous pulmonary disease OR idiopathic pulmonary fibrosis OR pulmonary fibrosis OR pulmonary sarcoidosis OR restrictive pulmonary disease
Respiratory Tract Infections, Cough	Pulmonary infection* OR lung infection* OR recurrent pulmonary infection* OR chronic pulmonary infection* OR recurrent lung infection* OR chronic lung infection* OR respiratory tract infection* OR lower respiratory tract infection* OR upper respiratory tract infection* OR chronic cough* OR phlegm OR non-chronic cough* OR non chronic cough* OR persist*nt cough*
Bronchial Hyperreactivity	Nonspecific bronchial reactivity OR non-specific bronchial reactivity OR non specific bronchial reactivity OR bronchial reactivity OR inflammatory pulmonary parenchymal syndrome* OR pulmonary parenchymal syndrome*

Forced Expiratory Volume, Respiratory Function Tests, Respiratory physiological Phenomena, Respiratory Insufficiency	"Change* in pulmonary function" OR "longitudinal decline in FEV1" OR "decline in forced expiratory volume" OR "decline in lung function" OR "change* in lung function" OR "decline in pulmonary function" OR "respiratory insufficiency"
EMBASE – emtree	**Text words**
Asthma, Wheezing	adult onset asthma OR adult-onset asthma OR allergic asthma OR non-allergic asthma OR non allergic asthma OR nonallergic asthma OR wheez* OR nonatopic asthma OR non-atopic asthma OR atopic asthma OR reactive airway disease
Chronic Obstructive Lung Disease, Emphysema, Lung Emphysema, bronchitis	COAD OR COPD OR chronic obstructive pulmonary disease* OR chronic obstructive airway disease* OR chronic obstructive lung disease* OR chronic airflow obstruction* OR bronchitis OR chronic bronchitis OR emphysema OR pulmonary emphysema OR lung emphysema
Interstitial lung disease, bronchiolitis, occupational lung disease, farmer lung, respiratory tract allergy	Extrinsic allergic alveolitis OR EAA OR hypersensitivity pneumonitis OR chronic eosinophilic pneumonia OR Carrington Syndrome OR Lo*fflers syndrome OR Lo*ffer pneumonia OR bronchiolitis obliterans OR constrictive bronchiolitis OR interstitial lung disease* OR farmer* lung OR eosinophilic pneumonia
Lung fibrosis, sarcoidosis, lung granumola, lung granulomatosis, chronic granulomatous disease,	restrictive lung disease OR sarcoidlike granulomatous pulmonary disease OR sarcoid-like granulomatous pulmonary disease OR idiopathic pulmonary fibrosis OR pulmonary fibrosis OR pulmonary sarcoidosis OR restrictive pulmonary disease OR besnier boeck schaumann disease OR besnier boeck schaumann syndrome
[recurrent infection AND lung infection], [coughing AND (chronic or persist*nt.mp)],	recurrent lung infection* or recurrent pulmonary infection* or chronic pulmonary infection* or chronic lung infection* or recurrent respiratory tract infection* or chronic cough* or phlegm or non-chronic cough* or non chronic cough* or persist*nt cough*
Forced expiratory volume, lung function test, respiratory failure	"Change* in pulmonary function" OR "longitudinal decline in FEV1" OR "decline in forced expiratory volume" OR "decline in lung function" OR "change* in lung function" OR "decline in pulmonary function" OR "respiratory insufficiency"
Lung parenchyma, [bronchus hypperreactivity AND nonspecific, non specific OR non-specific.mp]	Nonspecific bronchial reactivity OR non-specific bronchial reactivity OR non specific bronchial reactivity OR bronchial reactivity OR inflammatory pulmonary parenchymal syndrome* OR pulmonary parenchymal syndrome*

Table 2A.3. Reproductive outcome search terms.

MEDLINE – MeSH	Text words
Infant, Low Birth Weight, Obstetric Labor, Premature, Gestational Age	Low birth weight OR very low birth weight OR LBW infant OR LBW neonate OR LBW newborn OR neonatal underweight OR low birthweight OR very low birthweight OR premature labo*r OR pre-mature labo*r OR pre-mature birth OR premature birth OR small for gestational age OR small for date infant OR small for date newborn OR extremely low birthweight OR extremely low birth weight
Spontaneous Abortion (not exp), Stillbirth, Fetal Death	Miscarriage OR spontaneous abortion OR stillbirth OR stillborn baby OR f*etal death OR f*etus death OR antepartum death OR prenatal death OR intrauterine f*etal death OR intrauterine death OR pregnancy loss OR pre-natal death
Congenital Abnormalities, Chromosomal Aberration	Congenital anomaly OR congenital abnormalit* OR birth malformation OR birth defect* OR congenital defect OR development anomaly OR congenital disorder OR chromosomal aberration* OR chromosomal abnormalit*
Fetal Development, Fetal Growth Retardation	Intrauterine growth retardation OR intrauterine growth restriction OR f*etal growth retardation OR f*etal growth restriction OR altered f*etal development OR altered f*etal growth
Fertility, Infertility, Female Infertility, Sperm Analysis	Sperm concentration OR sperm motility OR spermatogenic effects OR sperm count OR semen volume OR spermatozoon quality OR spermatozoal quality OR spermatogenic effect* Subfertility OR delayed conception OR fecundability OR infecundit* OR fertility disorder OR fecundit* OR infertility OR sperm-ovum interaction*
Sex Distribution	Sex distribution OR gender composition OR sex ratio change OR sex ratio shift OR sex ratio depression OR gender distribution
EMBASE – emtree	**Text words**
Low birth weight, premature labor	Low birth weight OR very low birth weight OR LBW infant OR LBW neonate OR LBW newborn OR neonatal underweight OR low birthweight OR very low birthweight OR premature labo*r OR pre-mature labo*r OR pre-mature birth OR premature birth OR small for gestational age OR

	small for date infant OR small for date newborn OR extremely low birthweight OR extremely low birth weight
Congenital disorder (not exp), chromosome aberration (not exp)	Congenital anomaly OR congenital abnormalit* OR birth malformation OR birth defect* OR congenital defect OR development anomaly OR congenital disorder OR chromosomal aberration* OR chromosomal abnormalit*
Spontaneous abortion, fetus death	Miscarriage OR spontaneous abortion OR stillbirth OR stillborn baby OR f*etal death OR f*etus death OR antepartum death OR prenatal death OR intrauterine f*etal death OR intrauterine death OR pregnancy loss OR pre-natal death
Intrauterine Growth Retardation, prenatal growth	Intrauterine growth retardation OR intrauterine growth restriction OR f*etal growth retardation OR f*etal growth restriction OR altered f*etal development OR altered f*etal growth
Fertility, Infertility	Subfertility OR delayed conception OR fecundability OR infecundit* OR fertility disorder OR fecundit* OR infertility OR sperm-ovum interaction*
Sex Ratio	Sex distribution OR gender composition OR sex ratio change OR sex ratio shift OR sex ratio depression
Semen analysis, spermatozoon density, spermatozoon count, spermatozoon motility	Sperm concentration OR sperm motility OR spermatogenic effects OR sperm count OR semen volume OR spermatozoon quality OR spermatozoal quality OR spermatogenic effect*

Table 2A.4. Neurobehavioral outcome search terms.

MEDLINE – MeSH	Text words
Attention deficit and disruptive behavior disorders	Attention deficit and disruptive behavio*r disorder* OR ADHD OR attention deficit disorder with hyperactivity OR attention deficit hyperactivity disorder OR attention deficit disorder OR Oppositional defiant disorder* OR ODD OR conduct disorder*
Child development disorders, Pervasive	Autism OR autism spectrum disorder* OR autistic disorder* OR pervasive child development disorder* OR pervasive developmental disorder* OR PDD OR Rett syndrome OR asperger* OR asperger* syndrome OR childhood disintegrative disorder
Learning Disorders	Learning disabilit* OR learning disorder* OR impaired learning OR learning defici* OR learning impair* OR learning difficult* OR learning disturbance OR learning problem* OR learning disorder* OR dyslexia OR reading disorder* OR dyslectic child OR strephosymbolia OR reading difficult* OR reading deficit* OR reading diabilit* OR reading impair*
Developmental disabilities, mental retardation	Development* delay* OR development* disabilit* OR cognitive defici* OR abnormal development OR mental defici* OR mental* retard* OR neurocognitive dysfunction* OR cognitive disabilit* OR cognitive impair* OR development* neurotoxic* OR mental capacit* OR mental development* OR mental performance OR neuropsychological health effect*
Childhood behaviour disorders	Neurodevelopment* OR neurocognitive OR neurobehavio*r* OR Neuro-development* OR neuro-cognitive OR neuro-behavio*r*
EMBASE – emtree	**Text words**
Attention deficit disorder	Attention deficit and disruptive behavio*r disorder* OR ADHD OR attention deficit disorder with hyperactivity OR attention deficit hyperactivity disorder OR attention deficit disorder NOTE: would not recognize "ADD"
Autism	Autism OR autism spectrum disorder* OR autistic disorder* OR pervasive child development disorder* OR pervasive developmental disorder* OR PDD OR Rett syndrome OR asperger* OR asperger* syndrome OR childhood disintegrative disorder

Oppositional defiant disorder, conduct disorder	Oppositional defiant disorder* OR ODD OR conduct disorder*
Learning disorder, dyslexia	Learning disabilit* OR learning disorder* OR impaired learning OR learning deficit OR learning impair* OR learning difficult* OR learning disturbance OR learning problem* OR learning disorder* OR dyslexia OR reading disorder* OR dyslectic child OR strephosymbolia OR reading difficult* OR reading deficit* OR reading diabilit* OR reading impair*
Developmental disorder, cognitive defect, mental deficiency [childhood AND cognition]	Development* delay* OR development* disabilit* OR cognitive defici* OR abnormal development OR mental defici* OR mental* retard* OR neurocognitive dysfunction* OR cognitive disabilit* OR cognitive impair* OR development* neurotoxic* OR mental capacit* OR mental development* OR mental performance OR neuropsychological health effect*

Appendix 2B: Data abstraction tool

Data abstraction tool adapted from Modified Downs and Black Quality Assessment Tool (Wigle 2009), based on the Downs and Black Checklist for Measuring Study Quality (Downs and Black 1998).

DATE: dd/mm/yy
TOPIC: resp repro neuro
REFERENCE ID: ____ ____ ____REVIEWER: _____

FACTOR	SCORE
External Validity	
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	/1
Were the subjects who were prepared to participate representative of the entire population from which they were recruited?	/1
Subtotal	/2
Internal Validity – bias	
Was an attempt made to blind those measuring the main outcomes of the intervention?	/1
If any of the results of the study were based on "data dredging" was this made clear?	/1
In cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	/1
6. Were the statistical tests used to assess the main outcomes appropriate?	/1
Was compliance with the intervention reliable? (I.e.Was there potential for misclassification?)	/1
Were the main outcome measures used accurate (valid and reliable)?	/1
Subtotal	/6
Internal Validity – Exposure Measurement	
9. Were measures of exposure robust? Exposure status was either documented or determined via biomarker (2); used small area ecological measures, job titles, or was self-reported (1); was based on large area ecological measures (0).	/2
10 .Was there a sufficient exposure gradient? The degree of variability between categories of exposure frequency, duration, or intensity was high (2), medium (1), low/unknown (0).	/2

11. Were measures of exposure specific? Exposure measures were specific (2); based on broader, chemically-related groups (1); based on broad groupings of diverse chemical and toxicological properties (0).	/2
Were all critical exposure time windows measured and reported? Exposure time windows were all (2); partially (1); or not at all (0) defined, measured, and reported.	/2
Subtotal	/8
Internal Validity – Confounding	
Were the cases and controls recruited from the same population? Were study subjects in different exposure groups recruited from the same population?	/1
Were study subjects in different intervention groups, or were cases and controls, recruited over the same period of time?	/1
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? The study collected data on all major (2), some (including basic demographic only) (1), or no (0) potential confounders and assessed their effect in analysis.	/2
Subtotal	/4
TOTAL	/20

REVIEWER: _____

** Note: For questions 3, 5, 7, and 14, please interpret "intervention" as "exposure."

Appendix 2C: Data abstraction form

REVIEWER: _____

ID #	
Reference (First author, Year)	
Country (Province, State)	
Study Design	
Study population (age, sex, sample size etc.)	
Exposure index	
Type of exposure (i.e. pesticide)	
Exposure window	
Type of outcome	
Outcome ascertainment	
Risk Estimate/Results (i.e. OR, RR, CIs)	
Measured Confounders	
Notes/Comments	

References

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Downs S, Black N. 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Epidemiol Comm Health 52(6):377-384.

Chapter 3: Reproductive Health Outcomes and Pesticide Exposure

Study identification

From a total of 190 studies identified, 78 were retained from the primary screening of abstracts. Most excluded studies were irrelevant, duplicates, or review studies. After the secondary screening of the complete manuscripts, 75 studies were deemed to meet our inclusion criteria and be eligible for the review. One of the excluded manuscripts was a research letter (Cohn 2003). Another study (Jarrell 2005) compared levels of PCBs and some organochlorine pesticides in various body fluids (e.g., blood, amniotic fluid, breast milk, and umbilical cord blood) but did not measure any birth outcomes. The third excluded study did not include pesticides at all (Konishi 2009).

Overall study characteristics

Overall, there was a broad range in the quality of the studies that considered reproductive health outcomes. The mean assessment score was 14, with a range of 5–19, illustrating the varied quality across studies. Higher-rated studies tended to have better scores for factors related to exposure measurement. For example, the higher-quality studies often used a biomarker such as cord blood, breast milk, or maternal urine to measure exposure. These studies were also more likely to consider specific pesticides or groups of pesticides (e.g., fungicides or herbicides). The lower-quality studies generally used proxy measures of exposure, such as ecologic measures of residential exposures and job exposure matrices and/or broad job titles for occupational exposure, or considered exposure very generally as "pesticides" (yes/no). However, in some cases the ecologic measures of residential exposure were quite good (e.g., geospatial data that use pesticide use reporting systems to correlate exact timing and amounts of pesticides applied around individuals' homes). In addition, the lower-quality studies typically did not account sufficiently for potential confounders (e.g., smoking), resulting in an increased likelihood of bias in the findings and therefore less reliable conclusions. Given this broad range in the quality of the studies, we have organized the discussion of the synthesis of the results into those studies ranked above a score of 13, with specific emphasis on those scoring 17 or higher out of 20, and those studies assessed at a score of 13 or below. Note that scores mentioned are the average of the two assessors. We also divided the studies into those that assess for associations between presence of metabolites of organochlorines and deleterious reproductive outcomes, and those that do not. Many organochlorines have been banned in Canada, although several continue to persist in the environment, and could possibly be affecting reproductive outcomes many years later.

Summary of findings from the reproductive outcome papers studying non-organochlorine pesticides that were ranked >13/20

Fetal growth

The majority of highly-ranked papers in the reproductive section looked at various fetal growth-related outcomes. These include birth weight, head circumference, intrauterine growth restriction (IUGR), ponderal index (a measure somewhat comparable to body-mass index – BMI – and used frequently in studies of infants and children), and small-for-gestational-age (SGA). Typically, most studies considered a combination of these outcomes. There were ten papers (Barr 2010, Berkowitz 2004, Chevrier 2011, Eskenazi 2004, Hanke 2003, Levario-Carrillo 2004, Neta 2011, Ochoa-Acuna 2009, Whyatt 2004, Wolff 2007) in total in this section, the vast majority of which were cohort studies, and several that prospectively followed women during their pregnancy and obtained measures of exposure at more than one time point. Some of these papers considered only non-organochlorine pesticides ($n = 6$), while others considered both organochlorine and non-organochlorine pesticides ($n = 4$).

Six of the eight positive studies in this section considered decreased birth weight (Barr 2010, Chevrier 2011, Hanke 2003, Levario-Carrillo 2004, Ochoa-Acuna 2009, Whyatt 2004). Two of the six studied atrazine (Chevrier 2011, Ochoa-Acuna 2009), two studied organophosphates (Levario-Carrillo 2004, Whyatt 2004), and two studied a number of different pesticides of different groups (Barr 2010, Hanke 2003).

One investigation of a prospective cohort of 150 pregnant women and their infants in New Jersey (rated 16 out of 20) found an association between high ($\geq 75^{th}$ percentile) cord blood levels of metolachlor, a chloroacetanilide herbicide used for agricultural and residential weed control, and decreased birth weight (3605 g in the upper quartile vs. 3399 g; $p = 0.05$) (Barr 2010). However, the researchers were not able to replicate Whyatt's (2004) association between chlorpyrifos and birth weight.

A decrease in head circumference was also suggested in a few studies (associated with dichloran, atrazine, hexachlorobenzene, and domestic pesticide use). This is of particular concern given that head circumference has been found to be predictive of subsequent cognitive ability. For example, a case–control study (with score 18.5 out of 20) in an agricultural region in France reported a marginally significant association between small head circumference and exposure to atrazine (measured in maternal urine), a triazine herbicide used frequently in the corn crops of that region (OR = 1.7, 95% CI = 1.0–2.7) (Chevrier 2011). Fetal growth restriction was also associated with the presence of atrazine metabolites in maternal urine (OR = 1.5, 95% CI = 1.0–2.2). It is important to note that though the European Union banned the use of atrazine in 2001, this study showed the persistence of atrazine residues in drinking water samples and in the urine samples of pregnant women up to three years after this ban, demonstrating its persistence in the environment. Atrazine is one of the most widely used herbicides in Ontario and continues to be used today.

One very interesting and high-quality study (rated 15.5 out of 20) examined in utero exposure to chlorpyrifos, an organophosphate insecticide used widely in the US, and various fetal growth parameters (Berkowitz 2004). Maternal paraoxonase (PON1) activity was also measured. PON1

is an enzyme that hydrolyzes some organophosphate compounds, and can detoxify the active chlorpyrifos metabolite chlorpyriphos-oxon. The study found that higher maternal urinary levels of chlorpyrifos coupled with low maternal PON1 activity were associated with a significant reduction in head circumference ($p = 0.004$). This study is also important because pesticide exposure alone was not associated with any of the fetal growth indices, though when PON1 activity was included, associations were evident. This indicates that people vulnerable to the effects of pesticides may be those who possess less PON1 activity; once we are able to identify this segment of the population, they can exercise extra caution with respect to pesticide exposure. It also shows the importance of measuring this parameter when studying the effects of pesticides on humans.

Another well-designed study, part of an ongoing prospective cohort of minority mothers and newborns in New York City, looked at pollutants and a number of birth outcomes. This particular study (Whyatt 2004) analyzed maternal blood and umbilical cord samples of two organophosphate insecticides (i.e., chlorpyrifos and diazinon) at delivery, as well as maternal ambient air samples measured with personal air monitors worn by the mothers during late pregnancy. These were stratified into four exposure groups to determine dose–response relationships. The effects of pesticides on birth outcomes were assessed in the total cohort of women who were enrolled between 1998 and 2002, and then again after, stratifying by year of delivery to examine any effect of the US EPA regulatory action to phase out residential use of diazinon and chlorpyrifos in 2001. The study showed an inverse association between chlorpyrifos levels (in umbilical cord blood in a dose–response relationship) and birth weight and length in newborns born before the ban, suggesting that diazinon levels may also be associated with reduced birth weight and length. Levels of insecticide were lower in infants born after January 2001, and no association with fetal growth was apparent when regulatory bodies phased out residential use of chlorpyrifos and diazinon.

No significant associations for several growth indicators were found in an American cross-sectional study (Neta 2011). In this study, which scored 18 out of 20, the organochlorine insecticide chlordane (used for termite control and banned in 1988 but persistent in the environment) and the synthetic pyrethroid permethrin (used ubiquitously for human lice and scabies treatments) were measured in umbilical cord samples of newborns in a Baltimore hospital. The study found that neither of these pesticides was significantly associated with birth weight, length, head circumference, or gestational age. However, small newborns with small umbilical cords were excluded because they had insufficient volume of blood for collection. This would bias the sample to bigger babies so there would be less likelihood of finding smaller birth weight, length, and head circumference or lower gestational age. Similarly, no association was reported between organophosphate exposure and fetal growth in a cohort study in California (Eskenazi 2004). In fact, increases in body length and head circumference were associated with some exposure measures. A small but significant association was found between exposure to synthetic pyrethroids in the first or second trimester and decreased birth weight in a mid-quality retrospective cohort study in Poland (Hanke 2003). One study that considered IUGR found an association with exposure to pesticides (as a group, ascertained by questionnaire) as well as to organophosphates in particular (measured by acetylcholinesterase levels in maternal serum at delivery, and in infant cord blood) (OR = 2.33; $p = 0.04$) (Levario-Carrillo 2004).

Birth defects

The next largest group of highly-ranked papers considered birth defects (e.g., hypospadias, cryptorchidism, neural tube defects, and congenital diaphragmatic hernia). There are six papers in this section (Brender 2010, Dugas 2010, Felix 2008, Lacasana 2006, Meyer 2006, Weselak 2008), all of which found positive associations. Hypospadias, characterized by an abnormal positioning of the opening of the urethra in males, is one of the birth defects most commonly studied in the pesticide literature. Because sex hormones play a strong role in fetal genitourinary development, it is hypothesized that in utero exposure to endocrine-disrupting chemicals could contribute to hypospadias. In general, the endocrine-disrupting pesticides are persistent organochlorines; most of these have been banned in most countries worldwide, but persist in fat tissue and thus can be transmitted to fetuses placentally and to infants via breast milk. A recent systematic review of nine published papers suggests an increased risk of hypospadias with maternal occupational pesticide exposure (pooled RR = 1.36, 95% CI = 1.04–1.77) (Rocheleau 2009). However, these findings were marginally significant and considered broad categories of pesticides. Consequently, we considered primary studies of hypospadias in this review.

Two high-quality papers considered the relationship between hypospadias and non-organochlorine pesticides (Dugas 2010, Meyer 2006). A case–control study conducted in England found an increased risk of hypospadias with exposure to insect repellent (OR = 1.81, 95% CI = 1.06–3.11) (Dugas 2010). Similarly, a US case–control study suggested an association between exposure to the chlorophenoxy herbicide diclofop-methyl and hypospadias (OR = 1.08, 95% CI = 1.01–1.15) (Meyer 2006).

The other four studies in the birth defect category were mid-quality (i.e., average rank of 14). One found a marginally significant association between congenital diaphragmatic hernia and exposure to herbicides or insecticides (OR = 2.0, 95% CI = 1.0–4.1) (Felix 2008). Another suggested a relationship between use of pesticides in the home and neural tube defects (OR = 2.0, 95% CI = 1.2–3.1) (Brender 2010), and the last showed a positive association between maternal agricultural occupational exposure and development of anencephaly, a severe neural tube defect, in children (OR = 4.57, 95% CI = 1.05–19.96) (Lacasana 2006). Finally, a Canadian retrospective cohort reported an association between exposure to the herbicides cyanazine (a triazine) and dicamba (a benzoic acid) and various birth defects (OR = 4.99, 95% CI = 1.63–15.27 and OR = 2.42, 95% CI = 1.06–5.53, respectively) (Weselak 2008).

Preterm birth

Two studies investigated the relationship between pesticide exposure and preterm birth and/or gestational age. One very highly ranked study in this group (score 17.5) (Eskenazi 2004) found an association with gestational age in a cohort of low-income Mexican women living in an agricultural community in California. Exposure to organophosphate insecticides was assessed by measurements of the insecticides and their metabolites in maternal urine during pregnancy, measurements of cholinesterase from maternal blood during pregnancy, and from umbilical blood at delivery. Organophosphates inhibit cholinesterase in the blood, so this enzyme is measured to identify organophosphate exposure but is not reliably sensitive to low exposure levels. Six-week windows of exposure during pregnancy were analyzed, and all outcomes were adjusted for many important confounders, including maternal age and BMI, pregnancy weight gain, prenatal care, income, and some lifestyle variables such as smoking and consumption of caffeinated beverages. An association was found with organophosphate exposure and decreased gestational age (though

by less than half a week) (Eskenazi 2004), although despite this, the rate of preterm delivery was not higher than in the US referent population.

A retrospective cohort study conducted in Indiana found a significant association between the atrazine levels in drinking water in the third trimester and the entire pregnancy, and prevalence of SGA in infants (PR = 1.14, 95% CI = 1.03–1.24) (Ochoa-Acuna 2009). However it is not clear that drinking water levels are a good proxy for exposure to atrazine, as there could be other chemicals present that could be responsible for the observed increase in SGA. In addition, information on whether women use bottled or filtered water was not available.

Infertility

One study examined time-to-pregnancy/fecundability/infertility (Greenlee 2003). A case–control study of approximately 600 women in Wisconsin found that mixing and applying herbicides in the two years before attempting conception was more common among infertile women (OR = 27, 95% CI = 1.9–380), as was the use of fungicides (OR = 3.3, 95% CI = 0.8–13) (Greenlee 2003). These results are suggestive, although the broad confidence intervals due to the small sample size in the subcategories of analysis make the findings less reliable. In addition, the response rate was low and exposure was self-reported rather than measured directly by biomarker.

Summary of findings from the reproductive outcome papers studying non-organochlorine pesticides that were ranked ≤13/20

Overall, these studies typically considered exposure assessed by occupation or ecologic measures. For the former, questionnaire data, job title, or job exposure matrices were used, increasing the likelihood of exposure misclassification and therefore reducing the overall quality of the study. While ecologic studies are important for generating hypotheses, the analyses are based on groups and/or areas. Therefore, associations cannot be inferred at the individual level based only on ecologic studies.

Birth defects

The majority of papers in the group considered various birth defects (e.g., hypospadias, neural tube defects, cryptorchidism, male reproductive development, and gastroschisis). There are eight papers in total in this section (Bianca 2003, Brouwers 2007, Carbone 2006, Fear 2007, Heeren 2003, Pierik 2004, Waller 2010, Zhu 2006), most of which considered paternal exposure. One study (Ronda 2005) looked at "congenital anomalies" but was in fact studying fetal and neonatal death and so is not included in this section.

Heeren (2003) addressed "birth defects" as a group, and found seven times the risk to mothers exposed to "chemicals used in gardens and fields" compared with no reported exposure (OR = 7.18, 95% CI = 3.99–13.25). However, the response rate is not mentioned, and the exposure is self-reported and not quantified (i.e., ever/never).

The evidence for an association between pesticide exposure and hypospadias was mixed. One study reported positive associations (Bianca 2003) and the other three showed no association (Brouwers 2007, Carbone 2006, Pierik 2004). A case–control study that also examined another

male birth defect, cryptorchidism (maldescent of the testis), found an increased risk associated with paternal pesticide exposure as assessed by job type (OR = 3.8, 95% CI = 1.1–13.4) (Pierik 2004). A case–control study of paternal exposure to agrochemicals reported a positive association with neural tube defects (OR = 2.69, 95% CI = 1.09–6.65) (Fear 2007). However, these findings should be interpreted with caution, as exposure was based on the job titles included in hospital records and important confounders such as smoking were excluded. Finally, the only study that considered gastroschisis, a birth defect characterized by a defect in the abdominal wall, found an increased association with exposure in women who resided <25 km from a site of high atrazine concentration (OR = 1.6, 95% CI = 1.10–2.34) (Waller 2010).

Fetal growth

The next largest group of papers in this section looked at various fetal growth-related outcomes (i.e., birth weight, head circumference, IUGR, and SGA). Of these, seven papers (Bretveld 2008, Burdorf 2011, Dabrowski 2003, Jurewicz 2005, Petit 2010, Sathyanarayana 2010, Villanueva 2005) included birth weight (two positive associations and five negative). One of these was a prospective cohort study of approximately 6000 pregnant women in the Netherlands (Burdorf 2011). Using a job-exposure matrix, exposure to pesticides was associated with decreased birth weight (OR = 2.42, 95% CI = 1.10–5.34). However, these findings were not supported by self-reports of exposure in a questionnaire of the same study population, raising the possibility of misclassification of exposure. Findings from a prospective cohort study in France suggested an association between pesticide exposure and decreased head circumference, particularly exposure to pea crops to which organophosphate insecticides were applied (OR = 2.2, 95% CI = 1.2–3.6) (Petit 2010).

Spontaneous abortion

Five studies of spontaneous abortion (Bretveld 2008, Handal and Harlow 2009, Petrelli 2003, Ronda 2005, Settimi 2008) focused on greenhouse workers and/or workers in horticulture, and all found positive associations. For example, a study of approximately 700 female greenhouse workers in Italy found a marginally statistically significant association between applying pesticides and spontaneous abortion (OR = 2.6, 95% CI = 1.0–6.6) (Settimi 2008). This study assessed the outcome by questionnaire and exposure was assessed either through self-reporting or job title. While all found positive associations, it is important to consider that all used self-reporting or job title as measures of exposure. While valuable, these methods of exposure assessment introduce the possibility of misclassification, which may impact results, and partly explain why these studies were ranked of relatively lower quality. However, we did not find any studies of non-organochlorines and spontaneous abortion that were ranked >13 in quality.

Infertility

Measures related to infertility and time-to-pregnancy were considered in five studies (Bretveld 2008, Burdorf 2011, Hougaard 2009, Idrovo 2005, Sallmen 2003). Again, all examined greenhouse/horticultural workers as the population of interest and found mixed results (two positive and three negative). One paper in this group was a cross-sectional survey of approximately 2000 women who responded to questions about their first pregnancy. Working in flower production for two years or more was associated with reduced fecundability (fecundability OR = 0.73, 95% CI = 0.63–0.84) (Idrovo 2005). However, the women's first pregnancy could have been up to 10 years prior to the data collection by questionnaire, therefore introducing the potential for recall bias in the findings. A cross-sectional study used mailed questionnaires

administered to families of Finnish male greenhouse employers and employees. A low participation rate and small numbers resulted in a rating of 13 out of 20. This study suggested an association between unprotected exposure to pyrethroids, an insecticide, and reduced fecundability, measured by fecundability density ratio (FDR), which if less than 1.0, indicates increased time-to-pregnancy. The FDR was 0.40 (CI = 0.19–0.85) (Sallmen 2003). However, none of the other pesticides examined in this study (i.e., organophosphates, organochlorines, carbamates, and herbicides) were associated with reduced fecundability, providing limited support for the hypothesis that exposure to pesticides is associated with reduced fertility.

Preterm birth

Four studies (Bretveld 2008, Burdorf 2011, Villanueva 2005, Zhu 2006) investigated preterm birth and only one found positive associations (Zhu 2006). This investigation of 226 pregnancies of gardeners and 214 pregnancies of farmers from a national birth cohort in Denmark found an association between very preterm birth and occupation as a gardener (OR = 2.6, 95% CI = 1.1–5.9). However, this finding was based on only six cases. The study did not find any other significant associations, and concluded that there is little effect of occupational exposures to pesticides on pregnancy outcomes among gardeners or farmers in Denmark.

Summary of findings from the papers that considered the reproductive effects of organochlorine pesticides that were ranked >13/20

Organochlorine pesticides are fat-soluble persistent chemicals that remain in the environment and in animal and human fat tissue for many years. Dichlorodiphenyltrichloroethane (DDT) is an organochlorine insecticide that was registered for use in Canada in 1946 and then banned in the early 1970s due to concerns about potential harm to both human health and the environment. Despite widespread bans, numerous studies of DDT have shown its environmental persistence and its ability to bioaccumulate. For example, DDT residues can be found in food, stored in human body fat, and excreted in breast milk. Other organochlorine pesticides, such as chlordane and dieldrin, have also been banned in Canada. Some are still in use such as lindane (a hexachlorocyclohexane insecticide), banned since 2004 but still permitted for treatment of head lice, and the cyclodiene insecticide endosulfan (a phase-out began in 2011, to be complete by December 31, 2016). Consequently, we have included studies of the reproductive effects of organochlorine pesticide exposure in this review. There were 26 studies in this section; two papers were excluded, leaving 24 that were eligible for review.

The majority of the studies in this section were rated as good quality. A total of 17 papers were assigned a score >13/20 by both reviewers. The remaining 10 were rated ≤13, with the majority ranking below a score of 10 or having major methodological flaws making their conclusions somewhat unreliable. Consequently, this discussion will focus only on the highly rated studies (>13).

Fetal growth

Many of the studies considered outcomes related to fetal growth, including birth weight, length, and head circumference. Of the eleven papers that looked at fetal growth (Brucker-Davis 2010, Eggesbo 2009, Farhang 2005, Fenster 2006, Gladen 2003, Jusko 2006, Khanjani 2006a,b, Sagiv 2007, Siddiqui 2003, Wojtyniak 2010), four reported positive associations between exposure to DDT and low birth weight while the other studies did not report a statistically significant association.

A highly ranked study by Gladen (2003) done in Ukraine did not find a change in birth weight with exposure prenatally to a number of organochlorine pesticides. The study scored 18 out of 20, but the sample was not random, which introduces bias in the findings. One small case–control study of 30 babies in India with IUGR found associations between maternal blood levels of persistent chlorinated pesticides and IUGR (Siddiqui 2003). Significant ORs varied between 1.07 (CI = 1.01–1.13) and 1.61 (CI = 1.01–2.54) for different metabolites found in maternal blood, and between 1.07 (CI = 1.00–1.14) to 1.31 (CI = 1.00–1.75) for metabolites found in umbilical cord blood. Another cross-sectional study of 1322 pregnant women in Greenland, Ukraine, and Warsaw found a significantly decreased infant birth weight of up to 104 grams (CI = –202.5 to –6.1) and shorter gestational age by up to 0.6 weeks (CI = –1 to –0.2) associated with increased maternal blood levels of dichlorodiphenyldichloroethylene (DDE), a metabolite of DDT (Wojtyniak 2010).

Of the negative studies, one interesting study examined a cohort of over 20,000 women in San Francisco in the 1960s. Maternal levels of metabolites of DDT were measured during pregnancy, and growth outcomes were measured at birth and at five years of age. Researchers concluded that DDT compounds did not impair fetal or five-year growth (Jusko 2006).

Infertility

Four studies considered time-to-pregnancy (TTP). The highest quality study in this group investigated the effects of low level maternal and paternal persistent contaminant exposures (measured in blood at time of delivery) on fecundability among 41 couples from the general population in Hamilton, Ontario, for their first pregnancy (Cole 2006). High exposure to the organochlorine pesticide lindane was associated with decreased fecundability (OR = 0.30, 95% CI = 0.10–0.89). One study, rated 15 out of 20, found increased TTP among migrant farm workers in California with occupational pesticide exposure, who used pesticides in the home, and who lived within 200 feet of an agricultural field. However, increased TTP was not associated with increased maternal blood levels of DDT metabolites, indicating that changes in TTP could be due to current use of other pesticides and not the effect of persistent DDT (Harley 2008). Another study (Gesink Law 2005) found an association between DDE and TTP, but it was weak and inconclusive. Because some of the women were not primiparous and breastfeeding information was not available, the authors used estimates of post-partum subfertility and infertility, so TTP results may not have been accurate for some of the multiparous women in the study.

Preterm birth

Similarly, five studies investigated the association between pesticide exposure and preterm birth and two found an association. Wojtyniak (2010) found a shortening of gestational age of 0.2–0.6 weeks in Inuit and Warsaw cohorts of this multi-population cohort study. Torres-Arreola (2003)

did not find a significantly increased risk of preterm birth in a case–control study of 100 preterm infants. Women with preterm births had higher blood levels of DDE and HCB (hexachlorobenzene, a fungicide banned in the 1970s but persistent in the environment, and produced as a by-product of the production of various chlorinated chemicals, including organochlorine pesticides), but none of the findings was significant. The other study (Fenster 2006) also found an association between shortened gestational age and organochlorine exposure. Despite testing for several other organochlorines, the latter study only found an association with HCB. The study was limited by small numbers (low prevalence of adverse fetal growth outcomes), making it difficult to identify significant findings.

Seven studies (Bhatia 2005, Brucker-Davis 2008, Carmichael 2010, Damgaard 2006, Fernandez 2007, Longnecker 2007, Pierik 2007) of hypospadias and cryptorchidism reported mixed findings, with three studies finding a positive association. The studies with positive findings measured levels of a number of organochlorine pesticide levels in colostrum (Brucker-Davis 2008 and Damgaard 2006) and placental tissue (Fernandez 2007). All of the negative studies looked at different organochlorine pesticide levels in maternal serum, making it difficult to compare exposure levels with those reported in the positive studies. Longnecker (2007), a negative study, found the DDE levels in mothers to be 10-fold greater than comparable measurements taken in the USA, and felt that the Mexican babies studied had high in utero DDT exposure.

Fernandez (2007), a well-designed nested case–control study, looked at cryptorchidism (undescended testicles) and hypospadias in newborns in Spain, and residues of 16 organochlorine pesticides in placental tissue. Significant ORs ranged from 2.25 to 3.38. A nested case–control study conducted in Finland and Denmark measured levels of several organochlorine pesticides in the breast milk of mothers of cryptorchid boys and healthy boys (Damgaard 2006). Analysis of the eight most abundant persistent pesticides showed that pesticide levels in breast milk were significantly higher in boys with cryptorchidism ($p = 0.032$). A high-quality study rated 16.5 (Brucker-Davis 2008) measured a number of endocrine-disrupting chemicals, including metabolites of DDT, in colostrum of new mothers in France and compared their newborn sons' rates of cryptorchidism to those of controls. Babies exposed to elevated levels of DDT metabolites had a higher rate of cryptorchidism (OR = 2.03, $p < 0.05$).

The study by Carmichael (2010) did not find increased mid-pregnancy maternal blood levels of several persistent pesticides (including HCB) in infants with hypospadias, though the sample size was only 20 cases. Pierik (2007), a well-designed study scoring 18 out of 20, did not find an association between maternal pregnancy blood levels of several persistent pesticides and cryptorchidism. Bhatia (2005), a case–control study with a rating of 19 out of 20, did not find increased maternal blood levels of DDT metabolites in 75 boys born in San Francisco with cryptorchidism or hypospadias compared with controls.

Fetal loss

Lastly, three studies examined the association between DDT exposure and fetal loss (Khanjani 2006a, Toft 2010, Venners 2005), and one reported a statistically significant positive relationship. This highly rated paper (rated 18.5 out of 20) was a prospective cohort study in China of 388 newly married women. DDT levels were assessed preconception using serum samples, and then daily urine samples were taken to detect conception and early pregnancy losses. This is an

extremely important step, as some miscarriages occur before the woman knows she is pregnant, and neglecting this would underestimate fetal loss rates. The group with the highest level of preconception DDT, compared with the group with the lowest level, had an increased odds of early pregnancy loss (OR = 2.2, 95% CI = 1.26–3.57) (Venners 2005).

Another of these papers (rated 16 out of 20) also examined the association of miscarriage and sex ratio, among other reproductive outcomes, with exposure to DDT. Breast milk samples from approximately 800 mothers in Victoria, Australia (all primiparous in order to reduce the lowering effect that previous pregnancies have on breast milk organochlorine levels) were used for measuring the association between pesticide contamination and these reproductive outcomes (Khanjani 2006a). No significant association was found with the miscarriage rate or sex ratio (nor with other growth measurements studied, such as birth weight, head circumference, or small-for-gestational-age). However early miscarriage could have been missed, as the miscarriage rate was self-reported, and those occurring before the mother knew she was pregnant would not have been reported. In addition, the overall level of contamination of the breast milk samples was low, so effects due to higher levels cannot be determined based on this study.

For a summary of the review findings pertaining to this chapter, including a complete list of the articles assessed in order of quality scores, see Summary Table 1: Reproductive Health Outcomes and Pesticide Exposure, on page S2 of the supplement to this report.

Summary

This review provides evidence that non-organochlorine pesticides may cause deleterious reproductive outcomes (see Table 3.1). The most suggestive evidence is of an association between fetal growth outcomes and pesticide exposure. Of the ten studies that considered fetal growth outcomes, eight reported significant associations. Most of these positive associations were for birth weight, and were from well-designed cohort studies. Low-birth-weight babies are at increased risk of mortality, morbidity, and disability in infancy and childhood as well as long-term adverse health outcomes in adult life. As a result, reducing low-birth-weight rates is a priority for public health practitioners, clinicians, and researchers. However, the associations found for a given type of pesticide in one study were not always replicated in other studies of that pesticide (e.g., chlorpyrifos). These inconsistencies could be due to multiple reasons, including differences in sample size, methodology, and study design, and make it challenging to draw definitive conclusions. While it appears there is an association between pesticide exposure and birth weight, this relationship varies according to the type of chemical, with some displaying less consistent associations.

Aside from birth weight, a decrease in head circumference was suggested in several studies, which is of particular concern because small head circumference is linked to lower cognitive abilities in older children and adults. The lower-quality studies showed substantial inconsistency in their findings, particularly with regard to birth weight. In the case of the Burdorf (2011) paper, the findings differed depending on the method used to classify exposure, highlighting the variability that differences in measurement can introduce.

Table 3.1. Outcome of studies in the non-organochlorine group scoring >13 out of 20.

Outcome	Total no. of studies	No. of positive studies
Growth	10	8
Hypospadias, cryptorchidism	2	2
Neural tube defects (including anencephaly)	2	2
Time-to-pregnancy	1	1
Small-for-gestational-age, preterm birth	2	2
Other birth defects	2	2

All of the high-quality birth defect studies reported positive associations. However, as a group they considered a diversity of pesticides, which makes comparisons between them difficult. Nevertheless, associations were found with hypospadias, neural tube defects, and congenital diaphragmatic hernia. The associations with hypospadias are further supported by an earlier systematic review of nine other studies (Rocheleau 2009). However, the lower-quality studies of birth defects were more inconsistent in their findings. In particular for hypospadias, only three of four studies found a positive association, whereas of the studies ranked >13, both papers of hypospadias had positive findings. The finding of an association between gastroschisis and pesticide exposure is interesting given its largely unknown etiology and warrants further investigation.

Few studies examined preterm birth as an outcome, though the two that did both found positive associations. Both cited biologically plausible explanations for these effects (e.g., organophosphate pesticides could affect enzymes that stimulate contractions of the uterus, thereby decreasing gestational duration). Additional studies using individual-level data would provide further insight into these associations.

In contrast, there is less suggestive evidence in this review that the organochlorine pesticides have an effect on reproductive outcomes (see Table 3.2). Most of the studies were conducted in countries where DDT and other organochlorine pesticides had been banned for several decades and levels were generally low in the general population. As with the non-organochlorine studies, exposure measurements were almost all by biomarker.

Table 3.2. Outcome of studies in the organochlorine group scoring >13 out of 20.

Outcome	Total no. of studies	No. of positive studies
Growth	11	4
Time-to-pregnancy	4	1
Hypospadias, cryptorchidism	7	3
Early pregnancy loss	3	1
Preterm birth	5	2

It is possible that associations were not found due to the small numbers in most of the studies. Many authors also commented on the low concentrations of the organochlorines they were examining in maternal and cord blood and in breast milk. However, some of the studies in which levels were considered high still did not find associations, or if they did, the wide range of exposure levels, lack of a dose–response relationship, or other methodological deficiencies make it difficult to draw conclusions. Some of the studies did report a few positive findings that did not attain statistical significance and therefore were reported as negative; however, many of these findings did not follow a dose–response relationship and therefore could have been spurious.

Certainly, the results of this study would indicate that there are benefits to reducing the exposure of pregnant women to commonly used pesticides. The Whyatt study (2004), which found a significant increase in the birth weights of infants born after rather than before a household ban on two frequently used insecticides in New York City, illustrates the possible benefit of pesticide bans within a few years of implementation. In Canada, several provinces and many municipalities have mandated bans and phase-outs of many pesticides in the past several years, and research into reproductive outcomes resulting from these policies is recommended.

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Chapter 4: Neurodevelopmental/Behavioural Health Outcomes and Pesticide Exposure in Children

As pesticides are known to cross the placenta and blood–brain barrier and are found in cord blood and amniotic fluid, there is concern about their potential effects on the developing brain as a result of prenatal and early childhood exposure.

The systematic review included 32 studies of pesticide exposure and neurodevelopmental or behavioural outcomes in children. The range of outcomes, from primitive neonatal reflexes through age-specific developmental testing, to complex cognitive and behavioural outcomes such as intelligence testing and attention deficit disorder (ADD), reflects the various ways of assessing neurologic development depending on a child's age.

All studies were assessed for quality using the modified Downs and Black Quality Assessment Tool (see Chapter 2: Methods, Appendix 2B).

As a group, these are high-quality studies, reflecting biomarker exposure assessment and sophisticated measurement of neurodevelopmental outcomes and confounders. The mean assessment score of all included studies was 15.5 out of 20 (range 4.5–19) and the median score was 17. Twenty-two of the studies had assessment scores above 15.

Two studies were excluded at assessment: one because it was a small case series (Kofman 2006), and one because it did not report data on adolescents separately from adults (Rohlman 2007).

Study types

The studies reviewed included twenty that were reports from *longitudinal, prospective cohort studies*. Two of the cohort studies were from New York City; one exclusively included black or Dominican inner-city mothers. Two of the longitudinal cohorts were based elsewhere in the United States (i.e., California and New Bedford, MA) while one was in Spain and another in Mexico. All included populations were expected to be at higher risk of pesticide exposure; for example, the California cohort was drawn from Mexican-American farm workers' children. Many of the longitudinal studies featured biomarker exposure assessment and careful assessment of confounders such as lead levels, parental intellectual ability, and Home Inventory (a measure of the nurturing environment). Standardized outcome measures were used, for example, the Bayley Developmental Scales and multi-scale IQ tests such as the Wechsler Intelligence Scales for Children. For more information on the cohorts, see Appendix 4A.

One study used a *case–control design* investigating autism. There were eleven *cross-sectional studies*, including two based on the US National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States through a combination of interviews, physical exams, and blood or urine tests for biomarkers of pesticide exposure (CDC 2009). The NHANES-based studies have excellent generalizability, as the subjects have pesticide exposures that are representative of the

national US population. The cross-sectional studies were more variable in quality, with scores ranging from 4.5 to 18.5 on a 20-point scale.

Overview of results

Organophosphate (19) and organochlorine (11) exposures were most frequently studied, perhaps because of the availability of biomarkers for exposure. Seven studies examined organophosphates plus another insecticide (usually carbamate or pyrethrin) and in three the exposure was not characterized.

Most of the studies found a positive association between pesticide exposure and neurodevelopmental or behavioural outcomes such as reduced performance on the Bayley Developmental Scales or ADD. In studies considering an exposure gradient, more effects were consistently found at higher exposure levels, usually the upper 25% or 33%.

An important feature of the longitudinal studies is that particular neurodevelopmental deficits may not manifest themselves in early childhood but may be measurable in older children (Eskenazi 2007, Fenster 2007). Conversely, some deficits evident in earlier testing are no longer apparent as the children get older (Torres-Sanchez 2007, 2009).

The longitudinal and case–control studies were generally of better quality (mean score = 18.5) than the cross-sectional studies (mean score = 12.2).

Results by neurologic outcome

Newborn neurologic outcomes

Four studies reported on neurologic outcomes in newborns exposed in utero to either organophosphates (Engel 2007, Young 2005) or DDT/DDE (Fenster 2007, Sagiv 2008). All studies used the seven-scale Brazelton Neonatal Assessment Behaviour Scale (BNBAS) for outcome assessments.

Organophosphates. The CHAMACOS cohort from an agricultural area of California reported BNBAS findings for Mexican-American newborns (Young 2005). Six organophosphate (OP) metabolites representing the byproducts of 80% of the OPs used in the area were measured twice during pregnancy. There was a significant trend towards an increasing proportion of babies with >3 abnormal reflexes as the exposure levels increased for two OP metabolites measured ($p < .05$) and for total OP metabolites ($p < .01$). In babies in the highest 20% of total organophosphate exposure in utero, 33% had more than three abnormal reflexes. The most common abnormal reflexes were incurvation (40%), passive resistance – legs (39%), and walking (25%). The abnormality was usually absence or hypotonia. The postnatal OP metabolite levels were not associated with presence of abnormal reflexes or other neurologic abnormalities in the neonates.

A report with similar findings examined the inner-city Mt. Sinai–New York City cohort as infants (Engel 2007) for associations between neurodevelopment in 1–3-day-old babies and

prenatal OP exposure. Several urinary OP metabolites were measured during the third trimester of pregnancy (average 31 weeks). Infants whose mothers had any malathion exposure (21.6% of cohort) exhibited significantly more abnormal reflexes (RR = 2.24, $p < .05$). A significant increase in abnormal reflexes was also found for exposure to diethyl phosphates (metabolites of chlorpyrifos) (RR = 1.49; 95% CI = 1.12–1.98). Again, the abnormal reflexes were mainly absent or hypotonic. Infants born to the 30% of the cohort's women who had lower paraoxonase 1 (PON1) expression (meaning they were "slow metabolizers" of organophosphate pesticides) were more likely to have abnormal reflexes than were newborns of women who were normal or fast metabolizers ($p < .01$).

Organochlorines. Two studies reported on the association between the organochlorine pesticide DDT/DDE and newborn behaviour (Fenster 2007, Sagiv 2008). In the Mexican-American agricultural cohort (CHAMOCOS), there was no relationship between prenatal DDT/DDE exposure and the BNBAS scores for babies under two months old (Fenster 2007).

A birth cohort from New Bedford, MA, an area known to have high PCB levels, was also studied. Cord serum PCB and DDE levels were measured and BNBAS assessments conducted at two weeks of age (Sagiv 2008). Measures of alertness and attention declined with higher cord levels of PCBs ($p < .01$). For DDE, irritability increased with exposure quartile after adjusting for cord blood lead level ($p < .03$). The DDE levels were presented in different units in each paper, but the New Bedford cohort was considered to have generally low DDE exposure.

Neurologic outcomes in children up to age three years

Ten studies investigated associations between pesticide exposures and neurodevelopment in children aged three months to three years. Six studies measured organophosphate exposure (Engel 2011, Eskenazi 2007, 2010, Handal 2008, Horton 2011, Rauh 2006) and four organochlorine exposure (i.e., DDT/DDE) (Eskenazi 2006, Ribas-Fitó 2003, Torres-Sanchez 2007, 2009). In this age group, the standard outcome assessment is the Bayley Developmental Scales, which include scores on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scales. Normal is considered >85 on each scale.

Organophosphates and pyrethrins. The Columbia–New York City cohort included 254 children examined using Bayley scales at ages 12, 24, and 36 months (Rauh 2006). Children highly exposed to chlorpyrifos (levels > 6.17 pg g^{-1} on 31-week maternal samples) scored 6.5 points lower on the PDI ($p < .01$) and 3.3 points lower on the Bayley MDI ($p < .05$) at age 36 months than did all those with lower exposure levels. Other behavioural outcomes measured at age three years are reported in the PDD and ADHD outcomes.

The California CHAMCOS cohort (Eskenazi 2007) reported Bayley scores at six and 24 months of age. Increasing third-trimester levels of six organophosphate metabolites (DAPs) in urine were negatively associated with Bayley MDI scores at age 24 months ($p < .01$). Each log10 unit increase in OP metabolites was associated with a 3.6-point reduction in MDI ($p < .01$). The association was stronger in children with slow metabolizer mothers (MDI –6.9, –12.8 to –0.9, $p < .05$) (Eskenazi 2010). However, the authors cautioned that the relationships between slow metabolizer genes and health effects are complex and concluded that "we cannot provide firm evidence that the PON1 genotype or phenotype modifies the relation of exposure and mental development" (p. 1780).

The Mt. Sinai–New York City cohort (Engel 2011) has recently reported new data. Children in the multiethnic cohort were assessed at ages 12 and 24 months using the Bayley Infant Development Scales. At age 12 months, there were declines in the Bayley MDI scores of black and Hispanic babies with high-exposure mothers (MDI –3.29, 95% CI –5.88 to –0.70, $p < .05$); for white babies, higher exposures were associated with better MDI scores (MDI +4.77, 95% CI 0.69–8.86, $p < .05$). Black or Hispanic mothers who were slow metabolizers of organophosphates showed the most significant declines in 12-month MDI scores (MDI –4.71, 95% CI –7.59 to 1.83, $p < .01$).

The Columbia–New York City cohort reported on 36-month Bayley scales for a cohort exposed to pyrethrins and piperonyl butoxide (PBO), a pyrethroid synergist used in most formulations of pyrethrins but not other insecticides (Horton 2011). Children with higher prenatal exposure to PBO scored 3.9 points lower on the Bayley MDI than did lower-exposed children ($p < .05$). Pyrethrins were described as difficult to measure and this was the only study to investigate this insecticide, which is widely used indoors.

A lower-quality study from Ecuador (Handal 2008, assessment score 8.5 out of 20) investigated women who worked in floriculture and were thought to have high pesticide exposure; their children were tested at age 3–23 months for neurodevelopment using the Ages and Stages Questionnaire. Children with prenatally exposed mothers (gauged by work history) compared with mothers who did not work in the flower industry had lower fine motor skill scores (–13%, 95% CI = –22% to –5%, $p < .05$) and a higher risk of poor visual acuity (OR = 4.7, 95% CI = 1.1–20, $p < .05$).

Organochlorines. The CHAMACOS report on infants at age 6, 12, and 24 months (Eskenazi 2006) found significant reductions in the Bayley MDI at ages 12 and 24 months with increasing prenatal DDT exposure ($p < .01$). An important clinical point is that despite high DDT exposure levels in the cohort, breastfeeding was positively associated with Bayley developmental scores.

Two studies report on a cohort of 244 children with normal pregnancies and deliveries in Mexico. The study was conducted in an area with no known occupational exposure to DDT, but it was a malaria-prone area where DDT had been used. Torres-Sanchez (2007) measured maternal DDE levels pre-pregnancy and in each trimester. The children were assessed using the Bayley Developmental Scales four times over the first year of life, i.e., at 1, 3, 6, and 12 months of age. The first-trimester DDE levels were negatively associated with performance on the Bayley Psychomotor Development Index (PDI) throughout the first year of life, each 10-fold increase in DDE levels being associated with a two-point reduction on the PDI ($p < .01$). Lead levels were measured and did not confound the association between DDE and neurodevelopmental deficits. Breastfeeding improved the Bayley MDI scores by 1.14 (CI = .08–2.2), and an enriched home environment ($p < .05$) and higher birth weight ($p < .05$) were associated with significant increases in both PDI and MDI independent of DDE levels.

The next report on this cohort (Torres-Sanchez 2009) examined development in the children between 12 and 30 months. There was no longer any association between DDE levels and Bayley scores in this age group, but early home stimulation (measured using the HOME Inventory) was a significant factor in improving the scores of 24- and 30-month-olds ($p < .001$).

A Spanish dual-cohort study enrolled children from a small town that had background contamination with organochlorines and PCBs from previous industrial production; a second cohort came from an area free of known industrial sources (Ribas-Fitó 2003). The children were assessed at age 13 months using Bayley Developmental Scales. Significant score reductions in the mental and physical scales were associated with increasing cord serum DDE levels, where each doubling of DDE caused a decline of 3.5 points on the MDI and 4.01 points on the PDI (both $p < .05$). When the effects of breastfeeding were analyzed, the worst Bayley outcomes were for highly exposed babies breastfed for short periods, and the best for low-exposure babies breastfed for long periods (>16 weeks) ($p < .05$). This suggests that breastfeeding is protective only when a longer duration can neutralize some of the impacts of toxin transfer in the breast milk.

Neurologic effects in children over age three years

This group of studies includes cross-sectional studies from five countries on three continents. These are less homogeneous in the outcome measures, exposure assessment methodology, and subject age (i.e., three years to adolescence). Two studies examined child workers (Abdel Rasoul 2008, Eckerman 2007), five studies investigated organophosphates and neurologic outcomes (Abdel Rasoul 2008, Eckerman 2007, Harari 2010, Lizardi 2008, Lu 2009), two investigated organochlorines (Puertas 2010, Ribas-Fitó 2006), and in two the pesticide exposures were not defined but thought to be mainly to organophosphates (Grandjean 2006, Handal 2007).

Studies that reported on IQ, PDD, autism, or ADHD are grouped by similar outcomes elsewhere.

Organophosphates. Hispanic children living in an agricultural area of Arizona "continuously treated with OP pesticides" were studied at age seven years (Sanchez-Lizardi 2008). Exposed children, who were identified by elevated urinary OP metabolites in a previous health survey, took longer (on average almost 80 seconds longer) to complete the Trails B test than did unexposed children ($p < .01$). There were also positive associations between increased OP metabolites and several subtests of the Wisconsin Card Sorting Test, including increased number of errors ($p < .03$), increased number of perseverative responses and errors (both $p < .01$), and reduced conceptual-level responses ($p < .01$). Urinary pesticide testing was repeated on the day of cognitive testing and showed no correlation with any of the cognitive assessments, including the Trails B.

Occupational (child worker) studies. Two occupational studies of child workers found evidence that pesticide exposure was associated with neurobehavioural deficits. An Egyptian study (Abdel Rasoul 2008, assessment score 18 out of 20) examined adolescents working seasonally as pesticide sprayers in Egyptian cotton cultivation. Exposure assessment included work histories and acetylcholine (AChE) levels; personal protective equipment was not usually worn. Working children ($n = 30$) had deficits in all ten neurobehavioural measures compared with controls ($n = 30$) who had never worked as sprayers and were friends or relatives of the workers (all significant at $p < .04$). Compared with controls, children who applied pesticides had significantly more self-reported neurologic symptoms, such as difficulty concentrating (24% vs. 8%), depression (26% vs. 10%), and numbness (18% vs. 2%) (all $p < .05$). The children with three or more neurologic symptoms were more likely to have worked several years as sprayers than those with fewer than three symptoms (mean 6.2 vs. 4.3 years; $p < .05$). A deficit in Trails B completion was also found to correlate with more years worked ($p < .001$) and lower AChE levels ($p < .05$)

In a Brazilian child worker study (Eckerman 2007, assessment score 5 out of 20), deficits in exposed rural children (defined by work histories) were found in finger tapping and reaction time ($p < .01$), with the strongest effects in 10–11-year-old children. Methodological problems with this study included small sample size, poor exposure assessment, poor confounder assessment, and lack of detail about specific pesticide exposures.

Paraoccupational studies. A group of studies examined Ecuadorian children whose parents worked in floriculture (Grandjean 2006, Handal 2007, 2008, Harari 2010). The results of these studies are summarized in Table 4.1. Some of these studies were lower in quality, with some results having very wide confidence intervals. The exposure effects could have been related to paraoccupational exposure, dietary exposure, or, as suggested by one analysis, by playing in irrigation water. The studies are summarized in Table 4.1; Handal (2008) is also discussed in Section 2, "Neurologic outcomes in children up to age three years."

Table 4.1. Four cross-sectional studies of Ecuadorian children with parents employed in floriculture.

Grandjean (2006), 12/20	**Handal (2007), 8.5/20**	**Handal (2008), 8.5/20**	**Harari (2010), 14.5/20**
n = 79, grade 1–2 children	*n* = 142, children aged 24–61 mo.	*n* =121, infants aged 3–23 mo.	*n* = 87, children's median age 6.5 years
• prenatally exposed scored lower on design-copying test ($p < .05$) • currently exposed had slower reaction times ($p < .01$)	• children with mothers prenatally or currently in flower industry had better developmental scores (trend NS) • children playing in irrigation water had decreased fine motor and problem-solving skills ($p < .05$) • wide confidence intervals on many outcome measures	• prenatally exposed children had a 13% decrease in fine motor scores ($p < .05$) *and* 9–18-mo.-olds had increased risk of visual problems (OR = 4.7, 95% CI = 1.1–20)	• prenatally exposed children (maternal) showed deficits in simple motor speed, design-copying, and visual memory recall (all $p < .05$) • for paternal only prenatal exposure children showed visual memory deficits ($p < .05$) • current exposure: no significant deficits

Note: Numbers in parentheses behind the first author's names indicate quality assessment score out of 20.

Another lower-quality study (assessment score 9 out of 20) examined neurologic outcomes in 35 children aged 4–10 years from conventional and organic Costa Rican coffee farms in two towns 2.4 km apart (Lu 2009). The children in both groups had comparable pesticide exposures on two-spot urine tests for metabolites; for example, 68% of the organic farmers' children and 75% of the conventional had detectable 2,4-D. This may have reflected similar dietary patterns in both groups, low pesticide use in the high-altitude conventional coffee farms, or the physical proximity of the two towns. The groups *did* differ significantly in socioeconomic status, quality

of housing, and years of schooling, all favouring the conventional farmers who owned plantations. When the two groups were compared on neurologic tests, the conventional farmers' children performed better on three subtests, i.e., figure drawing ($p < .05$), corrected response to targets ($p < .01$), and average false alarm latency ($p < .01$). This difference was attributed by the researchers to higher socioeconomic status and earlier school attendance in that group (Lu 2009). The relationship between level of exposure and neurologic performance was not reported for either group. Some urinary organophosphate levels in both groups were noted to be lower than in the NHANES data, which represents a national sample of US children (Lu 2009).

Residential exposure study. In another low-quality study of residential exposure, Ruckart (2004, assessment score 9 out of 20) found inconsistent results in a group of 132 children in two US states whose homes had been illegally sprayed with methylparathion in the past. Environmental wipe samples from the households and urinary metabolite levels were done to assess exposure. However, the time since last spraying and frequency of spraying could not be determined, the recruitment rate was low, and children were exposed and tested at variable ages. None of the neurobehavioural scores showed statistically significant differences between the exposed and unexposed groups.

Organochlorines. A birth cohort in Granada, Spain, was randomly sampled when the children were aged four years to acquire 104 mother–child pairs with complete data on mirex levels in the placentas, and a full panel of other measured social and educational factors (Puertas 2010). Mirex is an organochlorine pesticide long banned but very persistent in the environment, including in the Great Lakes, and highly bioaccumulative in the aquatic food chain. It is considered a human endocrine disruptor. The children were assessed by psychologists blinded to their exposure status using the McCarthy Scales of Children's Abilities (MSCA). Exposed children had lower scores on the MSCA working memory scale (–5.1; 95% CI = –.83 to –9.4, $p < .02$) and quantitative scale (–7.33; 95% CI = –.30 to –14.36, $p < .04$). Both these scales are considered important for mathematical ability and school success (Puertas 2010). The motor development scores were not affected by mirex exposure.

More recently, a report on the same cohort at age four years found inverse relationships between cord DDE levels and the MSCA verbal and memory scales (Ribas-Fitó 2006). Cord DDE levels above 0.20 ng mL^{-1} were associated with declines of 7.86 points ($p < .05$) on the verbal scale and 10.86 points on the memory scale ($p < .01$) in an analysis including both genders. The declines were much greater for girls and not statistically significant for boys. Another report on this cohort examined the relationship between cord serum hexachlorobenzene (HCB) levels and social behaviour in four-year-olds (Ribas-Fitó 2007). When adjusted for PCB, DDE, and DDT, children in the highest 33% of HCB exposure (>1.49 ng mL^{-1} in cord serum) still had a higher probability of scoring <80 on the McCarthy Scales of cognitive function (MSCA) Social Competence Scale (RR = 5.63, 95% CI = 2.13–14.88). The Social Competence Scale was scored by the children's teachers only. The HCB levels were not associated with the MSCA.

Pervasive developmental disorder (PDD) and autism

There are two studies of pervasive developmental disorder (PDD) and one of autism. Eskenazi (2010) used the Child Behaviour Checklist, completed by mothers, to obtain PDD scores for two-year-olds from the CHAMOCOS cohort. PDD scores were significantly higher (OR = 2.3, 95% CI = .99–5.16, $p < .05$) for each 10-fold increase in prenatal organophosphate metabolite levels.

The same assessment tool was used in studying the Mt. Sinai–New York City cohort exposed to chlorpyrifos (Rauh 2006). In this study of three-year-olds, high prenatal exposure to chlorpyrifos was associated with an elevated risk of PDD (OR = 5.39, 95% CI = 1.21–24.11). It is interesting that the above cohort studies, Eskenazi (2010) and Rauh (2006), examined the association with pervasive developmental disorder and found strong positive associations with exposure. In another cohort study (Engel 2011), children with this diagnosis were excluded from analysis at age two.

A case–control study of autism from the agricultural Central Valley of California investigated the real-world problem of pesticide drift by examining rates of autism associated with spraying of pesticides within 500 m of the maternal residence during different critical periods of pregnancy (Roberts 2007, assessment score 12.5 out of 20). The analysis compared 465 children with diagnosed autism with 6975 controls. Children of preterm, low birth weight, and multiple births were excluded. Those in the highest 25% of exposure (by pounds of pesticides applied) had ORs of 4.2 (95% CI = 1.7–10.9) for autism if the application was during CNS development (7–49 days post fertilization) and 7.6 (95% CI = 3.1–18.6) if the application occurred 28–81 days post fertilization. Ten classes of pesticides were tested for association with autism; the agricultural-use organochlorine pesticides dicofol and endosulfan (accounting for >98% by poundage of pesticide applications) appeared to present the highest risk of association with autism. The data supporting this statement are not shown in the paper. An excellent aspect of this paper was its ability to attribute specific pesticide exposures in the critical periods of the first trimester.

Attention deficit disorders

Five studies assess the association between pesticide exposure and attention deficit hyperactivity disorders (ADHD). Three studies are cohort reports (Marks 2010, Rauh 2006, Sagiv 2010) and two are cross-sectional studies using NHANES data from the USA (Bouchard 2010, Xu 2011).

Organophosphates. The Columbia–New York City cohort study reported on the association between prenatal chlorpyrifos exposure and attention deficit in three-year-olds (Rauh 2006). Child behaviour was assessed by maternal completion of the Child Behaviour Checklist, which assesses behaviours in the previous two months. Compared with low-exposure children, high-exposure children were significantly more likely to have attention problems (10.6% vs. 1.1%; $p < .01$) and ADHD problems (10.6 vs. 2.2%; $p < .02$).

The follow-up on the CHAMACOS cohort at ages 3.5 and 5 years (Marks 2010) focused on specific assessments for attention problems and clinical ADHD. Outcome measures included the Child Behaviour Checklist, but also researcher-administered tests for ADHD at 3.5 and 5 years and psychometric assessments at age five using the Hillside Behaviour Rating Scale. In 3.5-year-olds, prenatal organophosphate metabolite levels were positively associated with attention problems and ADHD, but the results reached statistical significance only for boys ($p < .05$). For the five-year-old boys, there were significant positive associations between prenatal metabolite levels and two mother-reported ADD measures, i.e., attention scale ($p < .05$) and ADHD scale ($p < .01$).

A highly generalizable study using NHANES data from the general population compared rates of ADD in children aged 8–15 years with organophosphate metabolite levels (indicating current exposure) above or below the study median (Bouchard 2010). ADHD was diagnosed using a standardized diagnostic interview (DISC-IV) or based on a report of having taken ADHD medication in the last year; 13% of 1139 children had an ADD diagnosis. For each 10-fold increase in urinary dimethyl alkylphosphate DMAP organophosphate metabolites, children had a 2.13 times higher risk of the hyperactive/impulsive subtype of ADHD (OR = 2.13, 95% CI = 1.08–3.27). The associations between exposure and the inattentive and combined subtypes of attention deficit were in the same direction but not statistically significant after adjusting for gender, race, and ethnicity. The metabolite that best predicted ADHD (all subtypes) for boys and girls was dimethyl thiophosphate, a DMAP group metabolite produced by organophosphate pesticides such as malathion. Children whose levels were above the median for the national data had a significantly elevated risk of ADHD (OR = 1.93, 95% CI = 1.23–3.02).

Organochlorines. A second study using NHANES data (Xu 2011) examined the association between urinary trichlorophenol (TCP), an organochlorine compound, and ADHD in 2539 children aged 6–15 years. Trichlorophenol exposure occurs through multiple pathways, including chlorinated drinking water by-products, ingestion of food contaminated by the parent pesticides, exposure to pesticides in wood preservatives, and exposure to other fungicides. TCP was frequently found, 2,4,5-TCP in 29% and 2,4,6-TCP in 65% of children. ADHD was measured by parental report of physician diagnosis or taking medication for the condition. Only 2,4,6-TCP was associated with ADHD, and a dose–response relationship was found ($p < .006$). There was a non-significant trend for children with detectable levels below the national median for 2,4,6-TCP (< 3.58 ug g^{-1}) to have more ADHD diagnoses than did children with non-detectable levels (RR = 1.54). Children with 2,4,6-TCP levels above the median were significantly more likely to have an ADHD diagnosis (OR = 1.77, 95% CI = 1.18–2.66, p for trend <.006). The results were adjusted for lead exposure and environmental tobacco smoke, measured by whole blood lead and serum cotinine concentrations. This study is important for documenting the high rates of exposure to these chemicals and potential associated health effects; however, because of the multiple routes of exposure to this chemical group, the exposure route that is clinically significant for these effects is not known, and could be drinking water and not pesticides.

The second study of organochlorine exposure and ADHD was from a Spanish cohort of four-year-olds prenatally exposed to the organochlorine hexachlorobenzene (Ribas-Fitó 2007). The high-exposure tertile (cord blood levels >1.4 ng mL^{-1}) had a higher probability of having ADHD as assessed by the ADHD DSM-IV checklist administered by teachers (RR = 3.43, 95% CI = 1.24–9.51). The results were adjusted for the effects of other organochlorines.

Child IQ

Three studies investigated the effects of pesticide exposure on IQ. Two looked at mixed organophosphate exposures (Bouchard 2011, Engel 2011) and one focused on chlorpyrifos, an organophosphate insecticide banned for residential applications in 2001 but still widely used in agriculture (Rauh 2011). All three studies used the Wechsler Intelligence Scale for Children (WISC-IV) to assess intelligence.

The most recent report on the CHAMACOS cohort examines prenatal organophosphate exposure and IQ in 329 children at age seven years (Bouchard 2011). The seven-year-olds in the highest 20% of maternal organophosphate exposure had average IQs seven points lower than did those in the lowest 20% ($p < .01$). Deficits in IQ subscales were in working memory ($p < .01$) and verbal comprehension ($p < .01$). Verbal comprehension is an important predictor of school readiness. Current pesticide metabolite levels measured in the children were not consistently associated with IQ scores, suggesting that the prenatal exposure period is most critical for effects of pesticides on cognitive function. The median metabolite levels were higher than those of the general US population, but the authors calculated that 25% of pregnant women from the general population would have levels above the median found in this study (Bouchard 2011).

Reports on both New York City cohorts also deal with IQ outcomes. In the Mt. Sinai–New York City cohort, 169 children aged 6–9 were examined using the WISC-IV and another test, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) (Engel 2011). Many of the scales showed non-significant trends toward lower IQ with higher organophosphate exposure during pregnancy. The small group of children whose mothers were the slowest organophosphate metabolizers (the lowest 9% of the cohort for enzyme activity) had declines in WISC perceptual reasoning scores as exposure levels increased ($p < .05$).

The Columbia–New York City cohort tested IQ in 265 seven-year-old children and assessed its relationship to prenatal chlorpyrifos exposure (Rauh 2011). For each standard deviation increase in exposure, full-scale IQ declined 1.4% ($p < .02$) and working memory, an important predictor of school failure (Puertas 2010), declined 2.8% ($p < .0001$). In a subset of children that had lead levels drawn, these levels were not correlated with chlorpyrifos levels or with IQ.

Limitations

The studies included in this systematic review have a number of limitations. Although metabolite biomarkers have refined the exposure assessments in many studies, the organophosphate and pyrethrin metabolites have very short half-lives in the order of 24–48 hours, and the use of one sample could result in underrepresentation of true exposure. The consistent associations with neurodevelopmental outcomes found in the studies argue that this is not an absolute limitation. The metabolites currently measured for organophosphates do not differentiate exposure to the parent compounds from direct ingestion of the metabolites, which are frequently present on fruits and vegetables. This may be an important distinction, since the metabolites do not have cholinergic activity (Engel 2011).

The concept of a critical prenatal period for pesticide exposure is a potential limitation. Some researchers believe that first-trimester exposures, as in traditional teratology, are most important. Others point to the period of rapid brain growth in the third trimester and early childhood as the most critical. This group of studies includes findings of positive associations with first- and third-trimester measures of prenatal exposure, with a trend toward the first trimester being more critical for organochlorines and third trimester for organophosphates. However, the cross-sectional studies also find that current exposures of older children are associated with neurodevelopmental outcomes such as ADHD.

The longitudinal cohort design has many strengths, but a weakness of the current cohorts is they were recruited from areas where higher than normal exposure is expected. This limits their generalizability to cohorts with lower exposures, and at the same time may obscure important health effects that could occur at very low levels of exposure, as may be the case with the endocrine disruptors (Hirabayashi 2011, Myers 2009, Vandenberg 2012).

Finally, in some cohorts, a decision was made to exclude children with autism or pervasive developmental delay from the cohorts upon diagnosis. This probably reflects our uncertainty about the etiology of these conditions, but may have reduced opportunities to find out whether pesticide exposures were associated with these conditions.

For a summary of the review findings pertaining to this chapter, including a complete list of the articles assessed in order of quality scores, see Summary Table 2: Neurodevelopmental/ Behavioural Health Outcomes and Pesticide Exposure in Children, on page S14 of the supplement to this report.

Summary

The studies in this systematic review show that prenatal pesticide exposure is associated with consistent measurable deficits in child neurodevelopment across a wide age range.

In neonates, this is manifest as abnormal reflexes and deficits in attentiveness to stimuli with organophosphate exposure, and as irritability with organochlorine exposure. In pesticide-exposed children aged 12–24 months, there are consistent deficits in the Mental Development Index of the Bayley Developmental Scales and sometimes in the Psychomotor Development Index with organophosphates. For exposure to organochlorines such as DDT, there are deficits in both scales but with stronger effects for the PDI. For these early childhood deficits, the relative risks (RRs) are usually in the 1.5–2.0 range. However, even a small increase in the incidence of such complex conditions may impact both the health care system and the learning and earning potential of affected individuals.

In older children, attention problems such as ADHD, reduced overall IQ, and other conditions including autism spectrum disorder and pervasive developmental disorder are more common in children who had higher levels of organophosphate or DDT/DDE exposure during pregnancy. Typically, statistically significant health effects are seen primarily in children with the highest 20–25% of exposure. On the other hand, there are rarely unexposed control groups, which may result in underestimation of the risk of ADHD. Some studies of ADHD and autism associated with prenatal exposure have higher RRs in the 6.0–7.0 range. Knapp (2011) studied 30-year-olds from a birth cohort in the UK and found that both males and females diagnosed with attention deficit at age 10 had “lower employment rates, worse jobs, lower earnings if employed, and lower expected earnings overall.” Children diagnosed with ADHD also have a much higher likelihood of engaging in criminal behaviour as adults, with high attendant social costs (Fletcher and Wolfe 2009). They also suffer earlier death than those without ADHD, perhaps (as found in a longitudinal cohort now in midlife) because they start smoking at a younger age and are more likely to continue binge drinking as they age (von Stumm 2011).

In multi-scale IQ tests, working memory and verbal comprehension appear to be most consistently affected. The effects are modest, with RRs usually less than 2.0. However, the reductions in total IQ found (2–7 points) will have substantial impacts on school performance and later earning potential when viewed from an economic population perspective. In 2001, Environment Canada scientists estimated the cost of a loss of 5 IQ points at CAD 30 billion per year for Canada, and the cost of neurodevelopmental deficits and hypothyroidism at CAN 2 billion per year for Ontario alone. The proportion of those conditions (and costs) considered attributable to environmental exposures was at least 10% and as high as 50% (Muir and Zegarac 2001).

Our understanding of the association between pesticide exposure and child neurodevelopment has benefited from several large longitudinal studies of birth cohorts from the USA, Spain, and Mexico. These cohorts were all recruited from groups thought to have higher than average exposure to pesticides. In the future, it will be important to study the associations with health effects in cohorts with typical exposures. The NHANES data from the USA gives us a cross-sectional snapshot of current childhood exposure, which is important, with the limitation that prenatal exposures may be more predictive of neurodevelopmental deficits. In Canada, comparable monitoring data on levels of environmental contaminants in children over the age of five years are now available for organophosphate and pyrethrin metabolites (Health Canada 2010, Tremblay and Gorber 2007).

The value of longitudinal studies is illustrated by the emergence of significant exposure-associated health effects in older children, no effects being seen in the cohort when its members were younger. Some authors believe this is related to the limitations of testing neonates and young children for complex neurodevelopmental functions. In contrast, in one cohort, DDE effects seen in the first few weeks of life were no longer apparent by the age of two years.

Although the cross-sectional and case–control studies generally received lower quality scores, they offer valuable insight and in some cases support findings of the longitudinal studies. For example, ADHD was associated with pesticide exposure in both types of study, and autism was associated with pesticide spraying within 500 m of rural homes in the first trimester in a case–control study. Other studies made autism or pervasive developmental delay exclusion criteria, removing children (and potentially important information) from some of the longitudinal cohorts.

Taken as a whole, the results of the systematic review of pesticide exposure and child neurodevelopment suggest that children are experiencing neurodevelopmental problems of various types, starting in the newborn period and throughout childhood, that are associated with prenatal and childhood pesticide exposures. This suggests that vigilance is required to minimize the pesticide exposures of pregnant women and children from all potential sources, including dietary, indoor and outdoor air, water, and farm exposures. The current use organophosphates are consistently implicated in neurodevelopmental deficits, as is use of the organochlorines, still heavily used as crop pesticides in agricultural settings.

Appendix 4A: Characteristics of cohort studies of pesticide exposure and child neurodevelopment

Name of Cohort	Location and characteristics	Original cohort size	Retention rate in most recent publication
CHAMACOS	Agricultural Salinas Valley, CA; Mexican-American farm workers' children	*n* = 526 newborns	62%, age 7
Mt Sinai–New York City	Inner-city	*n* = 404 newborns	42%, age 6–9
Columbia–New York City	Low-income black and Dominican	*n* = 725	74%, age 7
Mexican	Area with endemic malaria but no occupational DDT exposure	*n* = 333	81% at age 30 months
Spanish	Birth cohorts from a highly contaminated industrial area and a less contaminated area	*n* = 102 (organochlorine-contaminated area) *n* = 482 (no known industrial contaminants, 86% organochlorine pesticides in cord serum)	69%, age 4 98%, age 4
New Bedford, Mass.	Area highly contaminated with PCBs	*n* = 788	77%, age 8

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Chapter 5: Respiratory Health Outcomes and Pesticide Exposure in Children and Adults

The respiratory tract is routinely exposed to many environmental chemicals, such as tobacco smoke, ozone, dust, and allergens, the inhalation of which is the leading cause of respiratory diseases. Exposure to pesticides, whether domestic or occupational, has been increasingly investigated for its effect on respiratory health after first being identified as a potential risk factor in agricultural populations over three decades ago. Exposure to pesticides, including herbicides, insecticides, and fungicides, has been hypothesized as leading to asthma, chronic obstructive respiratory conditions, decreased lung function, and increased rate of respiratory tract infections in both children and adults.

This systematic review selected studies of pesticide exposure and several respiratory health outcomes, including asthma, chronic obstructive pulmonary diseases, lung function changes and respiratory symptoms (e.g., cough and wheeze), respiratory tract infections, and interstitial lung diseases. Reactive airways dysfunction syndrome, a subtype of work-related irritant-induced asthma, was not assessed as only case series were found relating to pesticide exposures (Henneberger 2003). A total of 40 articles investigating both children and adults were reviewed.

Overview of results

The studies reviewed included 18 reports from longitudinal, prospective cohort studies or case–control studies, while the remainder were cross-sectional studies (n = 18). The mean score of included articles on the modified Downs and Black quality assessment tool was 13 out of a possible 20 points, with a range of 8–18 points. Four articles were excluded at assessment: three did not report on relevant outcomes of interest and one duplicated information included in another paper. Therefore, 36 articles are included in this summary. Prospective birth cohorts and studies analyzing data from the Agriculture Health Survey were generally of higher quality (>15 points out of 20), while many other studies employing a cross-sectional design provided low- to medium-quality evidence. Common limitations in studies scoring below 15 points included small sample sizes, self-reported exposure and outcome measurement, potential for selection bias, and cross-sectional design.

Mixed pesticide exposures were most frequently studied, as most studies were in agricultural settings. Seven studies examined organophosphates plus another insecticide (usually carbamate or pyrethrin), and three did not characterize the exposure. Most of the studies found a positive association between pesticide exposure and respiratory outcomes. Some studies looked at acute pesticide exposure and some at more chronic effects, although there is likely to be overlap in these effects. In studies considering a gradient of exposure, more effects were consistently found at higher exposure levels.

Summary by respiratory health outcome

Asthma

The increasing incidence of asthma over the past three decades is coincident with increased pesticide exposure from occupational, environmental, and residential use (Hernandez 2011, Selgrade 2006). In particular, organophosphate pesticides were introduced in the 1970s and have been extensively used since then as a replacement for organochlorines (Proskocil 2008). A significant association between asthma and pesticide use in farmers was first found in Saskatchewan in the 1980s, and has since been studied widely (Senthilselvan 1992).

The review included 12 studies investigating pesticide exposure and asthma, both atopic and non-atopic. Of these studies, six investigated asthma in children and six addressed adult-onset asthma. Populations in Canada, the USA, Europe, Australia, and Lebanon were studied. All but two reviewed studies found positive associations between exposure to organophosphate, carbamate, and organochlorine insecticides in particular, and diagnosis of asthma and wheeze in both children and adults. The majority (n = 7) of studies in this section received average quality scores, i.e., 12–14 points out of 20. Three large cohort studies, two in adults and one in children, scored above 15 points, while one cross-sectional study by Jones (2003) was of significantly lower quality.

Adult asthma. A diagnosis of adult-onset asthma was shown to be associated with exposure to insecticides in three of the six studies described in this section. Moreover, a retrospective cohort study of Australian outdoor workers exposed to insecticides found increased mortality from asthma relative to the general population (SMR 3.45; 95% CI = 1.39–7.10) (Beard 2003). Of the studies that showed a positive association, pesticide exposure was related primarily to the development of atopic asthma, with the strongest correlation with exposure to organophosphate insecticides.

Two studies by Hoppin (2008, 2009), one of farm women and the other of male farmers, used cross-sectional data from the Agricultural Health Survey (AHS) and provide the strongest evidence as assessed by quality scores. The AHS is a large, prospective cohort study conducted in Iowa and North Carolina that enrolled over 89,000 male and female participants between 1993 and 1997; it was designed to explore potential causes of disease among farmers and their families and among commercial pesticide applicators. Data were collected using either a self-administered questionnaire or a telephone interview. Asthma, as determined by self-reported physician diagnosis after the age of 20, was present in 2.7% of female and 2.2% of male farmers. The strength of the AHS data lies in the study's large sample size and analysis of specific pesticide groups. However, as the study population includes only individuals who are occupationally exposed, the degree of exposure may not be generalizable to the broader population. For farm women, exposure assessment included frequency of use, lifetime days of pesticide application, years on a farm, and total years of pesticide use. For male farmers/applicators, exposure assessment was based on lifetime pesticide use of 50 specific pesticides: ever-use, frequency of use, number of years used and decade of first use, pesticide use practices, and use of personal protective equipment. This information was used to create two metrics of lifetime pesticide use: lifetime days of use and intensity-adjusted lifetime days of use. In addition to pesticide

application information, there were also two measures indicative of ever having experienced elevated pesticide exposure: pesticide poisoning and high-pesticide-exposure events.

The results of the AHS studies showed that 12 of the 48 pesticides studied were associated with an increase in allergic asthma in male farmers, while four were associated with an increase in non-allergic asthma (Hoppin 2009). Three insecticides had statistically significant odds ratios exceeding 2.0 for allergic asthma, i.e., the organophosphate insecticides coumaphos and parathion, and the organochlorine insecticide heptachlor. Two fumigants also had odds ratios in excess of 2.0, i.e., 80/20 mixed carbon tetrachloride/carbon disulfide and ethylene dibromide. Self-reported high pesticide exposure events were associated with both allergic and non-allergic asthma. Of the 12 pesticides associated with allergic asthma, 10 also showed significant exposure–response trends when evaluating high and low exposure categories based on the median number of intensity-adjusted lifetime days of use for each pesticide. The paper highlighted that, "Given the variety of pesticides associated with allergic asthma, the possibility cannot be ruled out that some common ingredient in the pesticidal products may explain these results." Hernandez (2011) suggested that the aggravation of pre-existing asthma might be occurring.

Considering only farm women (n = 25,814) in the AHS, 10 pesticides were found to be associated with allergic asthma and one with non-allergic asthma (Hoppin 2008). The ten pesticides included: two herbicides, i.e., 2,4-dichlorophenoxyacetic acid (2,4-D) and glyphosate; seven insecticides, i.e., a carbamate (carbaryl), organophosphates (coumaphos, parathion, malathion, and phorate), an organochlorine (dichlorodiphenyltrichloroethane – DDT), and a pyrethroid (permethrin); and one fungicide, i.e., metalaxyl. Of these, the organophosphate insecticides parathion and coumaphos again showed the strongest associations, as did the fungicide metalaxyl. The insecticide permethrin was the only exposure associated with non-atopic asthma in women.

Results from a Lebanese case–control study also found that asthmatic cases, as independently confirmed by a hospital pulmonologist reassessing the answers to a self-administered questionnaire, had higher odds of exposure to pesticides (OR = 2.32, 95% CI = 1.47–3.68) (Salameh 2006a). Exposure was also determined through a self-administered questionnaire that inquired as to domestic, occupational, and paraoccupational exposure as well as residential proximity to pesticide-treated fields, and included a pooled category for any exposure type; however, pesticide type was not specified. Importantly, this study showed a positive association between non-occupational (including domestic and environmental) exposure and the odds of being asthmatic. However, the results could not be attributed to a specific pesticide, resulting in a relatively lower quality score than that of the AHS studies.

Two cross-sectional studies showed null and inverse associations between pesticide exposure and asthma. A European study used urinary ethylenethiourea as a biomarker of the carbamate fungicide ethylenebisdithiocarbamate (EBDC) exposure (Boers 2008) to confirm increased exposure in 248 occupationally exposed farmers working in various industries, including grape, vegetable, potato, and flower bulb growing. In this study, diagnoses of asthma, wheeze, asthma attack, and chest tightness were reported more often by non-exposed controls, resulting in an inverse association. These EBDC fungicides do not have cholinergic activity, which may explain the negative association.

Similarly, a 2003 repeat cross-sectional study in Arkansas compared 135 pesticide aviators and 118 community-based controls and reached null conclusions, although spot monitoring of one aviation firm showed exposures that were undetectable or below the acceptable limit to pesticides including organophosphates and pyrethroids, which could also explain the null outcome suggestive of effective protection measures (Jones 2003). Both of these studies had quality assessment scores below 13 points, with the Jones (2003) study scoring only nine points. High loss to follow up, poor exposure and confounder measurements, and selection bias from incentive recruiting methods contributed to the lower score.

Asthma in children. Seven studies assessed the association between pesticide exposure and a diagnosis of asthma in children; all reported a positive association with the exception of a Canadian farm study that reported no association. However, the studies differed markedly in both study population and exposure index. Four studies measured post-natal exposures in different age groups, while one study investigated pre-natal exposure. Insecticides, herbicides, fungicides, and dichlorodiphenyldichloroethylene (DDE) were studied and all were found to be associated with asthma and wheeze. Pre- and antenatal exposures were most strongly associated with asthmatic outcomes and maternal, but not paternal, exposures were correlated with increased risk of asthma and wheeze in children.

Two studies of a prospective Spanish cohort by Sunyer (2005, 2006) were of relatively higher quality than others in this topic area, with quality scores of 18 out of 20 points. The remaining studies in this section scored between 12 and 14 points. Retrospective exposure assessment, lack of pesticide specificity, and questionnaire-based exposure measurements contributed to the lower scores.

Four population-based birth cohorts and one study using data from the Children's Health Study were consistent in reporting an association between exposure to pesticides in the first year of life and higher odds of asthma and wheeze (Duramad 2006, Salam 2004, Sunyer 2005, 2006, Tagiyeva 2010). Specifically, Sunyer found that in utero exposure to the organochlorine insecticide metabolite DDE was associated with wheeze at age four (Sunyer 2005) and asthma at age six (Sunyer 2006) in a Spanish cohort. Notably, in the Spanish birth cohort, breast feeding showed a protective association with both wheeze and diagnosed asthma, despite bottle-fed children showing decreased DDE blood levels relative to breast-fed children at age four (Sunyer 2005). Tagiyeva (2010) found that maternal exposure to both biocides (i.e., products that control unwanted organisms through chemical or biological means) and fungicides during pregnancy or 21 months postnatally was associated with childhood wheeze from birth to 81 months in a birth cohort study from the UK; however, only postnatal exposure was associated with asthma at 91 months. In contrast, from the Children's Health Study, Salam (2004) found that exposure to herbicides and pesticides occurring before, but not after, the first year of life was associated with an increased risk of asthma.

One cohort study used T-helper 1 (Th1) and T-helper 2 (Th2) cytokine measurements as biomarkers of allergic asthma and reported on the association between agricultural environments and asthma at age two (Duramad 2006). Maternal occupational exposure to agriculture pesticides, assumed to be predominantly organophosphate and pyrethroid insecticides, as well as exposure to

any agricultural fieldworkers living in the household, were significantly associated with both increased levels of Th2 cells and asthma and wheeze at two years of age ($p < 0.05$). Increased expression of Th2 cytokines has been previously shown to be associated with allergic asthma, contributing to its development through the recruitment of mast cells and eosinophils to the child's airways (Izuhara 2006, Umetsu 2002, Wills-Karp 2001).

A large ($n = 3291$ participants) questionnaire-based cross-sectional study reported that both occupational and non-occupational exposure to pesticides in Lebanese school children aged 5–16 years resulted in an increase of asthma and chronic cough, chronic phlegm, and wheeze (Salameh 2003). Residential pesticide exposure was most strongly associated with recurrent wheeze, while occupational exposure of a household member was most strongly associated with asthma (OR = 4.61, 95% CI = 2.06–10.29). Interestingly, both this study and the Duramad (2006) study described previously showed that adults exposed to pesticides at work "take home" exposures to their children, posing a greater risk of children developing asthma than either the use of pesticides within the home or exposure from residential proximity to spraying. The Lebanese study did not specify whether prenatal exposures were accounted for, while Duramad (2006) did take into account in utero exposure.

A second large cohort study ($n = 3405$ children) used retrospective data from the Ontario Farm Family Health Study (OFFHS) to determine the association between in utero exposure to agricultural pesticides and the development of asthma and other health outcomes, including allergy and chronic bronchitis (Weselak 2007). A total of 173 cases were identified through self-report of a doctor's diagnosis of asthma, of which 114 had been exposed prenatally. No significant associations were reported between parental use of any pesticide and the development of asthma. Retrospective and indirect exposure assessment, as well as the small number of cases exposed to each pesticide type, contributed to a relatively lower quality score and may have weakened any potential association with in utero exposure.

Chronic obstructive pulmonary diseases

Three studies found significant positive associations between pesticide exposure and prevalent chronic bronchitis, while one Canadian study had results approaching significance only for female subjects (Weselak 2007, also reported in the "Asthma" section). Of studies reporting a significant association, two were based on data from the Agricultural Health Study (AHS) and received scores of 14 out of 20 points, and one was a case–control study of Lebanese adults scoring slightly lower. While all three studies demonstrated an effect of occupational exposures, the case–control study showed that non-occupational exposures are also associated with the development of chronic bronchitis.

Hoppin (2007b) studied farmers (20,400 male pesticide applicators and 508 female applicators) and found that three percent ($n = 654$) reported a history of physician-diagnosed chronic bronchitis diagnosed after age 20. Prevalent chronic bronchitis was significantly associated with 11 of the 49 pesticides studied in the adjusted model, with odds ratios ranging from 1.20 (herbicide chlorimuron-ethyl; 95% CI = 1.03–1.52) to 1.50 (organochlorine insecticide heptachlor; 95% CI = 1.19–1.89). Of the 18 pesticides significant in the unadjusted model, 14 were insecticides (i.e., two carbamates, five organochlorines, five organophosphates, and two pyrethroids) and four were herbicides. None showed a clear dose–response trend, although

prevalence was increased for applicators with a history of high pesticide exposure events. The second AHS study investigated 21,500 non-smoking female spouses of AHS-enrolled subjects. Valcin (2007) found an association of prevalent chronic bronchitis with the "ever" use of five pesticides. The herbicide paraquat had the highest odds ratio (1.91; 95% CI = 1.02–3.55), followed by the herbicides cyanazine and methyl bromide, organochlorine insecticide DDT, and organophosphate insecticide dichlorvos.

Any exposure to pesticides was also found to be positively associated with chronic bronchitis in a case–control study of Lebanese adults (OR = 2.46, 95% CI = 1.53–3.94) (Salameh 2006b). Regional exposure (i.e., living in a region heavily treated with pesticides), local exposure (i.e., living near a field treated with pesticides), and non-occupational exposure (i.e., personal use) were all significantly associated with a diagnosis of chronic bronchitis. Occupational exposure resulted in the highest odds ratio (15.92; 95% CI = 3.50–72.41). The lower score of this study resulted from its non-specific exposure information.

Chronic bronchitis in children. A single study investigated exposure during pregnancy to pesticides and the development of chronic bronchitis and cough, as well as asthma, hay fever, and allergies, in children of Ontario farm families (Weselak 2007). No significant associations were reported between cough and bronchitis and prenatal exposure to agricultural pesticides. However, when stratified by sex, the risk of developing cough and bronchitis increased after exposure to insecticides, approaching significance for female offspring (OR = 2.29, 95% CI = 0.95–5.35). Similarly, the use of the herbicide dicamba (3,6-dichloro-2-methoxybenzoic acid) and the carbamate insecticide carbaryl increased the risk of developing cough and bronchitis when both sexes were analyzed together. Unfortunately, all data were collected retrospectively through the OFFHS, meaning that participants were asked to recall exposures that happened in the past, and that information about the age of diagnosis of the children was not collected. These factors contributed to a relatively low quality score of 11 points out of 20.

Lung function and respiratory symptoms

The review included 15 studies that investigated lung function, as measured by ventilatory function tests and self-reported respiratory symptoms. All included studies focussed on occupationally exposed adults in various settings, with the exception of one study of individuals residing in a pesticide spray zone. All studies were cross-sectional with the exception of the AHS study. All populations studied were outside of North America with the exception of the AHS study and a study in Colorado, and included populations in Costa Rica, Spain, Croatia, Palestine, India, Sri Lanka, Philippines, Brazil, Ethiopia, and Lebanon.

Common measurements employed in the following studies included symptom questionnaires (to determine the presence or absence of chronic cough or phlegm, wheeze, diagnosis of asthma, chronic bronchitis, and dyspnea) and lung function measurements. Lung function measurements included: flow measurements, i.e., maximum expiratory flow volume (MEFV), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and the forced expiratory flow (FEF) at 75%, 50%, and the last 25% of the FVC (i.e., FEF25, FEF50, and FEF75); lung volume measurements, i.e., total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV); and diffusing capacity, i.e., diffusing capacity of the lung to absorb carbon monoxide (DLCO).

Twelve out of thirteen studies found significant positive associations between exposure to pesticides, primarily insecticides and herbicides, and the development of abnormal respiratory symptoms, as well as decreased performance on lung function tests. However, results were inconsistent across studies with respect to which lung tests were abnormal. In addition, many studies did not specify the pesticide(s) studied, making conclusions about the relative effect of different chemical groups difficult, and employed self-reported questionnaire-based exposure measurements. This was reflected in the quality scores, with the majority of studies ($n = 9$) scoring 12–14.5 points out of 20. Two studies were of poor quality, scoring below 10 points. The scores of studies in this section also reflected the difficulty of separating the effects of pesticides from those of other occupational exposures, including animals, grains, other chemical exposures, and organic allergens (e.g., dust).

Farm worker studies. Two Costa Rican studies investigated agricultural workers and respiratory outcomes. A high-quality cross-sectional study, scoring 17 out of 20 points, reported that for each unit increase in the total cumulative paraquat index (based on detailed work history), the odds of chronic cough increased by 1.8 (95% CI = 1.0–3.1), while the odds of shortness of breath with wheeze increased by 2.3 (95% CI = 1.2–5.1) (Schenker 2004). However, chronic bronchitis, persistent wheeze and asthma were not associated with increased paraquat exposure and no difference in pulmonary function measures, interstitial thickening, or restrictive lung disease was seen between exposure groups. Fieten (2009) reported a significant association between exposure to chlorpyrifos and the development of wheeze and shortness of breath among exposed women. When the results were stratified by smoking status, non-smoking women in this study had significantly increased odds of wheeze following exposure to chlorpyrifos (and organophosphate insecticide), terbufos (an organophosphate insecticide), and the herbicide paraquat (N,N′-dimethyl-4,4′-bipyridinium dichloride), with exposure to chlorpyrifos showing the strongest association (OR = 6.7, 95% CI = 1.6–28.0).

A cross-sectional study of 1379 Brazilian agricultural workers by Faria (2005) found that specific pesticide application activities were positively associated with symptoms of asthma and chronic respiratory disease, particularly among women, with associated odds ratios ranging from 1.82 (for washing clothes up to two days per month) to 2.54 (for cleaning equipment more than two days per month). Pesticide exposure included insecticides, fungicides, and herbicides, although no pesticide class was associated with symptoms. Peiris-John (2005) compared Sri Lankan farmers with environmentally exposed freshwater fishermen and with marine fishermen living away from organophosphate insecticide-sprayed areas. Farmers were found to have significantly lower FVC/FEV1 ratios than did both fishermen groups, with the FVC/FEV1 ratio decreasing during the spraying season compared with before the start of spraying. This study, which scored 16 out of 20 points, also reported that occupational, but not environmental, exposure led to decreased lung function results. A final cross-sectional study by Ejigu (2005) investigated health effects in Ethiopian farmers, and found that cough, phlegm, and wheeze were significantly more prevalent in farm workers than in controls ($p < 0.05$); however, the study received a very poor quality score and did not name specific pesticides.

A cross-sectional study in the Philippines of 102 cut flower farmers (Del Prado-Lu 2007) exposed to eight types of organophosphates reported symptoms of cough in 40% and abnormal peak flows in 88% of those examined. Red blood cell cholinesterase levels were depressed, but

no baseline measurements were made. A cross-sectional study in Colorado of 761 farm residents and spouses (Beseler 2009) with a history of pesticide poisoning examined respiratory symptoms, in addition to assessing lung function by spirometry in 196 individuals. In non-smokers, pesticide poisoning remained a significant predictor of cough with an OR of 2.44 (95% CI = 1.23–4.86).

Pesticide sprayer studies. A study of 89 pesticide sprayers and 25 farm worker controls in Granada, Spain, assessed respiratory function abnormalities following long-term exposure to pesticides; it used lung function tests in addition to investigating the contribution of paraoxonase (PON1) polymorphism on these outcomes (Hernandez 2008). The classes of pesticides most commonly used in the crop season studied were: insecticides (i.e., neonicotinoids, organophosphates, carbamates, and organochlorines), fungicides (e.g., dithiocarbamates), and herbicides (i.e., bipyridyls). Exposed subjects were more likely to experience irritative symptoms and tearing, while all other respiratory outcomes did not differ between groups. Paradoxically, sprayer status was associated with higher FEV1 and FEF 25–75% and organophosphate insecticide exposure was associated with higher FVC values, considered to be chance findings or a "healthy worker effect." Despite these results, exposure to endosulfan (an organochlorine insecticide) was associated with a significantly higher risk of respiratory symptoms (OR = 3.68, 95% CI = 1.16–11.68). In terms of restrictive lung changes, exposure to neonicotinoid insecticides was predictive of lower total lung capacity ($p = 0.013$), residual volume ($p = 0.001$), and functional residual capacity ($p = 0.015$). Exposure to bipyridyls was associated with a fall in diffusing capacity, suggesting subtle changes in the alveolar capillary membrane ($p = 0.041$).

This study (Hernandez 2008) was the only one to analyze isoforms of PON1, a gene coding for an enzyme that hydrolyzes organophosphate pesticides. It is hypothesized that the R isoform of PON1, which is related to polymorphism in PON1, is more highly active than other isoforms, and therefore will hydrolyze OP pesticides at a higher rate, resulting in a reduced effect of exposure. In the current study, subjects who carried the R isoform were found to have a three times lower risk of reporting symptoms related to occupational pesticide exposure, but did not differ in performance on lung function measures.

Two studies reported on the respiratory outcomes of male pesticide sprayers exposed to organophosphate insecticides. Mekonnen and Agonafir (2004) report that in 109 Ethiopian farm sprayers, exposure to the organophosphate insecticides chlorpyrifos, diazinon, and malathion resulted in reduced FVC and FEV1 in the youngest age group studied (15–24-year-olds), but did not show a significant positive association in the older age groups. This may indicate that the younger age group is more vulnerable to spraying. The prevalence of cough, breathlessness, wheeze, and phlegm did not differ significantly between exposed workers and the 69 farm area controls. Similarly, an Indian study of 376 agricultural pesticide sprayers exposed to organophosphate and carbamate insecticides found that pesticide sprayers had lower mean FVC, FEV1, FEV1/FVC ratio, and PEFR relative to 348 controls ($p < 0.001$) (Chakraborty 2009). In addition, significantly more farmers were diagnosed with both chronic obstructive pulmonary disease and showed an increased prevalence of respiratory symptoms, including wheeze, cough, loss of breath, and chronic bronchitis. However, the prevalence of asthma was not found to be increased in agricultural workers relative to controls.

A single study that investigated the lung function and respiratory symptoms of 250 male Palestinian farmers aged 22–77 years reported null associations (Abu Sham'a 2010). This study had poor exposure attainment, using only two questions: one regarding how many hours subjects sprayed pesticides per year and the other inquiring as to current pesticide use. The use of personal protective equipment was also assessed. The authors suggest the negative results may be attributable to an increased use of personal protective equipment in this population. However, the prevalence of chronic cough, wheeze, and breathlessness was found to be high.

Pesticide plant worker studies. Two studies with small sample sizes investigated the respiratory effects of occupational exposure to pesticides among pesticide plant workers and found associations with decreased lung function. In a Croatian study, female pesticide plant workers were at increased risk of chronic cough, dyspnea, and nasal catarrh (Zuskin 2008). Male pesticide plant workers were more likely than unexposed controls to experience dyspnea and nasal catarrh. The authors did not specify the type of pesticide being processed by the plant. Both male and female pesticide workers showed significantly lower FVC, FEF50, and FEF25 relative to predicted values (control subjects were not tested), while the difference between observed and predicted values for FEV1 measurements was not significant. Similarly, workers exposed to pyrethroids and carbamate pesticides in Lebanon had increased odds of abnormal respiratory function including FEV, FEV1/FVC ratio, and relative FEF 25–75%, with the largest effect seen for relative FEF 25–75% after adjusting for smoking status (OR = 16.5, 95% CI = 2.5–140.3) (Salameh 2005).

Agricultural heath study. Hoppin (2006) analyzed data from the Agricultural Health Study to compare pesticide exposure and respiratory outcomes between farmers and commercial applicators. Farmers' reports of wheeze in the past year were positively associated with current use of: the herbicides alachlor, atrazine, EPTC, petroleum oil, and trifluralin; the organophosphate insecticide malathion; and permethrin used on animals. Commercial applicators' reports of wheeze in the last year were positively associated with current use of the herbicide chlorimuron-ethyl and the organophosphate insecticides dichlorvos and phorate. For both groups, significant dose–response trends were observed for both chlorimuron-ethyl and chlorpyrifos.

Non-occupational. Petrie (2003) completed a before and after respiratory symptom survey of 292 residents of a New Zealand neighbourhood sprayed with aerial *Bacillus thuringiensis* (Foray 48B), an insecticide used to kill the larval stage of butterflies and moths. Resident health complaints increased after spraying; however, there was no significant increase in reports of cough or wheeze. The rate of resident reports of irritated throat did, however, double after spraying. This study received the second lowest score in this section, scoring only nine out of 20 points, primarily due to using small area ecological exposure measurement as opposed to individual assessment.

Overview of restrictive lung function changes

Peiris-John (2005), as described above in the section "Lung function and respiratory symptoms," found 25 Sri Lankan organophosphate-exposed farmers to have significantly lower FVC, suggestive of restrictive lung function changes. The study pointed out that in this group, limited

expansion of the thorax and/or reduced lung compliance were possibly due to thickening of the alveolar–capillary membrane.

As mentioned above by Schenker (2004), it is known that paraquat exposure in high doses causes oxidative damage to the lung, pulmonary fibrosis, and respiratory failure, raising concern that chronic, low-level exposures to paraquat may result in interstitial fibrosis. The study of 219 Cost Rican paraquat sprayers, however, while finding increases in cough and in shortness of breath with wheeze, found no difference in pulmonary function measures indicative of interstitial thickening or restrictive lung disease between exposure groups.

An additional study (see above), Hernandez (2008), found that in 89 sprayers with exposure to bipyridilium herbicides there was a fall in the diffusing capacity of the lungs, and that exposure to neonicotinoid insecticides was related to lower pulmonary volumes (i.e., total lung capacity, residual volume, and functional residual capacity), suggestive of restrictive lung disease.

Respiratory tract infections

Three studies investigated the relationship between DDE and lower respiratory tract infections (LRTIs) in infants. All three were cohort studies scoring 15 points or above and assessed the association of both pre- and postnatal exposures with LRTIs. Two studies found an effect of in utero exposure, although one was positive only for upper respiratory tract infections but not for LRTIs, while the third paradoxically showed a protective effect of higher levels of postnatal DDE exposure.

A high-quality cohort study based in Catalonia, Spain, studied the association between maternal organochlorines and LRTIs in 521 infants (Sunyer 2010). Only DDE was associated with LRTIs in infants during both the first six months of life (OR = 1.68, 95% CI = 1.06–2.66) and at age 14 months (OR = 1.52, 95% CI = 1.05–2.21). Results did not differ between infants who were breastfed and those who were not, suggesting that the effect occurred prenatally, a result that is consistent with other studies investigating pre- and postnatal pesticide exposure and respiratory outcomes. The authors suggest that this effect may be caused by immunologic suppression by DDE, which would suggest longer-lasting effects on both the immune and respiratory systems following exposure. This claim is corroborated by previous studies in both animals and humans linking increased DDE exposure to suppressed immune function (Daniel 2002, Glynn 2008, Vine 2001). Longer-lasting effects from lower respiratory tract infections earlier in life may include the development of asthma (Sigurs 2000).

A study in Nunavik, Canada, of Inuit infants and their mothers looked at both lower and upper RTIs at six and twelve months of age (Dallaire 2004). Adjusting for other confounders, they found that prenatal exposure to DDE in the 2nd quartile was associated with a 1.56 times higher risk of developing URTIs at age six months (95% CI = 1.05–2.33) and a 1.34 times higher risk at 12 months (95% CI = 1.00–1.78). No effect was seen in comparing the 3rd and 4th quartiles of exposure with the referent group. No significant association was shown between postnatal exposures and either type of respiratory infection. A third study by Glynn (2008) did not find a positive association in studying 190 pregnant women in Sweden and their infants at three months of age. Paradoxically, they found that higher levels of exposure to DDE were associated with a decreased risk of respiratory infections in infants (OR = 0.18, 95% CI = 0.06–0.60). It is

important to note that the effects of other organochlorines such as PCB congeners could not be differentiated from those of DDE in either of these studies.

Interstitial lung disease

Sarcoidosis. The association between environmental occupational exposures and sarcoidosis was investigated in a multi-centre case–control study in the United States with 706 cases and matched controls (Newman 2004). The diagnosis of sarcoidosis was found to be positively associated with exposure to insecticides at work, either agricultural or industrial (OR = 1.61, 95% CI = 1.13–2.28). Unfortunately, information about specific categories of insecticides was not collected and the exposure index was designed to capture environmental exposure broadly, resulting in the potential for misclassification of exposure resulting in a medium quality score.

Hypersensitivity pneumonitis. The most common type of hypersensitivity pneumonitis is farmer's lung, estimated by the Canadian Centre for Occupational Health and Safety to affect as many as 2–10% of Canadian farm workers (CCOHS, 2008). Hoppin (2006) studied farmer's lung among farmers in the Agricultural Health Study. "Ever" use of organochlorine or carbamate insecticides (e.g., DDT, lindane, and aldicarb) was associated with a diagnosis of farmer's lung (OR = 1.34, 95% CI = 1.04–1.74 and OR = 1.32, 95% CI = 1.03–1.68, respectively). High pesticide exposure events were also associated with increased odds of farmer's lung. High pesticide exposure events were defined as a positive answer to the question, "Have you ever had an incident or experience while using any type of pesticide which caused you unusually high personal exposure?" It was suggested that exposure to these pesticides may stimulate immune function and enhance the hypersensitivity effect of agents such as thermoactinomyces and other bacteria in mouldy hay that cause farmer's lung. The study received a quality score of 14.5 out of 20 points and was the only study to look specifically at farmer's lung.

Limitations

Agricultural workers are exposed to multiple respiratory toxicants during their daily activities, and many of these exposures are correlated to some degree. The cross-sectional nature of many of the reviewed studies may underestimate the impact of some exposures because more severely affected individuals may have changed their exposures as a result of disease diagnosis. Additionally, individuals may leave farming or an occupation with pesticide exposure as a result of severity or exacerbation of disease, which would result in the "healthy worker effect," i.e., enrolling working individuals in a study may bias the study toward null conclusions, as working individuals are healthier on average than their non-working counterparts. It may also be that asthma is triggered or exacerbated, but not caused, by pesticide exposure, and it would be difficult to disentangle the two effects (Hernandez 2011). Organic solvents present in many pesticide formulations may synergistically or independently contribute to outcomes. In addition, the generalizability of these studies to average environmental exposures is uncertain, as most studies were undertaken in the agricultural context. However, not only are pesticides frequently used indoors, but also, as shown by Duramad (2006), indirect exposure through parental occupation or residential proximity are significant factors in the development of respiratory symptoms.

For a summary of the review findings pertaining to this chapter, including a complete list of the articles assessed in order of quality scores, see Summary Table 3: Respiratory Health Outcomes and Pesticide Exposure in Children and Adults, on page S18 of the supplement to this report.

Summary

Overall, there is evidence that exposure to pesticides, and to organophosphate or carbamate insecticides in particular, is associated with the development of respiratory symptoms and a spectrum of obstructive and restrictive lung diseases. Studies of asthma in children reported an association between maternal exposure to organophosphate and organochlorine insecticides, as indicated by the presence of DDE, while respiratory tract infections in infants were linked to maternal exposure to organochlorine insecticide metabolites in two of three reviewed studies.

Twelve studies investigated the effects of asthma, of which nine were of medium to high quality, found a positive association between organophosphate and carbamate insecticides and atopic asthma, reporting a statistically significant odds ratio above 2.0. This association was found for occupational, domestic, and environmental exposures, particularly after exposure to the organophosphate insecticides parathion and coumaphos. While the possibility remains that these results could reflect the aggravation of pre-existing asthma, asthma-related respiratory problems are nonetheless associated with pesticide exposure. In children, the evidence is consistent, all included studies finding a positive association between asthma and related respiratory problems and pesticide exposure, specifically maternal exposure to organochlorine insecticide (indicated by the presence of DDE), organophosphate insecticide, biocide, and fungicide. Specifically, in utero and postnatal exposures in the first year of life were associated with asthma and wheeze up to six years of age. Breastfeeding was shown to have a protective effect, despite increased DDE levels in the infants.

The evidence linking chronic bronchitis to pesticide exposure in adults is not as prolific or as robust as that concerning asthma. While three studies did find a positive effect, the resulting odds ratios were below 2.0, with large confidence intervals. In particular, two studies that used data from the Agricultural Health Study found an association between exposure to insecticides and the development of chronic bronchitis. Organochlorine, organophosphate, carbamate, and pyrethroid insecticides all showed associations in farmers, while the herbicide paraquat showed the strongest relationship in their spouses through paraoccupational exposure. In addition, the only study to investigate chronic bronchitis in children found that only the association between insecticide exposure and the development of chronic cough and bronchitis approached significance. This study did have significant methodological limitations in using retrospective data, so despite the large sample size and exposed population, no clear effect was seen.

Studies of occupational workers across many industries that use pesticides (e.g., farming, pesticide plant work, and pesticide spraying) showed a subtle yet persistent association between decreased lung function and exposure to a broad range of herbicides and insecticides. Exposure to the organophosphate insecticide chlorpyrifos resulted in a particularly strong association with wheeze, chronic cough, and shortness of breath in many studies. Studying these occupationally exposed populations linked organophosphate and carbamate insecticides in particular with

decreased FEV1/FVC ratios, indicative of obstruction, as well as decreased FEF 25–75%. These outcomes may reflect effects of chronic exposures and as well possibly direct toxic effects on the airways due to inhibition of acetylcholinesterase and resulting bronchoconstriction.

Exposure to neonicotinoid insecticides and organochlorine also showed associations with decreased lung function. The negative effects of pesticides on measures of lung function were more pronounced in younger study populations, and showed a dose–response relationship across exposure categories in studies able to assess this metric. Finally, sarcoidosis and farmer's lung (i.e., hypersensitivity pneumonitis) were both associated with occupational exposure to insecticides. The risk of developing farmer's lung was increased after exposure to organochlorine and carbamate insecticides in particular.

The relationship between respiratory tract infections in children and exposure to organochlorine insecticide (indicated by the presence of DDE) was assessed in three high-quality studies with varying results. Two studies showed a positive association between in utero exposure and respiratory tract infections, while a third paradoxically showed that higher levels during pregnancy were in fact protective. In addition, one study found that upper, but not lower, respiratory tract infections in infants were associated with increased exposure to organochlorines.

The sum of the evidence would indicate that reducing or eliminating exposure to all pesticide types, and to organophosphate and organochlorine insecticides in particular, would be prudent in both occupational and domestic settings with respect to preventing negative respiratory health consequences. While the study of agricultural occupational pesticide exposure and negative health outcomes remains challenging, the accumulation of studies showing significant associations between exposure and asthma, chronic obstructive lung diseases, and decreased lung function highlights the importance of reducing exposure when possible and utilizing proper personal protective equipment when exposure is unavoidable.

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Chapter 6: Implications for Family Practice

Exposure to pesticides may lead to negative health effects across the lifespan, particularly when exposure occurs during pregnancy.

Pesticide exposure during pregnancy, especially in the first trimester, is associated with an increased risk of low birth weight, reduced head circumference, childhood asthma, and cognitive and behavioural problems in the child.

Each of these conditions limits a child's development or health. Low birth weight predisposes to later obesity, cardiovascular disease, metabolic syndrome in adolescence, and diabetes. Asthma restricts lung development and is a risk factor for adult obesity and diabetes. Asthma medications may cause growth restriction. Cognitive and behavioural problems predispose to increased learning problems, reduced IQ, more antisocial behaviour, increased jail time as an adult, and reduced adult earning power (Fletcher 2009, Knapp 2011).

The number of potential adult health effects as consequences of "early programming" provides strong motivation to focus on primary prevention to reduce prenatal and child pesticide exposure.

To assess the applicability of the current review's findings to our Canadian family practices, it is important to compare the contaminant levels found in included studies to those reported in Canadians. This is possible for some chemicals using Canadian Health Measures Survey data and data from a longitudinal Calgary study of organochlorine levels in pregnant women (Jarrell 2005); for other chemicals, such as pyrethrin metabolites, the Canadian measurements are not in a comparable format. Table 6.1 compares available Canadian data with data from studies in the review (from other populations as specified).

Table 6.1. Comparison of Canadian maternal/child contaminant levels with those reported in reviewed studies.

Contaminant	Median (review)	Median, CDN women age 20–39	Median, CDN children or cord blood	95%ile CDN F = women C = children
Organochlorines				
ppDDE (ug/L)	• .64 (USA) • 6.3 (Mexico) • .86, 1.03 (Spain, two cohorts) • all prenatal	• .55[1] • .76 Calgary women prenatal[2] • Baffin Is.: Inuit 2.2, Cauc. .96[3]	• not measured[1] • cord blood, mean .03 (Calgary)[2]	4.21-F
Hexachlorobenzene (ug/L)	• 0.73 (Spain)	• not detected[1] • .10 (Calgary)[2]	• not measured[1] • cord blood .14 (Calgary)[2]	.19-F
p,p DDE (ng/g lipid) lipid-adjusted DDE	• 1436 (USA, pregnant women) • 110 (USA, pregnant women • 299 (Greenland, pregnant women) • 654 (Warsaw, pregnant women)	• not detected[1] • 109.9 (Calgary pregnant women)[2]	• not measured[1] • cord blood 76.5 (Calgary)[2]	832-F
Organophosphate metabolites				
Dimethyl thiosphosphate (umol/L)	• .0137 (USA, prenatal)	• .0127[1]	• .0177[1]	0.389-C
Diethylthiophosphate (umol/L)	• .0047 (US)	• not detected	• not detected	.0284-C

Sources of Canadian data:
[1] Health Canada (2010)
[2] Jarrell (2005)
[3] Butler Walker (2003)

Examination of Table 6.1 shows that contaminant levels of Canadians are comparable to those found in the review, except for hexachlorobenzene, where the Canadian 95 percentile levels are approximately 20% of the mean levels found in a dual Spanish cohort. The patterns of organophosphate metabolite levels also differ from those in the USA. For the dimethyl metabolites (e.g., resulting from exposure to malathion), levels are very similar between Canada and the USA. For diethyl metabolites (e.g., resulting from exposure to Diazinon), the detection frequency in Canada is lower, but the highest 5% of children have levels five times higher than the US mean.

An alternate approach to determining Canadian contaminant burdens is the detection rates for chemicals of interest in the national health survey and in environmental monitoring data. Table 6.2 shows national detection frequencies in children for selected current-use pesticide metabolites from the Canadian Health Measures Survey. Concerning findings include the detection rate of nearly 100% for pyrethroid metabolites in Canadian children. Pyrethroids, or synthetic pyrethrins, are widely used for household insect control and on pets and livestock. Their main effect is axonal excitation, and they are considered likely carcinogens by the oral exposure route

(Health Canada 2010). They have suppressing effects on natural killer cells of the immune system in rats, which could have implications for carcinogenesis if similar effects occurred in humans. For organophosphate insecticides, the 72% rate of detection of the dimethyl metabolites of current-use insecticides such as malathion raises concerns about child exposure. Malathion was associated with hypotonic or absent reflexes in newborns (Engel 2007) and the dimethyl metabolites were the most highly correlated with ADHD in a US cohort study (Bouchard 2010), as well as being linked to the development of atopic asthma and abnormal respiratory function in children and adults.

Table 6.2. Detection rates of pesticide metabolites found in the Canadian Health Measures Survey.

Pesticide Metabolite	Parent compound	Detection rate, age 6–11	Detection rate, age 12–19	Pesticide class and use
3-PBA	• many, incl. permethrin, deltamethrin, cypermethrin	99%	100%	• pyrethroids – scabies Rx, pets, household, livestock, mosquito nets and coils
Cis-DCCA	• cis-permethrin • cis-cypermethrin	97%	99%	• pyrethroids – agricultural and livestock
4-F-3-PBB	• cyfluthrin • flumethrin	42%	51%	• pyrethroids – agricultural, indoor surfaces (for flying and crawling insects), insect-control strips in beehives
2,4-DCP (all from environment, not a human metabolite)	• 2,4-D herbicide • pharmaceuticals • wastewater chlorination	78%	83%	• phenoxy herbicides – lawns and crops; also a metabolite of other processes
Dimethyl thiophosphate (DMTP)	• malathion, azinphos-methyl (restricted), dimethoate, other insecticides	72%	72%	• organophosphate insecticides – gardens, food crops, forestry
Diethyl thiophosphate (DETP)	• Diazinon (currently used; in phase-out), terbufos, chlorpyrifos (banned)	55%	55%	• organophosphate insecticides – garden, food crops

Source: Health Canada (2010); all results rounded to nearest whole percent.

Interpreting the national survey data

The Canadian biomonitoring data were collected year-round for two years. While DDT/DDE levels would be expected to have minimal seasonal fluctuation, the metabolite levels for current-use pesticides including organophosphates have very short half-lives and could vary seasonally if the dominant source was agricultural or lawn/garden use, and not diet or drinking water. Despite

this limitation, there is a high rate of detection for organophosphate and pyrethrin metabolites in Canadian children (Table 6.2). In addition, environmental sampling shows that several pesticides associated with adverse health effects are frequently found in surface waters across the country (Environment Canada Water Science and Technology Directorate 2011). For example, atrazine, a corn herbicide and endocrine disruptor with anti-androgenic and anti-estrogenic effects, is consistently found in more than 90% of surface water samples in Ontario, while the current-use organophosphates malathion and Diazinon are found in about 15%. In contrast, chlorpyrifos, which has been banned for most uses in Canada, is present in only 3% of Ontario water samples and azinphos-methyl (restricted use) in less than 2% (Environment Canada Water Science and Technology Directorate 2011).

Summary: Reproductive health outcomes and pesticide exposure

The reproductive review examined 75 studies published since 2003. The strongest area of association is between current-use pesticides, including Diazinon and atrazine, and fetal growth, with 7 of 10 studies positive. This is a concern in Canada, as detection rates for the two metabolites of Diazinon are 36% and 77% for women aged 20–39. Atrazine is a high-volume agricultural herbicide used on corn crops and considered to be an endocrine disruptor. It has been banned in Europe for over a decade. There was no biomonitoring of atrazine in the 2007–2009 Canadian Health Measures Survey; based on health effects and its persistence in the environment, it would be a candidate for inclusion in the next survey.

In addition to low birth weight, there were other effects on fetal growth. Some studies showed reduced head circumference associated with elevated biomarkers of current-use pesticide exposure.

Fetal growth is becoming the most important predictor of multiple early and late health problems. Recently, a longitudinal study found that three factors, i.e., head circumference (<10th percentile), birth weight (<10th percentile), and obesity or overweight (BMI > 25), in one parent predicted onset of adolescent metabolic syndrome with a sensitivity of 91% and a specificity of 98% (Efstathiou 2012). This adds to the substantial evidence showing that low-birth-weight babies experience increased morbidity (including diabetes and cardiovascular events) throughout their life cycle.

Other studies showed associations between current-use pesticides and birth defects, including hypospadias and neural tube defects. One found an association between hypospadias and use of insect repellent during pregnancy. This result has implications for prenatal counseling: DEET is currently the only active ingredient in insect repellant for personal use, but its safety in pregnancy is now called into question. More risk–benefit analysis for the Canadian context is needed.

Summary: Neurodevelopmental/behavioural health outcomes and pesticide exposure in children

The studies of neurodevelopmental outcomes show that prenatal pesticide exposure is consistently associated with measurable deficits in child neurodevelopment across a wide age range from birth to adolescence.

In neonates, two cohorts found absent or hypotonic reflexes and inattentiveness to stimuli associated with increased organophosphate exposure. After organochlorine exposure the main deficit was increased irritability. In children aged 12–36 months exposed to organophosphate insecticides, there were consistent deficits in the Mental Development Index of the Bayley Scales for Infant Development in three large cohorts representing rural and urban settings. For exposure to organochlorines such as DDT, there were deficits in both scales but with stronger effects for the Psychomotor Development Index. For these early childhood deficits, the relative risks (RRs) are usually in the 1.5–2.0 range.

In older children, attention problems such as ADHD, reduced overall IQ, and other conditions including autism spectrum disorder and pervasive developmental disorder were more common in children who had higher levels of organophosphate or DDT/DDE exposure during pregnancy. Typically, statistically significant health effects were seen primarily in children in the highest 20–25% of exposure. Some studies of ADHD and autism associated with prenatal exposure had higher RRs in the 6.0–7.0 range. ADHD was also associated with pesticide exposure in a cross-sectional study, and autism was associated with pesticide spraying within 500 m of rural homes in the first trimester in a case–control study.

Complex behavioural problems in children have important public health consequences. Knapp (2011) found that 30-year-olds diagnosed with attention deficit at age 10 had "lower employment rates, worse jobs, lower earnings if employed, and lower expected earnings overall." Children diagnosed with ADHD are also more likely to engage in criminal behaviour as adults, with high attendant social costs (Fletcher 2009).

In multi-scale IQ tests, working memory and verbal comprehension appear to be most consistently affected by pesticide exposure. The effects are modest, with RRs usually less than 2.0. However, the reductions in total IQ found, ranging from –2 to –7 points, will substantially impact school performance and later earning potential when viewed from a population perspective. The cost of the loss of 5 IQ points is estimated at CAD 30 billion per year for Canada, and the cost of neurodevelopmental deficits and hypothyroidism at CAD 2 billion per year for Ontario alone. The proportion of those conditions (and costs) considered attributable to environmental exposures was 10–50%. In considering the cost of IQ loss on a population scale, it is important to realize that the loss of 5 IQ points increases the number of mentally challenged in the population by 60%, at the same time reducing the number of gifted individuals by 60%.

Overall, child neurodevelopment studies suggest a range of neurodevelopmental problems throughout childhood that are associated with pesticide exposures. Vigilance is required to minimize the pesticide exposures of pregnant women and very young children from all potential sources, including dietary, indoor and outdoor air, water, and farm exposures. The current-use

organophosphates are consistently implicated in neurodevelopmental deficits, and so are the organochlorines, still heavily used as crop pesticides in agricultural settings.

Summary: Respiratory outcomes and pesticide exposure in children and adults

The respiratory outcome studies showed consistent evidence that pesticide exposure in the prenatal period and first year of life increases the risk of asthma in children. The important classes in this respect are the organophosphates and carbamate insecticides, and with less evidence, pyrethroid insecticides. Farm children and those whose parents work in greenhouse, cut flower, pet grooming, and pesticide application jobs would be among the vulnerable groups in a family practice.

There were also several positive studies of adult respiratory effects of occupational exposure; studying these occupationally exposed populations linked organophosphate and carbamate insecticides in particular with decreased FEV1/FVC ratios, indicative of obstruction, and with decreased mid-expiratory flow rates (FEF 25–75%). Chronic diseases linked with pesticide exposure included sarcoidosis and hypersensitivity pneumonitis (e.g., farmer's lung). High-risk occupations would include pesticide applicators, greenhouse workers, and conventional (i.e., non-organic) market gardeners and farmers.

The US NHANES biomonitoring data are beginning to show us the frequency and levels of exposure to many chemicals, including pesticides, of American children. Comparable data for Canadian children are available for the organophosphate insecticides, but not for organochlorines. The Canadian data will be more useful for understanding health effects when studies associating contaminant levels and health outcomes are conducted. Contaminant levels in Canadian women of child-bearing age and children are clearly quite comparable to those found in multiple studies that found associations with adverse health impacts (Table 6.1).

Factors mitigating the effects of pesticide exposure

Several of the reviewed studies serve as reminders that social and economic factors are also powerful determinants of child health. In the Ecuador floriculture studies, the more highly exposed children had better development in some cases, attributed to the superior nutrition and health care enjoyed by families with employed parents in that society. Similarly, breastfed children in one of the American cohorts had better development than did non-breastfed children despite higher exposure to DDT/DDE. By age two, children highly exposed to DDT who showed neonatal deficits had achieved developmental catch-up with non-exposed peers if they had a stimulating home environment. Breastfeeding was also protective against childhood asthma despite higher contaminant levels.

An important clinical aspect of breastfeeding involves the duration of breastfeeding in women with higher body burdens of organochlorines such as DDE. In one study, neurodevelopmental outcomes were better with high organochlorine levels and long-duration breastfeeding than with

high levels and short duration (<4 weeks) (Ribas-Fitó 2003). Since organochlorines are known to be transferred in breast milk, the high-level short-duration type of breastfeeding may maximize the infant's contaminant exposure without conferring the balancing effects of more prolonged breastfeeding.

Summary

Family physicians can counsel to prevent or reduce pesticide exposure in several settings:

1. In preconception and prenatal patient encounters, counsel to reduce pesticide exposure and help reduce negative birth outcomes, neurodevelopmental problems, and childhood asthma associated with prenatal pesticide exposure. History taking should focus on occupational exposures and indoor use of insecticides. Prevention of these effects has an extended benefit in reducing the frequency of adult chronic diseases associated with suboptimal birth outcomes.
2. Advise parents to minimize exposure of children of all ages by reducing use of indoor and home and garden pesticides. Home exposure is common and preventable: there are multiple pyrethroid-containing products still approved for indoor use, including flea and tick sprays (for pets and homes), scabies treatments for children, indoor insecticides for plants, and ant, earwig, bedbug, and spider insecticides.
3. Alert new parents to the risks of paraoccupational (i.e., take-home) exposures and the protective benefits of wearing personal protective equipment for patients that have unavoidable occupational exposure.
4. Educate patients in occupations at high risk of pesticide exposure about the health effects associated with these exposures; identify patients, such as those with asthma or COPD, who may have special vulnerability to pesticide exposure.
5. Consider becoming involved in community-based education and action in circumstances in which children are being unnecessarily exposed to pesticides. Earlier bans on pesticides with high health effect burdens, such as chlorpyrifos, have been shown to reduce health risks to children and reduce detection frequency in children and the environment.

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SUPPLEMENT: SUMMARY TABLES

Summary Table 1: Reproductive Health Outcomes and Pesticide Exposure

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Bhatia, 2005	Nested case–control – Child Health and Development Studies (CHDS)	76 cases of cryptochidism, 66 cases of hypospadias, 4 cases of both, and 283 control infants enrolled in the CHDS in California, USA	Blood samples in women	Organochlorines DDT/DDE	After delivery or during pregnancy	Cryptorchidism and hypospadias determined through medical records obtained for original cohort	No significant associations were found between maternal serum concentrations of DDT/DDE and congenital defects in male offspring.	19
Chevrier, 2011	Case–cohort – PELAGIE	579 pregnant women residing in Brittany, France	Maternal urine	Atrazine	Prior to 19 weeks gestation	Fetal growth restriction, head circumference, and congenital anomalies identified through hospital records by pediatricians	Presence of atrazine metabolites in maternal urine was associated with increased odds of fetal growth restriction and decreased head circumference (OR 1.5; 95%CI 1.0–2.2 and 1.7; 95%CI 1.0–2.7, respectively).	19
Fernandez, 2007	Nested case–control	50 cases and 114 controls in a mother–infant cohort in Southern Spain	Placenta tissues and interviewer-administered questionnaires (face-to-face)	Organochlorines (16 types) and TEXB (total effective xenoestrogen burden)	At delivery	Cryptorchidism or hypospadias identified through physician examination	Detectable levels of TEXB, DDT, lindane, and mirex in addition to maternal agricultural and paternal occupational exposure to xenoestrogens was association with increased risk of infant urogenital malformations.	19
Sagiv, 2007	Prospective cohort – New Bedford, Massachusetts	722 mother–infant pairs residing near a PCB-contaminated harbour in New Bedford, USA	Cord blood and interviewer-administered questionnaire	Organochlorine pesticides DDT/DDE, HCB, and PCBs	At delivery	Birth weight, length, and head circumference determined through medical records	Small negative associations were seen between maternal serum levels of PCBs and infant birth weight.	19
Venners, 2005	Cohort	388 newly married textile workers aged 20–34 years working in Anhui, China	Maternal blood	Organochlorine DDT	Baseline – prior to stopping contraception	Pregnancy loss determined through daily urine sample for 1 year	Women in the highest tertile of serum DDT had increased odds of spontaneous abortions relative to the lower two tertiles (OR 2.12; 95%CI 1.26–3.57).	19
Carmichael, 2010	Case–control	20 cases and 28 controls in California, USA	Maternal blood sampled mid-pregnancy	PCBs, HCB, DDT, and DDE	15–18th week of pregnancy	Hypospadias as determined through linkage with medical records reviewed by the California Birth Defects Monitoring Program	No significant associations were found between levels of studied pesticides in maternal blood and infant hypospadia.	18

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Eggesbo, 2009	Cohort – Norwegian Human Milk Study (HUMIS)	300 mother–infant pairs enrolled in the HUMIS cohort in Norway	Maternal milk and self-administered questionnaire	Hexachlorobenzene (HCB)	Infants <2 months age; 8 samples	Birth weight, birth length, small for gestational age, gestational age, head circumference, ponderal index, and fetal growth restriction determined through the Medical Birth Registry of Norway	Increased levels of HCB in maternal milk were associated with decreased birth weight, head circumference, and crown-heel length in addition to small-for-gestational-age among women who smoked (p = 0.01).	18
Eskenazi, 2004	Cohort – CHAMACOS	601 low-income Latina women living in the agricultural area of Salinas Valley, California	Maternal interview, maternal urine, maternal blood during pregnancy and delivery and umbilical cord blood	Organophosphates, malathion, chlorpyrifos, and parathion	Approx 13 weeks, 26 weeks, and at delivery	Birth weight, length, head circumference, ponderal index, and gestational age determined through hospital records	Increased maternal exposure to organophosphate pesticides was associated with a decrease in gestational duration (p = 0.02).	18
Gladen, 2003	Cohort	197 singleton infants born in two cities in Ukraine	Maternal milk and self-administered questionnaire	Organochlorines (7 types)	At 4th or 5th day post-birth	Birth weight abstracted from medical records	No significant associations were found between concentrations of OC pesticides in maternal milk and infant birth weight.	18
Jusko, 2006	Cohort – Child Health and Development Studies (CHDS)	399 women with pregnancies over 35 weeks gestation enrolled in the CHDS in California, USA	Maternal serum	Organochlorine DDT	During pregnancy	Fetal growth (birth weight, gestational age, length, and head circumference) determined through medical records and 5-year growth assessed by a physician	No significant associations were found between maternal serum concentrations of DDT and any studied growth outcomes.	18
Neta, 2011	Cross-sectional	300 singleton babies born at the Johns Hopkins Hospital in Baltimore, USA	Cord blood	Permethrin and chlordane	After delivery	Birth weight, length, head circumference, ponderal index, and gestational age abstracted from medical records	No significant associations were found between cord serum concentrations of chlordane or permethrin and studied birth outcomes.	18
Pierik, 2007	Nested case–control	219 mothers of cases and 564 controls enrolled in a US birth cohort study of pregnancies (1959–1966)	Maternal serum	Organochlorines (HCE, HCB, and b-HCCH)	Every 8 weeks during pregnancy, at delivery, and 6 weeks postpartum	Cryptorchidism as determined by records obtained for original cohort study	No significant association was found between maternal serum levels of OC and cryptorchidism in infants.	18

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Whyatt, 2004	Prospective Cohort – Columbia Center for Children's Environmental Health (CCCEH)	314 African American or Dominican mother–infant pairs aged 18–35 years in New York, USA	Interviewer-administered questionnaire, cord blood, and personal air sample	Organophosphate and carbamate insecticides	Questionnaire during pregnancy and biomarkers during 3rd trimester or delivery	Birth weight, birth length, and head circumference abstracted from medical records	For each log unit increase in cord plasma levels of chlorpyrifos, birth weight decreased by 42.6 grams and birth length decreased by 0.24 cm (p = 0.03 and p = 0.04, respectively).	18
Brucker-Davis, 2008	Case–control	78 cases and 86 controls born in Nice area, France	Breast milk (colostrum) in 56 cases and 69 controls and cord blood in 67 cases and 84 controls	DDE, PCBs	Breast milk 3–5 days postpartum	Cryptorchidism identified by physician diagnosis at birth and confirmed at 3 and 12 months postnatally	Increased scores for exposure at birth (colostrum + cord blood) were associated with an increased risk of cryptorchidism (p = 0.02).	17
Cole, 2006	Cohort	41 couples having their first pregnancy and residing in Ontario, Canada	Each couple completed a questionnaire (self-report) and provided a blood sample at delivery	Organochlorines	At time of delivery	Self-report of time to pregnancy (TTP)	Maternal benzene hexachloride exposure in the highest tertile was associated with increased time to pregnancy and lower fecundability (OR 0.30; 95%CI 0.10–0.89) relative to couples in lowest 2 tertiles.	17
Fenster, 2006	Cohort – CHAMACOS	385 low-income Latina women living in the agricultural area of Salinas Valley, California	Maternal serum and maternal interview	Organochlorines (11 types)	Approx 26 weeks and at delivery	Gestational age, birth weight, and birth length as determined by through hospital records	Increased concentration of HCB in maternal blood associated with decreased gestational age (p = 0.05) but not with decreased birth weight or length.	17
Gesink Law, 2005	Cohort – Collaborative Perinatal Project	390 pregnant women enrolled at 12 US sites as part of the Collaborative Perinatal Project	Maternal serum	DDE and PCBs	3rd trimester	Self-report of time to pregnancy	No significant associations were found between maternal serum concentrations of DDE or PCBs and time to pregnancy.	17
Longnecker, 2007	Cross-sectional	781 mothers and newborn males in Chiapas, Mexico	Maternal serum	Organochlorines DDT/DDE	Postpartum period	Anogenital distance and penile dimensions measured by study team within 1–2 days post-partum	No significant associations were found between concentration of DDT or DDE in maternal serum and reduced androgen action in male offspring.	17
Barr, 2009	Prospective Cohort	150 mother–infant pairs delivering at term by cesarean section in New Jersey, USA	Self-administered questionnaire, maternal blood sample collected, at birth and cord blood	Pyrethroid, carbamate, OP insecticides, herbicides, repellents, fungicides	Samples collected at birth	Birth weight, birth length, abdominal and head circumference obtained through medical records	Increased concentrations of metolachlor in cord blood were associated with decreased birth weight (p = 0.05), while increased concentrations of dichloran were related to increased abdominal circumference (p = 0.03).	16

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Berkowitz, 2004	Prospective Cohort – Mount Sinai Hospital, NYC	404 singleton infants born to primiparous, multiethnic mothers in New York City, USA	Interview-administered questionnaire, maternal blood sample collected in the 3rd trimester, and cord blood	Indoor use pesticides	Questionnaire administered "during pregnancy"; biomarkers in 3rd trimester	Birth weight, birth length, head circumference, and gestational age determined through linkage with a perinatal database at Mount Sinai Hospital	With the exception of an association between decreased maternal PON1 activity and decreased infant head circumference (p = 0.014), no significant associations were found between indoor pesticide use and birth outcomes.	16
Damgaard, 2006	Nested case–control	62 cases and 68 controls born in Finland and Denmark	Maternal milk	27 organochlorine pesticides	Between 1 and 3 months postpartum	Physician diagnosis of cryptorchidism at birth and confirmation at 3 months of age	No association was found between individual pesticides; however, combined exposure to the top 8 pesticides was associated with an increased risk of cryptorchidism (p = 0.032).	16
Khanjani, 2006	Cross-sectional	815 primiparous, breast-feeding mothers of singleton babies in Victoria, Australia	Maternal milk	Organochlorines (cyclodienes, HCB, b-BHC)	6–12 weeks postpartum	Birth weight, head circumference, prematurity, miscarriage, still birth, and sex ratio determined through medical records	No significant associations were found between OC concentrations in maternal milk and any of the studied outcomes.	16
Khanjani, 2006	Retrospective cohort	815 primiparous, breast-feeding mothers of singleton babies in Victoria, Australia	Maternal milk	Organochlorines DDT/DDE	6–12 weeks postpartum	Birth weight, head circumference, prematurity, miscarriage, still birth, sex ratio, and small for gestation age determined through medical records	A weak correlation was reported between DDT in maternal milk and low birth weight in female babies only (p = 0.03). No other associations were significant.	16
Levario-Carrillo, 2004	Case–control	79 cases and 292 controls from singleton pregnancies born to mothers in agricultural communities in Mexico	Interviewer-administered questionnaire, maternal blood sample after delivery and cord blood	Organophosphate insecticides	During gestation (not specified)	Intrauterine growth retardation (IUGR) identified through hospital records	Presence of acetylcholinesterase activity in mother or cord blood was associated with increased risk of IUGR (p = 0.04).	16
Ochoa-Acuna, 2009	Retrospective cohort	24,154 infants in Indiana USA	Atrazine levels in drinking water collected through 3 databases	Atrazine in drinking water	Entire pregnancy	Small for gestational age (SGA) and preterm birth determined through medical records	No significant associations were found between levels of atrazine in the drinking water and SGA or preterm birth.	16

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Siddiqui, 2003	Case–control	30 cases of intra-uterine growth retardation and 24 controls presenting for antenatal care in Lucknow, India	Maternal blood, placenta, and cord blood	Organochlorines DDT, HCH	At delivery	Intrauterine growth retardation (IUGR) identified through physical exam and ultrasound	Increased concentrations of HCH and DDE in maternal blood, and HCH in cord blood, were associated with an increased risk of IUGR (p < 0.05). Body weight of the newborn was negatively correlated with DDE in maternal blood, and with HCH and DDE in cord blood (p < 0.05).	16
Torres-Arreola, 2003	Case–cohort	100 cases and 133 controls presenting for care in 3 hospitals in Mexico City	Maternal blood	Organochlorines DDT/DDE, HCH, and HCB	Shortly after delivery	Preterm birth defined as <37 weeks gestation identified through hospital cohort	No significant association was found between OC levels in maternal blood and preterm birth.	16
Wojtyniak, 2010	Cohort	1322 singleton births in Greenland (n = 547), Ukraine (n = 577), and Poland (n = 198)	Maternal blood	DDE and CB-153	During pregnancy (approx. 33 weeks for Polish cohort and 24 weeks for others)	Birth weight, gestational age, and preterm birth determined through questionnaire completed by medical staff	Increase in CB-153 in the serum of Inuit mothers of one unit (log scale) was associated with a decrease in birth weight of 59 g and in birth age of 0.2 weeks (p = 0.01 and 0.02, respectively).	16
Wolff, 2007	Prospective Cohort – Mount Sinai Hospital, NYC	404 singleton infants born to primiparous, multiethnic mothers in New York City, USA	Interviewer-administered questionnaire, cord blood, and maternal blood and urine in a random subset (n = 194)	Organophosphates, PCBs, and DDE	3rd trimester	Birth weight, length, head circumference, ponderal index, and gestational age determined from medical records	Increased concentration of DDE in maternal blood was associated with decreased infant head circumference (p = 0.03).	16
Brender, 2010	Case–control	184 Mexican-American case women and 255 comparison women residing in Texas, USA	Interview-administered questionnaire	Home use, occupational use, and residential proximity to pesticides (not specified)	3 months pre-conception and 3 months post-conception	Identification of neural tube defects (delivered or aborted) through a regional surveillance project including hospitals, clinics, birthing centres, and abortion clinics	Maternal exposure to pesticides in the home and living within 0.25 miles of crops was associated with an increased incidence of neural tube defects in offspring (OR 2.0; 95%CI 1.2–3.1 and OR 3.6; 95%CI 1.7–7.6, respectively).	15
Farhang, 2005	Cohort – Child Health and Development Studies (CHDS)	420 mother–infant pairs enrolled in the CHDS in California, USA	Maternal serum sample and interview at enrollment	Organochlorines DDT/DDE	Primarily postpartum	Preterm birth, small for gestational age, birth weight and gestational age determined from medical records	Weak association between preterm birth and DDE (OR 1.28; 95%CI 0.73, 2.23). No statistically significant results in study.	15

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Greenlee, 2003	Case–control	322 case couples and 322 control couples residing in Wisconsin, USA	Telephone questionnaire	Herbicides, insecticides, and fungicides	2 years before pregnancy attempt date	Female infertility determined through medical record review of patients seeking infertility treatment	Women mixing and applying herbicides 2 years before attempting conception or using fungicide had an increased risk of infertility (27; 95%CI 1.9–380 and OR 3.3; 95%CI 0.8–13).	15
Harley, 2008	Cross-sectional analysis – CHAMACOS	402 pregnant women enrolled in the CHAMACOS cohort in California, USA	Maternal serum in subset (*n* = 289 women) and questionnaire	Organochlorines DDT/DDE	Serum sample in 2nd trimester and questionnaire asked for information 6 months prior to conception	Report of time to pregnancy during interview (face-to-face) at 13 weeks gestation	No association was seen with serum levels of DDT/DDE and fecundability. Maternal occupational exposure to pesticides, residence within 200 ft of an agricultural field, and home pesticide use were all associated with significantly increased time to pregnancy.	15
Toft, 2010	Cohort	678 pregnant women, with at least one prior pregnancy, and their spouses residing in Poland, Ukraine, and Greenland	Maternal blood	DDE and CB-153	During pregnancy (approx. 33 weeks for Polish cohort and 24 weeks for others)	Self-report of fetal loss (miscarriage or stillbirth) in previous pregnancies during interview	Increased concentration of CB-153 in maternal blood was associated with increased odds of ever experiencing fetal loss when all countries were analyzed together (OR 2.4; 95%CI 1.1–5.5).	15
Axmon, 2006	Cohort	778 women and 1.505 women residing in Ukraine, Poland, Sweden, and Greenland	Blood samples in pregnant women and their partners	Persistent organochlorine pollutants (POPs) including DDE	Variable	Self-report of time to pregnancy	In Greenland cohort, serum concentrations of DDE and CB-153 in both men and women were associated with increased time to pregnancy.	14
Brucker-Davis, 2010	Cohort	86 mothers of healthy male infants in southern France	Cord blood and maternal milk 2–5 days postpartum	DDE, linuron, lindane, vinclozolin, procymidone, and hexachlorobenzene (HCB)	Milk 2–5 days postpartum	Birth weight, head circumference, and birth length determined through unspecified source	Increased concentrations of HCB in cord blood and maternal milk showed a negative correlation with infant head circumference (p = 0.037 and p = 0.013, respectively).	14
Dugas, 2010	Case–control	471 case and 490 control infants residing in southeast England	Telephone questionnaire	Several domestic-use pesticides (e.g., insect repellent)	During pregnancy	Hypospadias cases as confirmed by surgeon's records and case notes	Maternal use of insect repellant during the first trimester was associated with an increased risk of hypospadias (OR 1.81; 95%CI 1.06–3.11)	14
Felix, 2008	Case–control	47 cases of esophageal atresia and 63 cases of congenital diaphragmatic hernia and 202 controls in Netherlands	Self-administered questionnaire (both parents)	Herbicides, insecticides	from 1 month before conception to end of 1st trimester	Congenital diaphragmatic hernia and esophageal atresia (EA) identified through medical records	Parental contact with herbicides or insecticides was associated with a diagnosis of EA (OR 2.0; 95%CI 1.0–4.1).	14

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Hanke, 2003	Retrospective Cohort	104 women delivering singleton infants and` residing in an agricultural district in Poland	Interviewer-administered questionnaire (face-to-face)	24 pesticide categories	From 3 months prior to conception and throughout pregnancy (but this was generated from history of over 7 years of questions)	Birth weight abstracted from medical records	Maternal exposure to pyrethroid pesticides was associated with a decrease in infant birth weight (p = 0.02).	14
Lacasana, 2006	Case–control	151 cases of anencephaly and 151 controls of more than 20 weeks gestation in three Mexican states	Interviewer-administered questionnaire (both parents)	Pesticides (not specified) – agricultural exposures	1. From last 3 months before and 1 month after last period, and 2. prior to this	Anencephaly (type of neural tube defect) identified through death certificates and the Epidemiological Surveillance System of Neural Tube Defects in Mexico	Maternal employment in agriculture was associated with increased odds of having an anencephalic child (OR 4.57; 95%CI 1.05–19.96).	14
Meyer, 2006	Case–control	354 cases and 727 controls in Arkansas, USA	Estimate of pounds of pesticides applied through the National Agricultural Statistics Service (NASS) and geographic information systems (GIS)	38 types of pesticides	Gestational weeks 6–16	Hypospadias identified through the Arkansas Reproductive Health Monitoring System (ARHMS)	For every 0.05-pound increase in estimated exposure to diclofop-methyl use, the odds of hypospadia increased by 8% (OR 1.08; 95%CI 1.01–1.15). Negative associations were found with alachlor and permethrin, while all other studied pesticides had null results.	14
Weselak, 2008	Retrospective Cohort – Ontario Farm Family Health Study (OFFHS)	3,412 pregnancies of farm women in the OFFHS in Ontario, Canada	Self-administered questionnaires (3)	Specific chemical names	3 months prior to conception and 1st trimester	Self-report of birth defects	Farm women exposed to cyanazine and dicamba before conception had an increased risk of birth defects in male offspring (OR 4.99; 95%CI 1.64–15.27 and OR 2.42; 95%CI 1.06- 5.53, respectively).	14
Dabrowski, 2003	Case–control	117 cases and 377 controls delivering infants in rural Poland	Physician-administered questionnaire 1–2 days post-delivery and site visit (farm)	Pesticide (not specified)	During 1st and 2nd trimesters	Birth weight as determined by physician interview	Women exposed to pesticides in 1st and 2nd trimester delivered infants with lower birth weight by 189 grams (p <0.01).	13
Giordano, 2010	Case–control	80 cases and 80 controls recruited from mothers receiving care at two hospitals in Rome, Italy	Maternal interview, job exposure matrix, and maternal serum for small subset	Pesticides including hexachlorobenzene (HCB), DDE, and PCBs	From 3 months before to 3 months after conception	Hypospadias identified through medical records	Maternal serum HCB above the median was associated with an increased risk of infant hypospadia (OR 5.50; 95%CI 1.24 -24.31).	13

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Longnecker, 2005	Nested case–control – Collaborative Perinatal Project	1717 women (with a total of 5215 pregnancies ending with fetal loss) enrolled at 12 US sites as part of the Collaborative Perinatal Project	Maternal serum	DDT/DDE and 7 other organochlorines	3rd trimester	Report of fetal loss in previous pregnancies during face-to-face interview	Each increase of 60 g/L in DDE level in maternal serum was associated with increased odds of fetal loss (OR 1.4; 95%CI 1.1–1.6).	13
Sallmen, 2003	Cross-sectional	578 couples (families of male greenhouse workers) in Finland	Self-administered questionnaire, exposure assessment by occupational hygienist, pesticide data collected from employers, and the exposure results of previous studies in the population	11 categories of pesticides	Unknown	Self-report of time to pregnancy and calculation of fecundability density ratio (FDR)	Paternal occupational exposure to pyrethroids was associated with decreased fecundability as measured by the FDR (OR 0.40; 95%Ci 0.19–0.85). In addition, men who used PPE correctly were as fertile as unexposed men.	13
Villanueva, 2005	Cross-sectional	3510 births during the study period in Brittany, France	Maternal municipality of residence on date of birth	Atrazine in drinking water	Used measurements from 1990–1998 (not just pregnancy)	Preterm birth, low birth weight, and small for gestational age determined through birth records	No significant association was found between levels of atrazine the drinking water and studied birth outcomes.	13
Waller, 2010	Case–control	805 cases of gastroschisis and 3,616 controls selected from singletons born in Washington State, USA	Maternal residence and surface water concentrations of atrazine as determined through the United States Geological Survey Data	Atrazine in drinking water	Unknown	Gastroschisis identified through linkage with hospital records (ICD-9 codes)	Inverse relationship between maternal residence within 25 km of high-atrazine-concentration areas and fetal gastroschisis (p = 0.014).	13
Burdorf, 2010	Prospective Cohort – Generation R, Netherlands	6830 pregnant women (mean age 30 years) in Netherlands	Self-administered questionnaire and job-exposure matrix	Pesticide (not specified)	Unknown	TTP, preterm birth, and decreased birth weight determined through self-administered questionnaire and hospital registries	Maternal occupational exposure to pesticides as determined by the job-exposure matrix was associated with decreased birth weight (OR 2.42; 95%CI 1.10–5.34).	12
Carbone, 2007	Case–control	90 cases and 203 controls in agricultural area in the province of Ragusa, Italy	Interview-administered questionnaire	Pesticides (not specified)	From 3 months before to 3 months after conception	Hypospadias and cryptorchidism as determined by pediatric records and physician consultation	No significant associations were found between parental pesticide exposure and infant hypospadia or cryptorchidism.	12

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Idrovo, 2005	Cross-sectional	2085 primiparous women workers from flower production companies in Colombia	Maternal interview	Pesticides (not specified)	1 year before pregnancy, 2 years before, >2 years before	Self-report of time to pregnancy	Maternal employment in the flower industry was associated with an increased time to pregnancy with a trend toward increased TTP with increased duration of employment (OR 0.86; 95%CI 0.75–0.98 working <24 months and OR 0.73; 95% 0.63–0.84 >2 years).	12
Pathak, 2009	Case–control	23 cases and 23 control women who gave birth to full-term babies in India	Maternal and cord blood	Organochlorines	At delivery	Preterm birth determined through medical records	Maternal and cord blood levels of B-hexachlorocyclohexane (B-HCH) significantly correlated with preterm labor ($p < 0.05$).	12
Pierik, 2004	Nested case–control	78 cases of cryptochidism, 56 cases of hypospadia, and 313 control infants visiting child health care centres in Netherlands	Interviewer-administered questionnaire (face-to-face) and job exposure matrix	Pesticides (not specified)	Year before delivery	Cryptorchidism or hypospadias as determined by records obtained for original cohort study (physician diagnosis)	Paternal occupational exposure to pesticides was associated with an increased odds of cryptochidism in infants (OR 3.8; 95%CI 1.1–13.4).	12
Saiyed, 2003	Case–control	117 exposed and 90 unexposed male schoolchildren residing in 2 villages in India	Residing in the village below the cashew plantation	Endosulfan (insecticide)	Unknown	Male reproductive development ascertained by physician examination, Tanner stages of sexual maturity (SMR), and serum samples in a subset ($n = 70$ exposed and $n = 25$ controls)	Sexual maturity was negatively associated with serum levels of endosulfan ($p < 0.01$).	12
Sathyanarayana, 2010	Cross-sectional analysis – Agricultural Health Study (AHS)	2246 farm women who gave birth to a singleton baby within 5 years of enrollment in the AHS (Iowa and North Carolina, USA)	Self-administered questionnaire	27 pesticides	First 3 months of pregnancy	Self-report of infant birth weight	Ever use of the insecticide carbaryl was significantly associated with a decreased birth weight.	12
Zhu, 2006	Prospective Cohort – Danish National Birth Cohort (DNBC)	225 pregnancies in gardeners, 214 pregnancies in farmers, and 62,164 reference pregnancies in the DNBC	Interviewer-administered questionnaire	Pesticides (not specified) – agricultural and horticultural exposure	3 months prior to conception and during pregnancy	Late fetal loss, congenital abnormalities, preterm birth, small for gestational age, sex ratio, and multiple births ascertained through medical records	Maternal occupational exposure as a gardener was associated with an increased risk of very preterm birth (OR 2.6; 95%CI 1.1–5.9).	12

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Brouwers, 2007	Case–control	232 case–control pairs in Netherlands	Self-administered questionnaire	Pesticides (not specified)	3 months pre-conception or 1st trimester	Confirmed cases of hypospadia treated at a pediatric urology centre identified through hospital records	No significant associations were found between parental pesticide exposure and infant hypospadia.	11
Cioroiu, 2010	Cross-sectional	63 mothers living in Iasi, Romania	Maternal milk (colostrum)	Organochlorines DDE, DDT, and HCH	1st week postpartum	Self-report of preterm birth	No significant association was seen between OC levels in colostrum and giving birth to a preterm infant.	11
Fear, 2007	Case–control	594 cases and 526 controls living in England	Parental occupation abstracted by nurse from hospital records	Agricultural chemicals (not specified)	Unknown	Neural tube defects (NTD) identified through an NTD register	Paternal exposure to agricultural chemicals ("agrochemicals") was associated with increased odds of NTD in offspring (OR 2.69; 95%CI 1.09–6.65).	11
Heeren, 2003	Case–control	89 cases and 178 controls born to rural women residing in the Eastern Cape of South Africa	Interviewer-administered questionnaire (face-to-face)	Exposure to agricultural chemicals, dipping of animals for ticks, and use of reused containers that held chemicals	Unknown	Birth defects (several categories of ICD-9) determined through medical records	Maternal exposure to any chemicals (OR 7.18; 95%CI 3.99–13.25), dipping livestock (OR 1.92; 95%CI 1.15–3.14), and containers (OR 1.87; 95%CI 1.06–3.31) was associated with an increased risk of giving birth to a baby with a birth defect.	11
Jurewicz, 2005	Cohort	460 female greenhouse workers under age 45 working in Poland	Pesticide application registers for greenhouses	"Reproductive and developmental toxins" – pesticides	Worked at least 2 years in greenhouses; during pregnancy	Self-report of infant birth weight	Maternal employment in greenhouse during pregnancy was not significantly associated with infant birth weight.	11
Petit, 2010	Prospective Cohort – PELAGIE	3159 pregnant women residing in Brittany, France	Census records of agricultural activities at the municipal level	Pesticides (not specified)	Early pregnancy (not specified)	Birth weight, birth length, and head circumference abstracted from hospital records	No association was found between residential proximity to agriculture and birth weight or intrauterine growth. However, maternal residence in areas where peas were grown was associated with an increased risk of small head circumference (OR 2.2; 95%CI 1.2–3.6).	11
Ronda, 2005	Cross-sectional	587,360 records from the Stillbirth and Birth National Register of Spain (SBNRS)	Paternal occupation	Pesticides (not specified) – agricultural exposure	At conception	Fetal death from congenital anomalies as determined by the SBNRS	Housewives of male agricultural workers had an increased risk of fetal death (OR 1.68; 95%CI 1.03–2.73).	11

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Settimi, 2008	Cross-sectional	717 women greenhouse workers in Italy with a total of 973 pregnancies	Interviewer-administered questionnaire (face-to-face)	Work in a greenhouse (5 different categories of exposure)	At least 1 month in 1st trimester	Self-report of spontaneous abortion	Occupationally exposed women who reported re-entering the greenhouse within 24 hours of pesticide application (OR 3.2; 95%CI 1.3–7.7) or having applied pesticides (OR 2.6; 95%CI 1.0–6.6) had an increased risk of spontaneous abortion.	11
Bretveld, 2007	Case–control	4872 exposed greenhouse workers and 8133 controls in Netherlands	Self-administered questionnaire and job title	Pesticides (not specified)	6 months pre-pregnancy	Self-report of time to pregnancy (TTP), spontaneous abortion, preterm, LBW, sex-ratio, and birth defects	Maternal employment as a greenhouse worker was associated with an increased TTP (OR 1.9; 95%CI 0.8–4.4) and increased risk of spontaneous abortion (OR 4.0; 95%CI 1.1–14.0).	10
Petrelli 2003	Cross-sectional	184 male greenhouse workers aged 20–55 in Italy	Interviewer-administered questionnaire	10 pesticides	During and preceding pregnancy in spouse (not specified)	Self-report of spontaneous abortion in spouse	Spouses of exposed greenhouse workers had a significantly increased risk of spontaneous abortion (OR 11.8; 95%CI 2.3–59.6).	10
Salazar-Garcia, 2004	Cross-sectional	2,033 male antimalaria workers, providing information about 9187 pregnancies, working in Mexico	Interviewer-administered questionnaire	Organochlorines DDT/DDE	Not specified	Spontaneous abortions and stillbirths, sex ratio, and congenital anomalies determined through interviewer-administered questionnaire	Children born after paternal exposure to DDT had a higher risk of birth defects relative to those born before first exposure (OR 3.77; 955%CI 1.19–9.52).	10
Sugiura-Ogasawara, 2003	Case–control	45 cases of miscarriage and 30 controls presenting for care in Nagoya, Japan	Maternal blood	18 types of PCBs, HCB, and DDE	Unknown	Recurrent miscarriage defined as 3 or more consecutive 1st trimester miscarriages (method of ascertainment not specified)	No significant associations were found between concentrations of studied pesticides and recurrent miscarriage.	10
Waliszewki, 2005	Case–control	30 cases and 30 controls presenting for care at a hospital in Mexico	Maternal blood	Organochlorines DDE/DDT, HCH, and HCB	Post-partum (not specified)	Cryptorchidism identified through hospital diagnosis	Increased concentrations of HCB, DDE, and DDT in maternal blood were associated with an increased risk of having a child with undescended testes.	10
Bianca, 2003	Case–control	68 cases and 211 controls residing in an industrial and agricultural area in Southeastern Sicily, Italy	Neonatologist-administered questionnaire and parental occupation	Pesticides commonly used in hothouses	Unknown	Physician confirmation of hypospadias reported through a surveillance system (EUROCAT)	Parental work in a hothouse was associated with an increased risk of hypospadia in offspring (OR 2.9; 95%CI 1.01–8.55).	9

Reference	Study design	Population description	Exposure index	Pesticide	Exposure window	Outcome	Result	Mean score
Hougaard, 2009	Observed vs. expected rates	Comparison of women employed in agricultural versus general population in Denmark	Employment register	Pesticides (not specified) – horticultural exposure	Year preceding treatment for infertility	Infertility determined through national hospital register	No significant associations between employment in horticulture and female infertility seen at the ecological level.	9
Handal, 2009	Cross-sectional	153 Ecuadorian mothers with 2 or more pregnancies	Interviewer-administered questionnaire (face-to-face)	Pesticides used in cut-flower industry including organophosphates, carbamates, and dithiocarbamates	Previous 6 years	Maternal report of spontaneous abortion	Women employed in the cut-flower industry had an increased risk of spontaneous abortion that increased with duration of employment (OR 2.6; 95%CI 1.03- 6.7 increasing to OR 3.4; 95%CI 1.3–8.8 if worked 4–6 years) relative to women who did not.	8
Weiss, 2006	Unknown	21 couples reporting to infertility clinic in Germany	Maternal blood, follicular fluid, and semen	Organochlorines DDT/DDE	Day of oocyte pick-up	Pregnancy rates, semen mobility and morphology (method of ascertainment not specified)	No significant association was found between DDT/DDE and studied outcomes.	8
Tadevosyan, 2009	Cross-sectional/prevalence	30 mothers who had recently given birth residing in rural Armenia	Maternal milk	Organochlorines (DDT, DDE, and HCH)	2–3 days post delivery	Self-report of complications, preterm, stillbirth, miscarriage, and birth defects	Increased concentration of DDT in maternal milk was associated with an increased risk of infertility (OR 2.14; 95%CI 1.29–3.54).	7
Cocco, 2005	Retrospective Cohort	98 spouses of men exposed to DDT in a 1956–1950 anti-malarial campaign in Italy	Retrospective estimate based on the amount of DDT used in the anti-malarial campaign	DDT – occupational exposure during anti-malarial campaign	Unknown	Self-report of number of children, sex distribution, time to pregnancy, number of spontaneous abortions, and number of still births; information from public registrars	Spouses of exposed DDT applicators had an increased rate of stillbirth pregnancies.	6

Summary Table 2: Neurodevelopmental/Behavioural Health Outcomes and Pesticide Exposure in Children

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Eskenazi, 2010	Birth Cohort – CHAMACOS	371 children at 2 years of age from predominately Latino farm worker families in California, USA	Urinary DAP (2× during pregnancy), maternal blood, cord blood and 6 interviews	Organophosphates	Neurodevelopment – Bayley Scales of Infant Development	PON1 (108T) allele associated with poorer Bayley MDI scores ($p < 0.05$), however, PON1 enzyme levels not significantly associated with neurobehavioral outcomes.	19
Torres-Sanchez, 2007	Birth Cohort – Morelos, Mexico	244 mother–infant pairs residing in a malaria-endemic zone of Mexico; infants assessed at 1, 3, 6, and 12 months of age	Maternal serum levels of DDE before pregnancy and in each trimester, and interview.	DDE	Neurodevelopment – Bayley Scales of Infant Development (BSID-II).	Increased levels of DDE in maternal blood during first trimester of pregnancy associated with decreased scores on the Psychomotor Scale of the BSID ($p < 0.02$). Breastfeeding was associated with higher BSID, although not significantly.	19
Abdel Rasoul, 2008	Cross-sectional	50 exposed and 50 unexposed male pesticide applicators aged 9–18 years in Egyptian cotton industry	AChE measured in blood samples, occupational history questionnaire	Organophosphate (primarily chlorpyrifos)	Neurodevelopment – Wechsler Adult Intelligence Scale (WAIS), age appropriate version	In both younger (aged 9–15 years) and older (16–18 years) subjects increased OP exposure was associated with lower WAIS scores ($p < 0.05$).	18.5
Eskenazi, 2007	Birth Cohort – CHAMACOS	396 infants at 6 months of age, 395 at 12 months and 372 at 24 months from predominately Latino farm worker families in California, USA	Urinary DAP, MDA, and chlorpyrifos metabolite levels and 5 interviews (2 prenatal, 3 postnatal)	Organophosphates	Neurodevelopment – Bayley Scales of Infant Development (Child), Child Behavior Checklist (Mother)	Pre- and postnatal DAPs associated with pervasive developmental disorder at 24 months (OR 2.25; 95%CI 0.99–5.16, 1.71; 95%CI 1.02–2.87, respectively)	18.5
Torres-Sanchez, 2009	Birth Cohort – Morelos, Mexico	270 mother–infant pairs residing in a malaria-endemic zone of Mexico; infants assessed at 12, 18, 24, and 30 months of age	Maternal serum levels of DDE before pregnancy and in each trimester, and interview	DDE	Neurodevelopment – Bayley Scales of Infant Development (BSID-II).	Prenatal exposure to DDE is not associated with infant neurodevelopment beyond 12 months of age. Breastfeeding also had no influence on BSID scores at this age.	18.5
Eskenazi, 2006	Birth Cohort – CHAMACOS	330 infants at 6 months of age, 327 at 12 months, and 309 at 24 months from predominately Latino farm worker families in California, USA	Serum levels of p,p-DDT, o,p-DDT and p,p-DDE with interview	Organochlorines (DDE and DDT)	Neurodevelopment – Bayley Scales of Infant Development	A 10-fold increase in p,p-DDT levels at 6 and 12 months was associated with a decrease of 2 points on the PDI scale ($p < 0.05$). Breastfeeding was associated with higher scores.	18
Ribas-Fito, 2007	Birth Cohort – Menorca and Catalonia, Spain	475 children aged 4 years living in Catalonia and Menorca, Spain	Cord blood tested for HCB, delivery and postnatal maternal interview.	Hexachlorobenzene (organochlorine)	Neurobehavioral – California Preschool Social Competence Scale, ADHD	Increased prenatal exposure to HCB was associated with decreased Social Competence scores (RR 4.04; 95%CI 1.76–9.58) and increased risk of ADHD (RR 2.71; 95%CI 1.05–6.96). No association was found with cognitive or motor performance.	18
Ribas-Fito, 2006	Birth Cohort – Menorca and Catalonia, Spain	475 children aged 4 years living in Catalonia and Menorca, Spain	Cord blood tested for DDT, delivery and postnatal maternal interview	Organochlorines (DDE and DDT)	Neurodevelopment – McCarthy Scales of Children's Abilities (MSCA)	Increased prenatal exposure to DDT was significantly associated with a decrease in verbal and memory scores on the MSCA ($p < 0.01$). DDE was not significantly associated.	18

Bouchard, 2011	Birth Cohort – CHAMACOS	329 children aged 6 months, 1, 2, 3.5, 5, and 7 years from predominately Latino farm worker families in California, USA	Prenatal (mother) and postnatal (child) urinary DAP metabolites (DMAP, DEAP)	Organophosphates	Neurodevelopment – Wechsler Adult Intelligence Scale (WAIS) at 7 years of age	Prenatal DAP concentration associated with poorer intellectual development in 7-year-old children ($p < 0.01$).	17.5
Fenster, 2007	Birth Cohort – CHAMACOS	303 neonates and their mothers from predominately Latino farm worker families in California, USA	Prenatal (maternal) DDT/DDE serum samples and interview	Organochlorines (DDE and DDT)	Neurobehavioral – Brazelton Neonatal Behavioral Assessment Scale (BNBAS)	No association between in utero exposure and performance on Brazelton scale.	17.5
Marks, 2010	Birth Cohort – CHAMACOS	348 3.5 and 5-year-old children from predominately Latino farm worker families in California, USA	Urinary DAP metabolite levels (both DMAP and DEAP concentrations) 2× prenatal, 2× postnatal.	Organophosphates	ADHD – NEPSY-II visual attention (3.5 years), Conners' Kiddie Continuous Performance Test (5 years), Child Behavior Checklist (mother), Hillside Behavior Rating Scale (psychometrist)	Prenatal DAPS not significantly associated with ADHD at 3.5 years. Prenatal DAPS associated with lower scores on the KCPT and increased risk of ADHD behaviors (OR 3.5; 95%CI 1.1–10.7). Postnatal DAPS were associated to a lesser extent.	17.5
Rauh, 2011	Birth Cohort – Columbia Center for Children's Environmental Health	265 children at aged 7 years of non-smoking black and Dominican mothers aged 18–35 years living in low-income neighborhoods in New York City	Cord blood tested for chlorpyrifos, pre- and postnatal maternal interview.	Chlorpyrifos	Neurodevelopment – Wechsler Intelligence Scale for Children (IV) at 7 years of age	Prenatal exposure to chlorpyrifos was associated with decreased IQ and working memory score on the WISC ($p < 0.05$).	17.5
Sagiv, 2010	Birth Cohort – Massachusetts	607 children aged 7–11 years residing near a polychlorine biphenyl (PCB)-contaminated harbour in Massachusetts, USA	Cord blood tested for PCBs and DDE	Organochlorines (DDE and PCB)	ADHD – Conners' Rating Scale for Teachers (CRS-T)	Higher levels of p,p-DDE associated with higher risk of ADHD-like behaviors as assessed by the CRS-T, particularly in the highest quartile of exposure ($p < 0.05$)	17.5
Young, 2005	Birth Cohort – CHAMACOS	381 infants ≤62 days old from predominately Latino farm worker families in California, USA	Urinary DAP metabolite levels (both DMAP and DEAP concentrations) and interview	Organophosphates	Neurobehavioral – Brazelton Neonatal Behavioral Assessment Scale (BNBAS)	An increase in prenatal OP metabolite levels was associated with an increased number of abnormal reflexes in infants older than 3 days of age ($p < 0.05$). No association with postnatal OP metabolite levels was found.	17.5
Engel, 2007	Birth Cohort – Mount Sinai Children's Environmental Health Study	311 neonates aged 1–3 days in New York, USA	Urinary DAP and MDA metabolite levels, DDE in blood sample, and questionnaire in 3rd trimester of pregnancy	Organophosphates and DDE	Neurobehavioral – Brazelton Neonatal Behavioral Assessment Scale (BNBAS)	Total DAP levels and MDA levels were both associated with an increase in abnormal reflexes (RR 1.32; 95%CI 0.99–1.77; RR 2.24; 95%CI 1.55–3.24, respectively). No association found for DDE.	17
Engel, 2011	Birth Cohort – Mount Sinai Children's Environmental Health Study	200 infants at 1 year, 276 at 2 years, 169 children aged 6–9 years in New York, USA	Prenatal urinary DAP metabolite levels in 3rd trimester of pregnancy	Organophosphates	Neurodevelopment – Bayley (1 and 2 years) and Wechsler (6–9 years)	Increased levels of prenatal DAP are associated with lower neurodevelopment scores at 12 months (Bayley test) ($p < 0.01$).	17
Puertas, 2010	Birth Cohort – Environment and Childhood Study	104 Caucasian mother–son pairs followed from birth to 4 years of age in Granada, Spain	Placental levels of mirex	Mirex (chlorinated hydrocarbon, organochlorine)	Neurodevelopment – McCarthy Scales of Children's Abilities (MSCA)	Presence of mirex associated with decreased scores on the working memory and quantitative scales of the MSCA ($p < 0.05$).	17

Sagiv, 2008	Birth Cohort – Massachusetts	542 neonate–mother pairs residing near a PCB-contaminated harbour in Massachusetts, USA	Cord blood tested for PCBs and DDE	Organochlorines (DDE and PCB)	Neurobehavioral – Neonatal Behavioral Assessment Scale (NBAS)	Neonates exposed to prenatal PCB and DDE showed decreased scores on the NBAS, particularly on alertness and attention-associated measures.	17
Horton, 2011	Birth Cohort – Columbia Center for Children's Environmental Health	Non-smoking black and Dominican mothers aged 18–35 years and newborns aged 36 months living in low-income neighborhoods in New York City; 342 completed permethrin air samples, 272 completed blood tests and 230 completed piperonyl butoxide air samples	Air samples, cord blood, and plasma samples; maternal questionnaire	Pyrethroid insecticides (primarily permethrin) including piperonyl butoxide (PBO) a pyrethroid synergist	Neurodevelopment – Bayley Scales of Infant Development	Permethrin in air and blood not associated with Bayley Scale scores. Increased exposure to PBO in air associated with decreased Mental Development Index scores (OR 2.49; 95%CI 0.95–6.54).	16.5
Rauh, 2006	Birth Cohort – Columbia Center for Children's Environmental Health	254 children at aged 12, 24, and 36 months of non-smoking black and Dominican mothers aged 18–35 years living in low-income neighborhoods in New York City	Cord blood tested for chlorpyrifos, pre- and postnatal maternal interview	Chlorpyrifos	Neurodevelopment – Bayley Scales of Infant Development (Child), Child Behavior Checklist (Mother)	Prenatal exposure to chlorpyrifos was associated with decreased scores in motor development, mental development, ADHD problems, and pervasive developmental disorder (OR 6.5; 95%CI 1.09–38.69; OR 5.39; 95%CI 1.21–24.11).	16.5
Ribas-Fito, 2003	Birth Cohort – Catalonia, Spain	92 infants aged 13 months living in Catalonia, Spain	Cord blood tested for OC, delivery and postnatal maternal interview	Organochlorines (hexachlorobenzene and DDE)	Neurodevelopment – Bayley Scales of Infant Development and Griffith Mental Development Scales	Prenatal exposure to DDE was associated with delayed mental and psychomotor development at 13 months (p <0.05). Short-term breastfeeding (<16 wks) was associated with lower scores while long-term breastfeeding was protective (associated with higher scores).	16.5
Bouchard, 2010	Cross-sectional data from NHANES	1139 participants and 119 cases of ADHD (all subtypes) aged 8–15 years from general US population	Urinary DAP metabolite levels (both DMAP and DEAP concentrations)	Organophosphates	ADHD – Diagnostic Interview Schedule for Children IV (DISC-IV)	A 10-fold increase in di-methyl containing OPs was associated with increased odds of any ADHD subtype (OR 1.55; 95%CI 1.14–2.10).	15.5
Harari, 2010	Cross-sectional	84 children aged 6–8 years living in northern Ecuador and attending public school	Prenatal exposure interview (mother) and postnatal (child) OP metabolites in urine and AChE activity in blood	Organophosphates	Neurodevelopment – Wechsler Intelligence Scale for Children (IV), Santa Ana Form Board, Reaction time, Stanford Binet copying test	Prenatal exposure was associated with decrease in motor speed functions and visual memory (p < 0.05); current exposure was associated with increased reaction time (p < 0.10).	14.5
Xu, 2011	Cross-sectional data from NHANES	200 cases of ADHD and 2339 controls aged 6–15 years from general US population	Measurement of 2,4,5-TCP and 2,4,6-TCP in child's urine	Trichlorophenols (organochlorine compounds)	ADHD – Parental report	An increase in urinary levels of 2,4,6-TCP was associated with an increased odds of parent-reported ADHD (OR 1.77;95%CI 1.18–2.66).	14.5

Sanchez Lizardi, 2008	Cross-sectional	48 Hispanic children (mean age 7 years) from Children's Pesticide Survey in agricultural communities in Arizona, USA	Urinary DAP metabolite levels (both DMAP and DEAP concentrations)	Organophosphates	Neurodevelopment – Wechsler Intelligence Scale for Children (III), Children's Memory Scale, Wisconsin Card Sorting Test, Trail Making Test (children), Children's Behavior Checklist (parents), Teacher Report Form (teacher)	Exposed children performed more poorly on the trail making test ($p < 0.01$) but did not show significant differences on any other test.	14
Roberts, 2007	Case–control	465 cases of autism spectrum disorder (ASD) and 6975 controls born between 1996 and 1998 residing in California, USA	Residential proximity (radius and temporal window) to pesticide applications during gestation using small area geocodes.	Wide range of agricultural pesticides and fungicides (see Appendix 1, p. 1487 of study)	Autism Spectrum Disorder (ASD) – Diagnostic codes and service usage records	Maternal proximity within 500 m of organochlorine pesticide application was associated with increased odds of ASD (OR 6.1;95%CI 2.4–15.3) particularly during gestation weeks 1–8.	12.5
Grandjean, 2006	Cross-sectional	35 exposed and 37 control subjects in 2nd and 3rd grades in northern Ecuador (up to 9 years of age)	AChE measured in blood samples, DAP metabolites measured in urine in children; questionnaire to mothers	30 pesticides, primarily organophosphates and diethyldithiocarbamates	Neurodevelopment – Wechsler Intelligence Scale for Children (IV), Santa Ana Form Board, Reaction time, Stanford Binet copying test	Prenatal exposure associated with decreased visuospatial performance, current exposure associated with increased reaction time.	12
Ruckart, 2004	Retrospective cohort	147 exposed and 218 unexposed children in Mississippi, 104 exposed and 183 unexposed children in Ohio aged 6 or younger	Urinary metabolite of MP (para-nitrophenol levels) and environmental wipe samples for MP	Methyl parathion (MP), an organophosphate	Neurobehavioral – Pediatric Environmental Neurobehavioral Test Battery (PENTB).	Exposed children showed decreased performance on tests of short-term memory and attention; however, results were not consistent between geographic sites.	12
Lu, 2009	Cross-sectional	35 children, 18 exposed and 17 unexposed whose parents work on traditional and organic coffee plantations in Costa Rica	Two urine samples to test for organophosphate and pyrethroid metabolites	Organophosphates and pyrethroid insecticides	Neurobehavioral – Behavioral Assessment and Research System (BARS)	Exposed and unexposed children did not differ in levels of urinary pesticide metabolites; however, they did differ in BARS performance. This was attributed to differences in SES.	9.5
Handal, 2008	Cross-sectional	121 infants aged 2–23 months living in rural Ecuador	Interview with mother to determine prenatal exposure	Organophosphate and carbamate pesticides (prenatal)	Neurodevelopment – Ages and Stages Questionnaire, Prehension and Visual Skills	Maternal employment in the flower industry associated with lower infant scores for communication, and fine motor skills and with poor visual acuity.	8.5
Handal, 2007	Cross-sectional	142 children aged 2–5 years living in rural Ecuador	Interview with mother to determine prenatal exposure	Pesticide not specified; agricultural pesticides used in flower industry	Neurodevelopment – Ages and Stages Questionnaire, Visual Motor Integration Test	Maternal employment in the flower industry associated with increased developmental scores.	8.5
Eckerman, 2007	Cross-sectional	38 rural (exposed) and 28 urban (unexposed) school children aged 10–18 years	Self-report of exposure collected by interview	Unspecific agricultural pesticide	Neurobehavioral – Behavioral Assessment and Research System (BARS)	Motor and attention deficits shown in adolescents engaged in farming ($p < 0.01$).	4.5

Summary Table 3: Respiratory Health Outcomes and Pesticide Exposure in Children and Adults

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Sunyer, 2005	Prospective Cohort – Menorca, Spain	468 mother–infant pairs presenting for antenatal care in Menorca, Spain, with complete outcome data at 4 years	Maternal interview and DDE/DDT in cord serum	Organochlorines DDE/DDT	Maternal report of wheezing at age 4, maternal report of doctor-diagnosed asthma at age 4	Diagnosis of wheeze at age 4 years increased with serum DDE levels at birth (RR 2.63; 95%CI 1.19–4.69).	18
Sunyer, 2006	Prospective Cohort – Menorca, Spain	462 mother–infant pairs presenting for antenatal care in Menorca, Spain	Maternal interview and DDE/DDT in cord serum and in blood at birth and at 4 years	Organochlorines DDE/DDT	Maternal report of wheezing at any age, maternal report of doctor-diagnosed asthma at age 6.5	Diagnosis of asthma at age 6.5 and wheeze at age 4 years associated with serum DDE levels at birth, but not with serum DDE levels at 4 years of age (OR 1.18 and 1.14, respectively). Breastfeeding increased the mean DDE level, but protected against asthma diagnosis at age 6.	18
Schenker, 2004	Cross-sectional – Study of Agricultural Lung Disease (SALUD)	380 Costa Rican farm workers aged 40 years and older	Interviewer-administered questionnaire	Paraquat (herbicide)	Respiratory function measures – TLC, DLCO, FVC, FEV_1/FVC, VO_2, and VE/VCO_2 – and respiratory symptoms	Each 1-unit increase in paraquat index associated with a 1.8× (1.0–3.1) increase in odds of chronic cough and a 2.3× (1.2–5.1) increase in odds of shortness of breath with wheeze. However, no clinically significant increase in interstitial thickening or restrictive lung disease was noted for any pulmonary function tests.	17
Sunyer, 2010	Birth cohort	520 mother–infant pairs recruited prenatally in Catalonia, Spain	Interviewer-administered questionnaire during 6- and 14-month followup	Organochlorines including DDE	Maternal report of doctor diagnosis of lower respiratory tract infections (LRTIs) including bronchitis, bronchiolitis, or pneumonia during an interviewer-led questionnaire	DDE levels above the first tertile of exposure were associated with LRTI at 6 months (OR 1.68; 95%CI 1.06–2.66) and 14 months (1.52; 95%CI 1.05–2.21) as well as recurrent LRTIs (2.40; 95%CI 1.19–4.83).	17
Dallaire, 2004	Prospective Cohort – Nunavik, Canada	199 Inuit infants up to 12 months of age living in Nunavik, Canada	4 maternal interviews (1 pre- and 3 postnatally), maternal blood, cord blood, and infant blood at 7 months	Organochlorines DDT/DDE and PCBs	Chart review by nurses for any lower or upper respiratory tract infection (LTRI, UTRI)	Infants in the second quartile of prenatal DDE exposure were significantly more likely to develop an URTI at 6 and 12 months of followup (RR 1.05 and 1.0, respectively) than were infants in the lowest quartile of exposure.	16

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Glynn, 2008	Prospective Cohort – Uppsala, Sweden	190 primiparous women seeking prenatal care in Uppsala, Sweden who presented for followup with their infants at 3 months of age	Interviewer-administered questionnaires: 2 prenatal and 1 postnatal; maternal breast milk and pre/postnatal blood sample, infant blood sample	Organochlorine DDE	Interview-administered questionnaire, maternal report of respiratory symptoms in infant, or doctor diagnosis of respiratory infection	No association was found between prenatal serum levels DDE and respiratory infections in the infants. Postnatally, all associations were null with the exception of the second quartile of exposure, which was reported to have a protective effect against respiratory infection (RR 0.18; 95%CI 0.06–0.60).	16
Hoppin, 2008	Cross-sectional analysis – Agricultural Health Study (AHS)	25,112 farm women, including 702 cases of asthma, enrolled in the AHS (Iowa and North Carolina)	Self-administered questionnaire (81%) or telephone interview (19%)	48 pesticides	Self-report of doctor-diagnosed asthma after 19 years of age	Atopic asthma was significantly associated with use of 10 pesticides: 7 insecticides, 2 herbicides and 1 fungicide. Exposure to the organophosphate insecticide parathion resulted in the highest odds ratio (OR 2.88; 95%CI 1.34–6.20).	16
Hoppin, 2009	Cross-sectional analysis – Agricultural Health Study (AHS)	19,704 male farmers, including 441 cases of asthma, enrolled in the AHS (Iowa and North Carolina)	Self-administered questionnaire	48 pesticides	Self-report of doctor-diagnosed asthma after 19 years of age	High pesticide exposure events doubled risk of reporting both atopic and non-atopic asthma. Atopic asthma was associated with exposure to 12 pesticides including 3 herbicides and 6 insecticides. The organophosphate insecticide coumaphos showed the strongest association (OR 2.34; 95%CI 1.49–3.70).	16
Peiris-John, 2005	Repeat cross-sectional	25 occupationally exposed farmers, 22 environmentally exposed fishermen and 40 controls in Sri Lanka	Occupation, self-report of pesticide exposure, residential proximity to agricultural areas, and AChE levels	Organophosphate pesticides (not specified)	Respiratory function measures – FEV, observed to predicted FVC ratios, FEV_1, FEF25–75%, FEV_1/FVC ratio –both between exposure periods and between study groups	FVC and FEV_1 was found to be significantly lower in farmers than in controls ($p < 0.001$ and $p < 0.05$, respectively) and FVC ratio was decreased during the exposure season. The FEV_1/FEV ratio did not differ between groups.	16
Hernandez, 2008	Cross-sectional	89 exposed (pesticide sprayers) and 25 unexposed farm workers in southern Spain	Interviewer-administered questionnaire (face-to-face) and serum measurement of PChE and AChE levels	10 agricultural pesticides including endosulfan, neonicotinoids, bipyridilium-class herbicides, fungicides, and carbamates	Respiratory function measures – FVC, FEV_1, FEV_1 to FVC ratio, FEF25–75%, TLC, and RV – in addition to physical examination and questionnaire	Restrictive lung disease was found to be associated with exposure to neonicotinoid insecticides (TLC, RV, and FRC) and decreased diffusing capacity with exposure to bipyridilium-class herbicides ($p < 0.05$). Carrying the PON1 R isoform found to be protective against abnormal respiratory symptoms (OR 0.31; 95%CI 0.10–0.92).	15

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Hoppin, 2006	Cross-sectional analysis – Agricultural Health Study (AHS)	20,175 farmers and pesticide applicators enrolled in the AHS in Iowa and North Carolina	Self-administered questionnaire	40 pesticides	Self-report of wheeze in the previous year based on the question "How many episodes of wheezing in your chest have you had in the past 12 months?"	Exposure to herbicide chlorimuron-ethyl was associated increased risk of wheeze in a dose-dependant manner (OR 1.62; 95%CI 1.25–2.10) in commercial pesticide applicators. Use of the OP insecticide chlorpyrifos for at least 20 days a year was associated with wheeze in both farmers and applicators ($p < 0.01$).	15
Hoppin, 2007b	Cross-sectional analysis – Agricultural Health Study (AHS)	20,908 farmers (20,400 male and 508 female) including 654 cases of chronic bronchitis, enrolled in the AHS (Iowa and North Carolina)	Self-administered questionnaire	50 pesticides	Self-report of doctor diagnosis of chronic bronchitis after age 20	Ever use of 11 pesticides was associated with prevalent chronic bronchitis, with heptachlor having the highest odds ratio (OR 1.50; 95%CI 1.19–1.89 in adjusted model). Ever use of five organochlorine and five organophosphate pesticides was also significantly related to prevalent chronic bronchitis.	15
Duramad, 2006	Birth cohort – CHAMACOS	412 children born to mothers in Salinas Valley, California, with followup at both 12 and 24 months of age	Six maternal interviews including 2 during pregnancy, 1 at birth, and at 6, 12, and 24 months postpartum, and environmental home inspections	Organophosphate pesticides	Medical records used to determine diagnosis of asthma, eczema, bronchitis, bronchiolitis, or pneumonia	Maternal employment in agriculture was associated with a 25.9% ($p = 0.04$) increase in Th2 cytokines, biomarkers of allergic asthma.	14
Hoppin, 2007a	Cross-sectional analysis – Agricultural Health Study (AHS)	21,393 farmers and 30,242 spouses enrolled in the AHS in Iowa and North Carolina	Self-administered questionnaire	50 pesticides	Self-report of doctor-diagnosed farmer's lung (hypersensitivity pneumonitis)	High pesticide exposure events (HPEE), carbamate and organochlorine insecticides were positively associated with a diagnosis of farmer's lung, with HPEE having the highest odds ratio (OR 1.75; 95%CI 1.39–2.21). A significant dose-response relationship was seen between increased pesticide exposure and report of farmer's lung ($p < 0.0005$).	14
Salam, 2004	Nested case-control – Children's Health Study (CHS)	691 children, including 279 cases and 412 controls, enrolled in the CHS in Southern California, USA	Telephone interview with mother	Pesticides (not specified)	Maternal report of physician-diagnosed asthma by age 5	Ever exposure to pesticides was significantly associated with development of asthma before age 5, particularly if exposure occurred in the first year of life (OR 4.58; 95%CI 1.36–15.43).	14

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Valcin, 2007	Cross-sectional analysis – Agricultural Health Study (AHS)	21,541 non-smoking female spouses of farm workers, including 583 cases of chronic bronchitis, enrolled in the AHS in Iowa and North Carolina	Self-administered questionnaire	50 pesticides	Self-report of doctor's diagnosis of chronic bronchitis after age 20	Five pesticides were associated with prevalent bronchitis in the non-smoking spouses of farmers including one OC and one OP insecticide, 2 herbicides, and methylbromide. Paraquat exposure resulted in the highest odds of chronic bronchitis (OR 1.91; 95%CI 1.02–3.55).	14
Chakraborty, 2009	Cross-sectional	376 exposed and 348 unexposed agricultural workers residing the rural villages of West Bengal, India	Self-administered questionnaire (AChE activity measured but not used to classify exposure for analysis)	Organophosphate and carbamate insecticides	Researcher-administered questionnaire based on the American Thoracic Society National Health and Lung institute Division of Lung Diseases questionnaire and lung function measurement: PFT, FVC, FEV1/FVC, FEF25–75%, and PEFR. Diagnosis of COPD was based on the GOLD criteria (Global Initiative for Chronic Obstructive Lung Diseases).	Exposed workers had higher prevalence of upper and lower respiratory symptoms as well as decreased lung function relative to controls ($p < 0.001$). A diagnosis of COPD was made in 10.9% of workers versus 3.4% of controls ($p < 0.05$).	13
Faria, 2005	Cross-sectional	1,379 Brazilian farmers aged 15 and older with at least 15 hours of weekly agricultural activity	Interview-administered questionnaire	Agricultural pesticides (11 groups) including organophosphates, pyrethroids, triazines, and others	ATS-DLD questionnaire and face-to-face interview to determine self-report of asthma (2 or more episodes of wheezing with shortness of breath), chronic bronchitis (self-report of cough and phlegm most days for 3 or more months per year, for at least 2 years), and chronic respiratory disease	Increased exposure through pesticide application, mixing, spreading, equipment cleaning, and washing work clothes was associated with an increase in asthma when the activity was undertaken 2 or more days per month ($p = 0.0005–0.13$).	13
Fieten, 2009	Cross-sectional	69 exposed and 58 unexposed Costa Rican farm women	Interview-administered questionnaire	Organophosphate insecticides including terbufos, chlorpyrifos, and paraquat	Respiratory function measures (FVC and FEV_1) and respiratory symptoms based on the European Community Respiratory health Survey	No difference found in prevalence of chronic cough, asthma, and atopic symptoms between exposed and unexposed women. Report of wheeze associated with exposure to chlorpyrifos and terbufos in a dose-dependent manner ($p < 0.05$), particularly among non-smokers. Pulmonary measures of FVC and FEV_1 did not differ between groups.	13

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Newman, 2004	Case-control	706 cases of sarcoidosis over 18 years of age and 706 matched controls residing in the USA	Interviewer-administered questionnaire	Insecticides (not specified) and employment in agriculture	Tissue confirmation of noncaseating granulomas within 6 months of enrollment and clinical symptoms consistent with sarcoidosis upon presentation to the medical clinic	Exposure to insecticides at work was associated with an increased risk of sarcoidosis in a multivariate model controlling for other exposures (OR 1.61; 95%CI 1.13–2.28). Employment in agriculture was positively associated with sarcoidosis in the univariate analysis (OR 1.46; 95%CI 1.13–1.89).	13
Salameh, 2005	Cross-sectional	62 exposed and 19 unexposed pesticide factory workers in Lebanon	Interviewer-administered questionnaire	Pyrethroid and carbamate pesticides	Respiratory function measures: FEV_1, FEF25–75%, FEV_1/FVC ratio, and FVC	Exposed workers had a 5.6× higher risk of abnormal FEV_1/FVC ratio and a 16.5× higher risk of abnormal FEF25–75% ($p < 0.001$). Acute exposure did not show any effect.	13
Zuskin, 2008	Cross-sectional	82 exposed (pesticide plant) and 60 unexposed (bottling plant) workers in Croatia	Duration of employment and job title from employment records	Pesticides (not specified)	Respiratory function measures – MEFV, FVC, FEV_1, FEF_{50}, and FEF_{25} – and chronic respiratory symptoms as recorded by physicians using the British Medical Research Council questionnaire on respiratory symptoms	Female pesticide workers had increased odds of chronic cough, and both sexes had increased odds of dyspnea and nasal catarrh (p <0.05). Pesticide workers had significantly decreased FVC, FEV_{50}, and FEF_{25} compared with predicted ($p < 0.01$). No difference in FEV_1 was noted.	13
Abu Sham'a, 2010	Cross-sectional	250 male Palestinian farmers aged 22–77 years	Interview-administered questionnaire	Agricultural pesticides including organophosphates	Interview-administered ATS-DLD and respiratory function measures: FVC, FEV1, and FEF25–75%	No significant association was found between exposure to agricultural pesticides and lung function.	12
Boers, 2008	Cross-sectional – EUROPIT study	248 exposed and 231 unexposed farmers and greenhouse workers in the Netherlands, Italy, Finland, and Bulgaria	Job title and ethylenethiourea in urine	Ethylenebisdithiocarbamates (EBDCs), fungicides, and other pesticides (not specified)	Self-administered questionnaire using elements of the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire	Exposure to EBDCs and other pesticides was not found to be associated with the development of asthma and asthmatic symptoms.	12
Mekonnen, 2004	Cross-sectional	102 male agricultural pesticide sprayers and 69 non-sprayers working on 4 different farms in Ethiopia	Occupation (job title)	Agricultural pesticides, primarily organophosphate insecticides chlorpyrifos, diazinon, and malathion	Respiratory function measures: FVC, FEV, FEV_1/FVC, PEFR, and MMF	No significant association between farmers who sprayed and decreased or abnormal respiratory function was found relative to farmers who were not pesticide sprayers.	12

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Salameh, 2003	Cross-sectional	3,291 children, including 409 diagnosed with chronic respiratory conditions, attending public school in Lebanon	Questionnaire completed by parents	Pesticides: not specified, although pesticides in common use included organophosphates, pyrethroids, bipyridyls, and carbamates	Parental completion of ATS questionnaire, physician confirmation of asthma diagnosis	Exposure to pesticides was associated with an increased risk of asthma, chronic phlegm, and wheeze, with the highest risk of asthma associated with paraoccupational exposure (i.e., occupational use by a household member) (OR 4.61; 95%CI 2.06–10.29).	12
Salameh, 2006a	Case-control	245 cases of asthma and 262 controls recruited from hospital centres in Lebanon	Self-administered questionnaire	Pesticides (not specified)	Self-administered ATS questionnaire, confirmation by pulmonologist through consulting the self-reported symptoms	Any exposure to pesticides was associated with an increased risk of asthma, while living in a region heavily treated with pesticides presented the highest risk (OR 2.91; 95%CI 1.48–5.71).	12
Salameh, 2006b	Case-control	110 cases of chronic bronchitis and 262 controls, all recruited in hospital centres in Lebanon	Self-administered questionnaire	Pesticides (not specified)	Diagnosis of chronic bronchitis by a hospital-based pulmonologist and self-report of symptoms in an ATS questionnaire	Any exposure to pesticides was associated with an increased risk of chronic bronchitis, while occupational use resulted in highest odds ratio in the adjusted model (OR 8.85; 95%CI 1.15–66.67).	12
Tagiyeva, 2010	Prospective Cohort – Avon Longitudinal Study of Parents and Children (ALSPAC)	Children in the UK followed up every 12 months from age 6 months (n = 11,398) to 91 months (n = 8131)	Exposure ratings derived from retrospective self-report of parental occupation	Biocides and fungicides	Maternal report of childhood wheeze during each time period and physician-diagnosed asthma at 91 months	Maternal antenatal and postnatal exposure to biocides and fungicides was associated with an increased risk of childhood wheeze up to 81 months of age (OR 1.23 and 1.22, respectively), while post-natal exposure increased the likelihood of asthma at 91 months of age (OR 1.47; 95%CI 1.14–1.88).	12
Weselak, 2007	Retrospective cohort – Ontario Farm Family Health Study (OFFHS)	3405 children of farm families enrolled in the OFFHS and living in Ontario, Canada	Self-administered questionnaire	13 agricultural pesticides including herbicides, insecticides, and fungicides	Parental report of doctor diagnosis of cough, asthma, allergy/hay fever, or chronic bronchitis in their child	No significant association between any pesticide exposure and cough, bronchitis, or asthma was found. Female offspring exposed to dicamba (herbicide) and carbaryl (carbamate) showed a trend toward a higher risk of cough or bronchitis; however, the effect did not reach significance (OR 2.29; 95%CI 0.95–5.35).	12
Beard, 2003	Retrospective cohort	1999 exposed and 1984 unexposed male outdoor workers in Australia	Chemical use patterns from occupational records	DDT, arsenic, and other chemicals	Matching with national death registers and health insurance records and self-administered survey of surviving cohort members	Insecticide applicators reported an increase in asthma and in having a child diagnosed with asthma relative to unexposed controls ($p < 0.05$).	11

Reference	Study design	Population description	Exposure index	Pesticide	Outcome	Result	Mean score
Del Prado-Lu, 2007	Cross-sectional	102 cut-flower farmers aged 15–68 years working in La Trinidad, Philippines	Interviewer-administered questionnaire, blood cholinesterase levels, and farm activity analysis	Organophosphate pesticides (not specified)	Physician physical assessment and interviewer-administered health questionnaire	Symptoms of cough were reported in 40% of farmers examined, while abnormal peak flows were found in 88%. RBC cholinesterase levels were depressed; however, no baseline measurements were made.	11
Beseler, 2009	Cross-sectional – Colorado Farm Family Health and Hazard Survey (CFFHHS)	761 farmers and their spouses enrolled in the CFFHHS in Colorado, USA	Interviewer-administered questionnaire	Agricultural pesticides (not specified)	Self-report of respiratory illness from pesticide exposure and pesticide poisoning including cough and wheeze	In non-smokers, pesticide poisoning remained a significant predictor of cough with an odds ratio of 2.18 (95%CI, 1.03–4.64).	9
Jones, 2003	Cross-sectional	100 exposed pesticide aviators and 100 unexposed controls from Arkansas, USA	Self-report of occupational exposure	Agricultural pesticides: insecticides and herbicides (not specified)	Self-report of symptoms using the ATS-DLD survey on respiratory function	Results did not differ significantly between occupationally exposed aviators and community controls.	9
Petrie, 2003	Cross-sectional	292 residents (males and females over 18 years) living within the Ministry of Agriculture and Forestry West Auckland spray zone	Spraying data from the Ministry of Agriculture and Forestry	Foray 48B – insecticide	Self-administered questionnaire derived from the Subjective Health Complaint Scale to rate 25 symptoms	Respiratory symptoms increasing after spraying included irritated throat (p = 0.0001), cough (p = 0.10) and upper airway symptoms including wheeze (p = 0.11).	9
Ejigu, 2005	Cross-sectional	82 exposed male farmers and 47 controls working on two farms in Ethiopia	Self-administered questionnaire	Pesticides (not specified)	Self-administered questionnaire on respiratory symptoms	Farmers working at one of the two studied farms had a significantly increased prevalence of respiratory symptoms, including cough, phlegm, and wheeze, relative to controls (p < 0.05).	8