

Chapter 9 — Reproductive Outcomes

Introduction

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

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

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

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

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

Adverse Reproductive Effects

Congenital Malformations – Table 1

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

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

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

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

Fecundability or Time to Pregnancy (TTP) – Table 2

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

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

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

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

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

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

Fertility – Table 3

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

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

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

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

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

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

Altered Growth – Table 4

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

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

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

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

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

Fetal Death – Table 5

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusions

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

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

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

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

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

Chapter 9 — Reproductive outcomes

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Chapter 9 — Reproductive outcomes

Summary Tables

Table 1 Congenital Malformations

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

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

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

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

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

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

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

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

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

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

* The last two papers are repeated in various tables.

Table 2 Time to Pregnancy

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

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

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating (Observations)
greenhouse workers. <i>Scandinavian Journal of Work, Environment & Health.</i> 29(2):85–93.	pregnancy" ?	pesticide application or handling of treated plants.				the exposed greenhouse workers who were inefficiently protected (FOR = 0.67 (CI 95% 0.33-1.35), 0.92 (CI 95% 0.45–1.88) and 0.77(CI 95% 0.46–1.29) for high, moderate and low exposure respectively.	
Thonneau,P., Abell,A., Larsen,S.B., Bonde,J.P., Joffe,M., Clavert,A., Ducot,B., Multigner,L. & Danscher,G. 1999. Effects of pesticide exposure on time to pregnancy: results of a multicenter study in France and Denmark. ASCLEPIOS Study Group. <i>American</i>	France and Denmark 362 French rural workers (142 exposed and 220 controls). 449 Danish farmers (326 conventional (exposed) and 123 controls). Cross sectional survey (with retrospective information).	Job title, type of work, pesticide exposure of the man during the year before pregnancy, list of pesticides. Questionnaire, given to males and they returned by mail.	Age, parity, smoking, contraceptive method used.	Time for pregnancy (TTP) in months. Censored at 13 months. Most recent born child.	TTP in months for (Fecundability OR crude and adjusted) Discrete Cox model	France: FOR adjusted: 1.17 (CI 95% 0.89 - 1.55) Denmark: Pesticide exposure FOR = 1.09 (CI95% 0.82 - 1.43) Green house worker FOR = 0.83 (CI 95% 0.69 - 1.18)	5,4=4.5 Lacking of precise exposure measurements. The crude fecundability ratio for exposure to pesticides did not differ from 1 in any population.

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

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

Table 3 Fertility (Male and Female)

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

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Harkonen et al. 1999. Aneuploidy in sperm and exposure to fungicides and lifestyle factors. ASCLEPIOS. A European Concerted Action on Occupational Hazards to Male Reproductive Capability. <i>Environmental & Molecular Mutagenesis.</i> 34, 39–46.	Denmark 30 Healthy Danish Farmers 29–49 years Occupationally exposed to fungicides Donate semen specimens Prospective cohort	Occupational exposure to fungicides before season and after. Total hours sprayed with only fungicides, hours sprayed with all agricultural chemicals. Within time window (35–50 days before sperm sample) hours sprayed with fungicides, with all pesticides	Age and sperm concentration, life style factors	Disomy (sperm with 1-1-7 or 1-7-7 chromosome complement) and diploidy (1-1-7-7) in each category and pooled as the sum of aneuploid sperm cells Fluorescence In Situ Hybridization (FISH)	Poisson regression. Sum of hyperploid sperm before and after exposure. Sign test, Mann-Whitney U-test, Spearman rank order, Pearson correlation.	The mean frequencies of aneuploid sperm in the study population were 0.12% for disomy 1-1-7, 0.05% for disomy 1-7-7, and 0.11% (before exposure) and 0.9% (after exposure) for diploidy 1-1-7-7.	4,4=4 Exposure to fungicides was not associated with sperm aneuploidy. Smoking was significantly associated with sperm carrying and extra chromosome 1 and with diploid sperm as well as with the aggregate frequency of aneuploid sperm.
Heacock et al. 1998. Fertility among a cohort of male sawmill workers exposed to chlorophenates fungicides. <i>Epidemiology.</i> 9, 56–60	Canada Exposed: 23829; Non Exposed: 2658 (All of them sawmill workers.) Retrospective cohort.	Occupational exposure: Self-report, records Index of cumulative chlorophenates exposure duration for each workers, based on job history	Age, calendar year	Fertility rate for each year (Average number of live births per year per 1000 men)	Poisson regression	RR for E: 0.89 (0.84–0.93) Crude SFR according five categories of exposure (combined comparison) 0.79 (<120h), 0.71 (120–1999), 0.74 (2000–3999), 0.78 (4000–9999), 0.76 (>9999). Male / female ratio for E: 1.06 (provincial norm 1.05)	6,4=5 There is little evidence for a reduction in fertility among chlorophenates exposed sawmill workers in British Columbia. The analyses indicate the importance of time since hire, as a potentially strong confounder in this type

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

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
risk of male infertility. <i>Human Reproduction</i> . 16, 1768–1776	their first infertility consultation Cross-sectional	Past and present jobs and lifestyle habits, contact with chemical substances or physical agents. Industrial hygienist verified correlation between job and declared exposures	intercourse frequency, length of abstinence, and testicular volume. BMI, season, annual income, smoking, alcohol consumption	normal spermatozoa), and concentration of reproductive hormones.		seminal volume 6.6 (1.4-31.4), sperm concentration 1.8, sperm output 1.8, sperm motility 5.8 (1.0-32.7). There was a significantly higher oestradiol/testosterone ratio in the pesticide-exposed group.	with sperm threshold value well below the limit for male fertility, in men with both primary and secondary infertility. Selected population, possible selection bias. Low Power.
Padungtod et al. 1999. Sperm aneuploidy among Chinese pesticide factory workers: scoring by the FISH method. <i>American Journal of Industrial Medicine</i> . 36, 230–238.	China 32 (exposed) from a large pesticide manufacturing plant and 43 (unexposed) from textile factory free from pesticides. Cross-sectional	Occupational, self-report, biological sampling Exposed: Production line workers from pesticide factory plant that manufactures organophosphate pesticides (3 months prior to sample collection). Pesticide residues over an entire 8 hr shift by attachment of 5x5 gauze to nine body areas	Inter-technician effect, age, duration of employment, duration of marriage, number of pregnancies fathered.	Sperm aneuploidy Numerically abnormal count or proportion of sperm exhibiting aneuploidy divided by total number of three disomy types by the number of sperm being scored for each person	Nonparametric Wilcoxon rank-sum test Poison Regression	Exposed vs. Unexposed (including 1OL) Disomy: XY (chi ² =2.6, p=0.10), XX (chi ² =1.1, p=0.30), YY (chi ² =6.9, p<0.01), 18 (chi ² =0.00, p=1.000), Total (chi ² =2.93, p=0.087) Without 1OL: Disomy: XY (chi ² =4.0, p=0.04), XX (chi ² =1.4, p=0.24), YY (chi ² =9.0, p<0.01), 18 (chi ² =0.07, p=0.80), Total (including the 3 types)(chi ² =4.4, p=0.04)	4,4=4 Occupational exposure to organophosphate pesticides moderately increases the prevalence of sperm aneuploidy. Small sample (power), not study of important confounders like smoke and design.

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

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

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

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

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
		scheme was used in which only presumably highly exposed subjects were considered to be exposed.	levels				
Tomenson et al. 1999. An assessment of fertility in male workers exposed to molinate. <i>Journal of Occupational & Environmental Medicine.</i> 41, 771–787.	USA 272 at three plants for semen samples, 222 provided reproductive history. Prospective Cohort	Occupational, industrial hygienist review. Determined for industrial hygiene measurements, estimates of number of hours. Hours of exposure in the spermatide stage (30-60 days before sample). The exposure for each period was calculated by multiplication of the geometric mean exposure to molinate vapour by the number of hours of molinate exposure mcg/m ³ *hours.	Sex, race, marital status, birth date, number of children, education level, smoking history, exposure to warm (sauna, fever), illness (mumps), etc.	Sperm parameters (volume, viscosity, concentration, motility, presence of white blood cells and Mg and Zn levels) and serum hormone levels (FSH, LH and testosterone). Number of children.	Mean of the three replicate samples collected in each period. Mean levels of sperm parameters. log Transformations for hormone levels. Standardized fertility analyses for SFR. GEE (Generalized Estimating Equations) for each period.	Workers' mean exposures to molinate during the monitoring periods ranged from 12.7 mcg/m ³ to 210.9 mcg/m ³ . The only regression findings that might be interpreted as evidence of a molinate-related effect were the falls in sperm concentration and motility score (and the corresponding increase in percent non-motile sperm) at Richmond as exposure increased in the second monitoring period.	6,4=5 There was little evidence that sperm and serum hormone levels at the start of the study were related to the total number of hours of exposure to molinate before the study. The analysis the changes over the four monitoring periods also did not indicate an effect of molinate exposure. Possible selection Bias. Intraindividuality variability in sperm parameters. Design, samples collection and power are strengths.

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

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

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

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

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

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

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

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

* Papers asterisked were considered in various tables.

Table 5 Fetal Death

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

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

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

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

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

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

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

* Papers asterisked are repeated in various tables.

Table 6 Other Reproductive Outcomes

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

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

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

Reference	Population Description (Design, Country)	Pesticides Type and Exposure Assessment	Covariates	Health Outcomes and Measurement	Statistical Analysis	Measures of Association and Values	Global Rating
Parathion, a cholinesterase-inhibiting plaguicide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study. <i>Gynecologic & Obstetric Investigation. 52, 269-275.</i>	women living in a urban area. Cross-sectional					unexposed, diameter 17.5*16.4 cm and 19*16cm respectively Qualitative results: Placental characteristic a) surface aspect: Velvet appearance in exposed and unexposed b) surface texture: nonhomogenous (exposed); homogenous & finely granular (unexposed) c) characteristics of tertiary villi: bulous or fungiform ending with incomplete sulci and numerous plaquest of frbrinoid material (exposed); normal (unexposed) d) presence of microvilli: some areas devoid of microvilli (exposed); all villi covered by microvill (unexposed) e) characterstics of microvilli: some microvilli showed bullous ending and others were bifurcated (exposed); normal (unexposed).	
Levario-Carrillo M, Chavez-Corral D, Ramos-Martinez E, Solis F, Gonzalez-Horta C, Sanin LH. Exposicion de mujeres a	Chihuahua, Mexico 300 women, and subset of 68 with microscopic assay Cross-sectional	Lab diagnosis, self-report AChe level, also agricultureal vs urban community, and <5 km from fields	maternal nutrition via: pre-pregnancy weight/height ² or BMI, body composition post partum (amount of fat)	Lab diagnosis: macroscopic placental characteristics: weight, diameter, presence of infarction, etc.	multivariate logistic regression t-test for descriptives, Odds ratio	OR for placental ischaemia or infarction 3.5 (2.1-5.85) for rural vs urban OR for AChe units/gm hemoglobin depression (i.e. <43.14 at least 25% less than "normal", about lower two tertiles) approximately 2.2	5.5 Lack of bio-marker for sub-chronic exposure. (Geographic and ACHE activity

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

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