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Pregnancy Pesticide Exposures, Birth Defects & Child Health Outcomes In the Ontario Farm Family Health Study

by

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The Department of Epidemiology and Community Medicine
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ABSTRACT

The use of pesticides has served to enhance the economies and health of nations around the world by amplifying crop production and reducing crop loss. At the same time, studies have linked pre- and post-natal pesticide exposures to certain childhood cancers, neurological deficits, and adverse pregnancy outcomes. We explored the relationship between parental pesticide exposure during the pre-conception (3 months prior to conception) and post-conception (first trimester, entire pregnancy period) periods on specific child health outcomes. Our results suggest that pre-conception exposure to cyanazine and dicamba increase the risk of birth defects in male offspring. There is also evidence suggesting that hearing problems and allergies or hayfever are more common in male offspring who are exposed to pesticides during pregnancy. However, given the limited research in this area and the self-reported nature of the exposure and outcomes in this study, the present findings should be considered primarily as hypothesis generating.

Dedication

To my husband Kevin for knowing my goals, my strength and my heart. Your endless support and encouragement was a force that kept me going. Also, to my parents for giving me the confidence to always follow my heart and pursue my goals.

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CHAPTER 1: INTRODUCTION

1.1 Farming and Pesticides

There is no question that the advent of pesticides has dramatically enhanced the health and economy of countries by amplifying crop production, decreasing food spoilage, and reducing pests[1]. Along with agriculture applications, pesticides have found use in public health, highway weed control, and in dry cleaning processes for rugs and other fabrics. They can be found in shelf papers, paints, automatic dispensers in public buildings, and the chemical mixtures of pools[2;3]. Many occupational groups, ranging from crop duster pilots to paint manufacturers, are potentially exposed to pesticides, although agriculture remains the largest user of pesticides[2]. In 1998, it was estimated that over 5 million kilograms of pesticide active ingredients were used on field, fruit, vegetables, and other agricultural crops in Ontario[4].

Although the benefits of pesticides are well-recognized, the potential adverse effects of such compounds on human health remain unclear. Studies have shown that a number of pesticides can act as endocrine modulators[5-7], neurotoxicants[8-11], immunotoxicants,[12] and carcinogens[13] in animals and humans including some still registered for use in Canada.

1.2 Pesticides and Children's Health

Over the past decade, the unique vulnerability of infants and children to environmental exposures has been increasingly recognized[14;15]. Both animal and human studies have shown that the fetus and young children are more vulnerable to the toxic effects of a number of environmental exposures including environmental tobacco smoke

(ETS), polycyclic aromatic hydrocarbons, particulate matter, nitrosamines, polychlorinated biphenyls, metals, and radiation[16]. Some studies have linked pre- and post-natal exposures to pesticides with childhood cancers[13], neurological deficits[17], fetal death[18], intrauterine growth retardation, preterm birth[19;20] and birth defects[21;22]. Moreover, scientists are increasingly recognizing the impact of the fetal environment on the future health of the child and adult [23;24].

1.3 Objectives

The Ontario Farm Family Health Study (OFFHS) was conducted between 1990 and 1993 with the primiary objective of retrospectively assessing the relationship between phenoxy herbicides and spontaneous abortion[25]. Other analyses of the OFFHS have investigated the risk of spontaneous abortion[26;27], paternal pesticide activities and miscarriage, pre-term delivery, small for gestational age, sex ratio[19], and time to pregnancy[28] in relation to direct and indirect farm pesticide exposures. This thesis will build on this work by exploring the effects of direct and indirect pesticide exposures during defined critical windows in the pre-conception and gestational periods on the risk of birth defects and specific child health outcomes.

Primary Objectives

The primary objectives of this research are to explore whether:

1) farm couples exposed to pesticides during the pre and or post-conception periods of pregnancy are at an increased risk of having offspring with any type of birth defect; and

2) farm couples exposed to pesticides during the pre and or post-conception periods of pregnancy are at an increased risk of having offspring with musculoskeletal birth defects;

Seconday Objectives

A secondary objective is to examine whether

1) farm couples exposed to pesticides during pregnancy have an increased risk of having a child who will develop: frequent ear infections, persistent cough or bronchitis, hearing problems, epilepsy, allergies or hayfever, or asthma.

1.4 Outline of the Thesis

This thesis consists of 8 chapters. Chapter 2 provides a comprehensive literature review of birth defects and pesticide exposures, while Chapter 3 summarized the literature on the impact of *in utero* pesticide exposures on child health. This review focuses mainly on the immunotoxic and neurotoxic effects of such exposures. Chapter 4 details the design and conduct the Ontario Farm Family Health Study. The methods used in the analysis of the Ontario Farm Family Health Study are described in Chapter 5. The results of the study are presented in Chapter 6 and 7: Chapter 6 focuses on birth defects and Chapter 7 focuses on child health outcomes. Finally, Chapter 8 provides an overall assessment of the results of the study and their implications for population health risk assessment.

CHAPTER 2: LITERATURE REVIEW, PART I

2.0 Pesticides and Birth Defects

Experimental studies have shown specific pesticides to increase the risk of several birth defects in rodents and amphibians including: cardiac anomalies[29], cleft palate[30], skeletal anomalies[31], cryptorchidism[32], hypospadias[32], retained nipples[33], and limb deformities[34]. However, the effect of pesticides on human fetal development remains unclear. In order to examine this issue, a comprehensive literature review was conducted on parental pesticide exposures and birth defects. Pesticide exposures during the pre- and post-conception periods were considered. The review draws on peer reviewed articles written in English identified through Medline between 1966 and 2003. Key words include pesticides, herbicides, insecticides, fungicides, nematocides, occupations, agriculture, or farming and congenital anomalies, birth defects, or malformations. In addition, reference list searches were carried out in order to identify any additional articles.

2.1 Pesticides

A pesticide has been defined as "any substance that is intended for preventing, destroying, or controlling any pest or is administered to animals for the control of insects and other pests in or on their bodies"[35]. The term "pesticide" covers a broad range of compounds used in pest control and includes insecticides, herbicides, fungicides, rodenticides, biologics, plant or insect growth regulators, nematocides, and non-specific biocides.

Despite historic limited use of elemental sulphur and oil mixtures as insectides by the Greeks and Romans, the modern uses of chemicals to control insects was not widely

introduced until World War II with the introduction of the insecticide dichlorodiphenyltrichloroethane (DDT). Due to limited availability, its use was first devoted to the protection of military personnel against malaria, typhus, and certain vector borne diseases. However, by 1946 there was widespread use of DDT for agricultural use initially in the US and then later in other countries[36]. Since 1970, it has been estimated that approximately 2800 million kilograms of pesticide active ingredients have been sold representing 900 active ingredients and 50 000 commercial pesticide formulations [37].

Today, the most commonly used agricultural pesticides include insecticides, fungicides and herbicides. Insecticides are used to control insects that may destroy or damage crops, or communicate disease to humans or domesticated animals. Before the advent of chemical insecticides, other materials such as the extracts of pepper and tobacco, fish oil brine, and lye were used to supposedly repel insects. The earliest accounts of insecticide use were in folklore and Greek writings. Records of "Brimstone" (sulfur) burning as a fumigant, and the use of gall from green lizards to protect apples from worms and rot were noted [38]. Some modes of action through which chemical insecticides work include those associated with neurotoxins, desiccants, sterilants, and pheromones. Others use more physical means by clogging air passages[15]. A few commonly used classes of insecticides include chlorinated hydrocarbons, organophosphates, and carbamates.

Fungicides are used to control plant molds and other diseases. They work by inhibiting metabolic processes of fungal organisms, preventing fungal infections, or retarding fungal growth before damage can occur[15]. Captan, benomyl, and mancozeb provide examples of some commonly used fungicides.

Herbicides represent another class of pesticides used in large quantities. In 1998, herbicides comprised 75% of all pesticide use in Ontario[4]. Herbicides are used to control weeds that compete with crop plants for water, nutrients, space, and sunlight. They have several modes of action, including those that cause damage to the leaf cell and dehydrate the plant. Others alter nutrient uptake or photosynthesis, inhibit seed germination or seedling growth, while some are applied to the foliage and kill on contact, destroying the leaf and stem cell systems[15]. Some common herbicide active ingredients used in Canada include dichlorophenoxyacetic acid (2,4-D), atrazine, alachlor, cyanazine, and glyphosate.

2.1.1 Farm Exposures to Pesticides

Farmers may be exposed to pesticides through both direct and indirect routes. Direct exposures may occur while mixing chemicals, loading spray equipment, applying pesticides, equipment cleanup, and disposal of empty containers[39]. During pesticide application, farmers are likely to be exposed on the back of their hands, their palms, forearms, and possibly the face and trunk-of-the-body[40]. Additional factors such as the type of mixing system (enclosed or open), use of a tractor with an enclosed cab, the frequency with which farmers wash their equipment after application, and whether they wear gloves or change clothes after a spill can impact exposure levels[41]. The type of spray nozzle (flat fan, tapered-edge, wide angle, or hollow-cone nozzle) as well as the amount of pressure used to produce a suitable spray pattern may also affect exposure. Some types of sprayers can produce spray swaths up to 50 feet in diameter . Depending on treatment needs, the amount of total herbicide spray can vary from 1 to 500 gal/acre[42].

Pesticides can enter the home through residues on work boots[43], as well as on dust and tracked in soil, which readily accumulates in carpets[44;45]. House dust acts as a sink for semivolatile contaminants[46]. In one study[47], vacuum dust had pesticide concentrations 10 to 100 times greater than those found in surface soils surrounding the subjects' homes. In this regard, Lu et al.[43] established that house dust concentrations of organophosphorus pesticides were 7 times higher in the homes of agricultural families than a referent group in Washington State.

Pesticides in house dust may be ingested while eating food, or by direct dermal absorption through the skin[46]. Other potential routes of exposure in the home include dermal absorption from contaminated clothing laundered with other household laundry[19], inhalation of airborne pesticides from the use or storage of pesticides in the home[41], and ingestion of contaminated well-water[48].

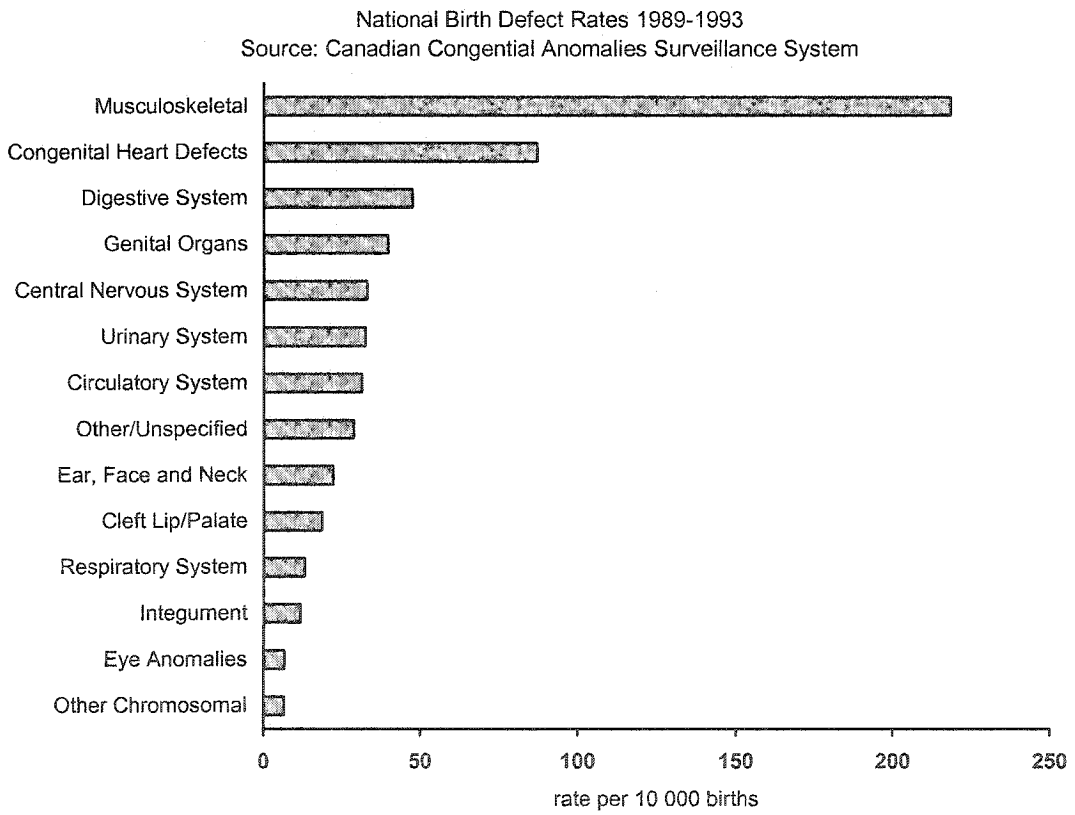
2.2 Pesticides and Birth Defects

A birth defect has been described by the March of Dimes as "an abnormality of structure, function or metabolism, whether genetically determined or as the result of an environmental influence during embryonic or fetal life"[49]. They include both gross structural malformations in progeny as well as microscopic malformations, inborn errors of metabolism, physiological disturbances, and mental retardation. Cellular, subcellular, and molecular anomalies are also of concern. Major anomalies are those that have an adverse effect on either function or social acceptability, while those with neither structural or cosmetic consequences are considered minor[50]. Anomalies may occur in isolation or multiples (two or more major defects from different categories). A total of 19

categories (ICD-9: 740-750) of congenital anomalies have been defined by the International Classification of Disease, 9th revision[51] .

Historical evidence of human malformations dates back several thousand years. A 6500 BC marble figure of conjoined twins was found in Turkey, and statues of individuals with various forms of congenital dwarfism were discovered in ancient Egyptian treasures of 2000 BC [52]. Today, the cause of human birth anomalies remains mysterious with 50% having unknown etiologies[53].

Figure 1: National Birth Defect Rates



In Canada, approximately 5% of all births result in a birth defect, with musculoskeletal and congenital heart defects being the most common[54]. Known causes include genetic factors such as consanguinity[55;56], and chromosomal abnormalities

(aneuploidy, monosomy, trisomy 21, trisomy 13, trisomy 18, triploidy, and tetraploidy)[50]. Recognized risk factors include increasing maternal age[57-59], diabetes[60;61], thyroid disorders[62], and hyperthermia[63-66], physical factors such as intra-uterine compression and amniotic bands[67;68], infectious agents such as rubella, cytomegalovirus, herpes simplex 1 and 2, toxoplasma, *T. pallidum*, varicella[50], dietary factors such as isotretinoin, and decreased folic acid[69;70] and lifestyle factors such as alcohol use, and tobacco smoke[71-75]. Exogenous and environmental agents are thought to be responsible for approximately 7% of all birth defects[53]. Exogenous agents known to cause birth defects include ionizing radiation[76], methylmercury[77], and therapeutic agents such as chemotherapy[78], antineurotics[79], thalidomide[80], diethylstilbestrol[81;82], valproic acid[83;84], and 13-cis-retinoic acid (Vitamin A)[85].

2.2.1 Biological Mechanisms

The possibility that exogenous agents could affect the developing human was not fully realized until recent decades. In 1941 a rubella outbreak was linked to a rare eye defect[86], and in the early 1960's reports emerged associating thalidomide with limb-reduction malformations[87;88]. Later in the 1970's diethylstilbestrol (DES) was identified as a transplacental carcinogen[89]. These human tragedies served to highlight the unique vulnerability of the developing embryo and fetus.

2.2.1.1 Exposures During Development

According to Stevenson[52], there are two basic principles that form the foundation of human embryology: (1) the instructions for embryologic construction are derived from gametes (egg and sperm) through which the conceptus gains heritable traits from each

parent and instructions for producing the human form, and (2) all structures regardless of their complexity must be constructed of simple cells. At approximately one week after implantation, the embryonic disc contains less than 100 cells, from which billions of cells must be produced, differentiated and aggregated into tissue forms, organs of specific function and the final human form[90]. Postconceptual exposure to environmental toxicants can affect the developing fetus through one main mechanism, i.e., by interfering with molecular processes that control prenatal growth and development (i.e. cell division, migration and differentiation). Preconceptual exposure to environmental toxicants can cause fetal germ cell or somatic cell mutations that are not expressed until later in life, e.g, as cancer.

Organogenesis

During the 3rd to 8th week of development, most of the major organs and body regions are being formed. Maternal exposures to teratogens during organogenesis is the best-known pathway by which birth defects can be induced[91]. Before this time, insults are more likely to either kill the embryo, or be compensated for by regulatory properties of the early embryo[53].

Hormonal Effects

Hormones play critical roles in the *in utero* development and function of specific tissues[92]. It has been hypothesized that hormone levels in mammals are associated with determination of the sex of offspring[93]. High parental levels of testosterone and estrogen are associated with male offspring, while high parental levels of gonadotropins and progesterone are associated with females[94]. Unusual maternal hormone levels, conceivably those predisposing to one gender, may be the cause of some congenital

malformations. Such evidence exists for polydactyly[95], oral clefts[96], and transpostion of the great arteries[97]. For example, polydactyly rates are strongly male biased, and there are substantially higher rates (about 10 fold) in U.S. black women compared to U.S. white women. Pregnant black women have been observed to have significantly higher testosterone levels compared to similar white women at 66 days gestation. Support for this observation is provided by the fact that polydactyly rates are inversely associated with maternal age, decreasing from 95 per 100000 births at ages less than 20 years, to 40 per 100 000 births at ages 40 and over. There is also evidence that androgen levels decline with increasing maternal age [95].

Given the important role of hormones during development, it seems plausible that any interference by an exogenous hormone or endocrine disruptor may alter the course of development. An endocrine disruptor (ED) has been defined by the World Health Organization as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations"[98]. These chemicals affect the endocrine system by: (1) mimicking endogenous hormones; (2) antagonizing normal, endogenous hormones; (3) altering the pattern of synthesis, transport, and metabolism of natural hormones; and (4) modifying hormone receptor levels[99]. Studies in experiemental animals have shown that a number of pesticides can act as endocrine disruptors[5-7]. The Centers for Disease Control and Prevention (CDC) in Atlanta has recently classified 48 compounds as endocrine disruptors, of which 38 are pesticides (see Table 1) [100].

Table 1: Chemical Types of 48 Endocrine Disrupting Chemicals

Chemical Type*		Chemicals	Those Licensed for use in Canada[101]
Pesticides	Fungicides	benomyl, *hexachlorobenzene*, mancozeb, maneb, metiram, tributyltin chloride, zineb, ziram	Benomyl, mancozeb, maneb, metiram, tributyltin, chloride, zineb, ziram
	Herbicides	*alachlor*, amitrole, amitrole, 2,4-D, metribuzin, *nitrofen*, 2,4,5-T, trifluralin	Amitrole, atrazine, 2,4-D, metribuzin,
	Insecticides	beta-BHC, gamma-BHC (lindane), carbaryl, chlordane, p,p'-DDD, p,p'-DDE, p,p'-DDT, dicofol, dieldrin, endosulfan, heptachlor, heptachlor epoxide, methomyl, methoxychlor, mirex, trans-nonachlor, oxychlordane, parathion, pyrethroids(synthetic), toxaphene.	carbaryl, parathion, methoxychlor, methomyl, endosulfan,
	Nematocides	Aldicarb, 1,2-dibromo-3chloropropane	

*Classified by the Centers for Disease Control and Prevention[100]

In adults, only extremely high doses of hormonally active compounds have been shown to alter endocrine function. However, the ability of the fetus to regulate subtle changes to his endocrine milieu is unknown[102]. The timing of exposure may be more critical than the dose of endocrine disrupting chemicals[103;104]. Exposure to lower doses of endocrine disrupting chemicals during critical developmental periods when cells are differentiating may change the course of development of these tissues resulting in persistent changes[105;106].

Testicular descent illustrates the importance of maternal hormones during development. Animal studies have demonstrated that estrogen exposure during pregnancy has resulted in the development of hypospadias and cryptorchidism in male offspring of mice[107]. Testicular descent requires the formation of the inguinal canal within the abdominal musculature for the testis to pass through. This process occurs during early pregnancy before maternal hormone levels rise significantly, and is believed to be influenced by endogenous estrogen levels[108]. Sharpe et al.[109] suggest that the process is based on the normal development and secretion of estrogen by the Sertoli cells in the

fetal testis. In co-operation with the Leydig cells, Sertoli cells produce a number of hormones including, androgens, estrogens, and inhibins[110]. Follicular Stimulating Hormone (FSH) drives estrogen production in the Sertoli cells and most likely stimulates the secretion of Mullerian inhibiting substance (MIS), which prevents the production of structures that give rise to the female reproductive tract (Mullerian ducts). It is believed that MIS plays a role in the transabdominal phase of normal testicular descent. A disturbance in MIS because of a decrease in FSH secretion from the fetal pituitary due to elevated maternal estrogen levels may play a role in undescended testis[109]. Additionally, higher maternal endogenous estrogen levels may exert an effect on testicular descent by lowering testorsterone levels through the inhibition of Leydig cell development[108].

2.2.1.2 Paternally-Mediated Mechanisms

Far less research has been conducted relating to paternally-mediated mechanisms of birth defects, especially in relation to pesticide exposure. In the 1960's, Lutwak-Mann[111] demonstrated paternally mediated effects of thalidomide in rabbits. Subsequently, it has been suspected that many chemicals are able to pass through the blood-testes barrier[50].

Germ-cell Mutation

There is only one plausible mechanism for preconceptual exposure to environmental toxicants to affect the developing fetus, i.e., by causing parental germ cell mutations. The development of mature sperm from primordial sperm cells occurs in a cyclical cycle, starting at puberty and continuing through the male reproductive period. In humans, this cycle takes approximately 74 days[112]. Sperm aneuploidy (missing or extra chromosomes), occurs due to non-disjunction (the failure of homologous pairs of

chromosomes to separate)[50]. An abnormal number of sex and autosomal chromosomes in male germ cells may cause chromosomal and malformation syndromes in newborns[113]. Further, experimental studies have indicated that spermatozoa with DNA damage are still able to fertilize the oocyte, providing a mechanism for male-mediated reproductive effects[114].

Men occupationally[115] or residentially[116] exposed to pesticides have exhibited an increased risk for sperm aneuploidy. Recio et al. [116] analyzed urine and semen parameters of men who had resided for at least 15 years in an agricultural community of Mexico whose main crop was vegetables. Those men with high levels of the organophosphate pesticide metabolites DEP, DMTP and total DAP showed an increased risk of sex null aneuploids. Previous to this, Padungton et al.[115] found that men working in a pesticide manufacturing plant were more likely to experience sperm aneuploidy (RR=1.56, 95% CI=1.27-1.93), as compared to subjects working at a nearby textile factory, in which pesticdes were not used.

Seminal Fluid

Other mechanisms by which birth anomalies may be induced by fathers include the transmission of a teratogenic agent through seminal fluid[91;112;117;118] or the attachment of the chemical to spermatozoa[119;120]. Joffe et al.[121] reported that a variety of drugs are absorbed through the vaginal mucosa in mice, and a human case report[122] has described the systemic absorption of chemicals in semen by women.

2.3 Epidemiological Studies of Pesticides and Birth Anomalies

Since the 1960's, a number of epidemiological studies have analyzed birth anomalies in the offspring of parents exposed to pesticides. The majority examined potential occupational exposures, while fewer examined residential exposures to pesticides. Inaccuracies in exposure assessment has been a major concern in studies undertaken in this area. A number of studes relied on job title only as a measure of exposure, while others did not specify the type of pesticide considered in the exposure assessment. Only two studies employed biomarkers of exposure to pesticides in infants[123], or in the mothers of infants[124] with birth anomalies.

2.3.1 Exposure Assessment

2.3.1.1 Ecological Exposures

Several studies chose to use a regional measure of pesticide exposure. In this respect, district or county measures of exposure were defined by areas of aerial pesticide spraying[125-127], residential proximity to farmland or agricultural crops[128;129], regional agricultural production[130;131], regional pesticide use[128;131-136], or regions with pesticide contaminated food[137-139]. Other studies looked at Vietnam villages that were sprayed with Agent Orange during the Vietnam War[140;141].

2.3.1.2 Job Title

Several studies have explored the reproductive effects of potential parental pesticide exposure by using job title as a proxy for pesticide exposure. Parental work in agricultural, horticultural, and forestry, as well as Vietnam veteran status, has been used in this context. One study used farm holder status on census data as an indicator of exposure[142], while another focused exclusively on pesticide spray-plane pilots[143].

Occupational data was collected though subject interviews, or determined by linkage with or linked from birth certificates medical registries, population census data, or tax authority information sheets.

2.3.1.3 Pesticide Use

A variety of studies collected information on parental pesticide use and the risk of birth anomalies among their offspring. Pesticide use data was most often collected from the parents via questionnaires or interviews, while some studies included an industrial hygienist or expert review to identify and quantify pesticide exposures. Uniquely, Louik et al.[144] applied a "job exposure matrix" (JEM) to more accurately represent exposure. Other studies focused on distinct occupational cohorts, such as pesticide applicators, floriculture or greenhouse workers, and pesticide production plant staff. Only a few studies identified the pesticide class, family and/or active ingredient in which the parent was exposed[22;129;145-155]; four of these were case reports[148;150-152].

2.3.1.4 Biomarkers of Exposure

Biological markers, or biomarkers, have been described as indicators that signal an event in biological systems. They are classified into three types: biomarkers of exposure, biological effect, and susceptibility[156]. When seeking to establish a causal association between an exposure and an outcome, laboratory-based biomarker measures generally increase the sensitivity, specificity and power of a epidemiological study[157]. Several organic pesticides such as DDT and hexachlorocyclohexanes (HCHs) are characterized by their persistence, low water solubility, and high lipophilicity, which allow them to bioaccumulate in the fatty tissues of living organisms[158]. Residue levels of these compounds and their metabolites in body fat or in lipid fractions of breast milk or

blood are often used to measure environmental exposure[157]. Only two studies have attempted to measure biomarkers of pesticide exposure to determine its association with birth anomalies[123;124]. The studies both used a case-control study design. Hosie et al.[123] measured adipose tissue organochlorine levels of children with cryptorchidism, while Longnecker et al.[124] examined the serum DDE levels of mothers in their third trimester of pregnancy.

2.3.1.5 Critical Exposure Windows

Critical periods of development have been described as the specific stage in tissue or organ development when environmental factors can modify cells to produce an effect apparent only later in life[15]. In the epidemiologic literature on pesticides and birth defects, maternal and paternal occupations were frequently analyzed separately, but the majority did not analyze critical exposure windows (see Table 2 and Table 3). Further, only five studies to date have examined exposures to a specific pesticide class, family, or active ingredient during a distinct exposure window[145;147;149;155;159].

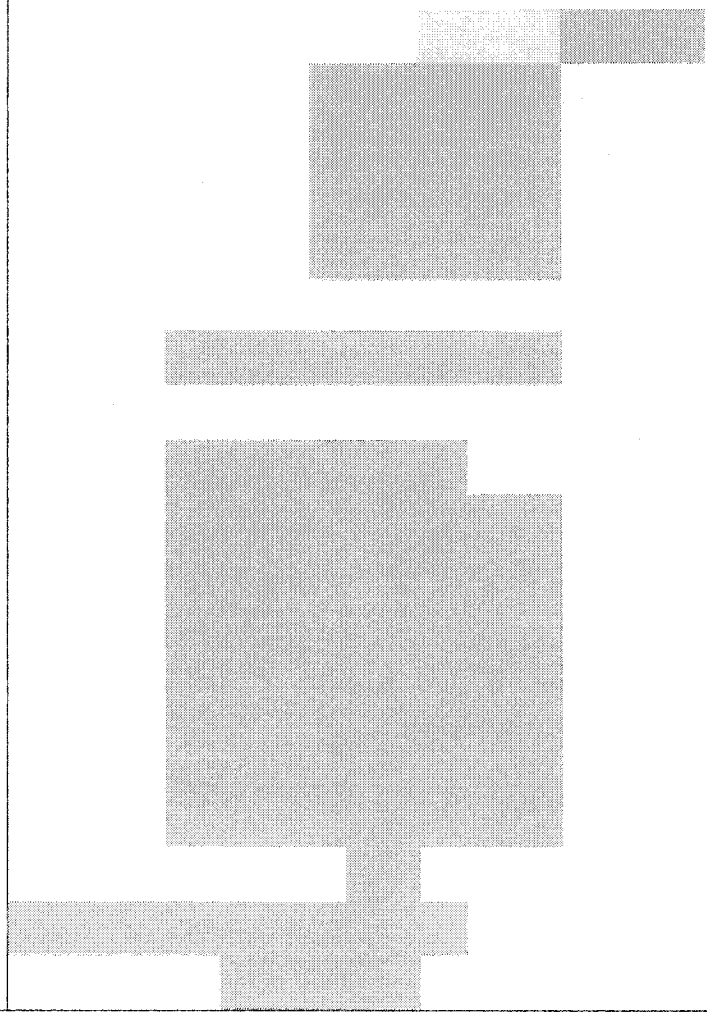
Maternal critical windows were most often defined as exposures during the 3 months before and after conception. Few studies looked at critical exposure windows for fathers. When examined, paternal exposure windows were defined as the time of conception[160] or six[161] to three[149;162] months prior to conception and one month after conception.

Table 2: Maternal Critical Exposure Windows

Study	Maternal Pesticide Exposure	Exposure Window
		Pre conception months -3 -2 -1 / *Conception Date* 0 / *1st trimester* 1 2 3
Correa-villasenor,[163]	Any	
Fixler, [164]	Any	
Loffredo, [147]	Herbicides & Rodenticides	
Shaw, [155]	Fungicides, Insecticides, Herbicides. Carbamate insecticides, Chlorophenoxy Herbicides	
Shaw, [165]	Any	
Torfs, [166]	Any	
Garcia,[149]	Aliphatic hydrocarbons, Carbamates, Chloroalkythio fungicides, Chlorophenoxy herbicides, Dithiocarbamates, Organophosphates, Pyridil derivatives, Active Ingredients: Captan, Glyphosate, Malathion, MCPA	
Garcia, [162]	Any	
McDonald, [167]	Any	
Shaw,[145]	Any Insecticides	
Tikkanen,[168]	Any	
Kurpa,[169]	Any	
Tikkanen,[170]	Any	
Tikkanen, [171]	Any	
Zhang, [172]	Any	
Pastore, [173]	Any	
Nuriminen, [174]	Any	
Blatter, [175]	Any	
Mcdonald, [176]	Any	
Gibson,[177]	Any	
Hourani, [178]	Any	

Table 3: Indirect & Paternal Critical Exposure Windows

Study	Pesticide Exposure(s)	Exposure Window
		Pre conception months (-6 -5 -4 -3 -2) *Conception* (-1 0) *1st trimester* (1 2 3) *2nd trimester* (4 5 6)
Indirect		
Thomas*, [179]	Aerial Spraying: Malathion	
White, [127]	Aerial Pesticide Spraying of 7 pesticide categories together: fentrothion formulations; aminocarb formulations; other forest insecticides; Herbicides phenoxy; Chlorinated herbicides; Non-chlorinated herbicides	
Either Parent		
Crisostomo,[180]	Any	
Paternal		
Blatter, [181]	Any	
Garcia,[149]	Aliphatic hydrocarbons; Carbamates; Chloroalkythio fungicides; Chlorophenoxy herbicides; Dithiocarbamates; Organophosphates; Pyridil derivatives ; Active Ingredient: Captan ; Glyphosate ; Malathion ; MCPA	
Garcia, [162]	Any	
Shaw,[182]	Any	
McDonald, [160]	Any	
Schnitzer, [161]	Any	
Dimich-Ward,[159]	Chlorophenate wood preservative (Fungicide)	



** examined two exposures window*

2.3.2 Exposed Populations

2.3.2.1 Ecological Exposures

a) Agricultural Regions

The amount and type of pesticide used varies greatly by the variety of crop grown. Different regions may also use more pesticides per capita than others. For

instance, southern Ontario used close to 3 million kilograms of pesticides in 1998, while Eastern Ontario used just over 400 000 kilograms[4]. Over the past 30 years, a series of ecological studies have looked at the risk of birth anomalies in relation to residential proximity to a range of agricultural crops.

Studies in California have found that the odds of neural tube defects, conotrunctal heart defects, and fetal death due to congenital anomalies increases relative to a family's proximity to agricultural crops[129] and pesticide applications[133]. In addition, Schwartz et al.[131] found that mothers who resided in California counties with high agricultural productivity were at increased risk of having offspring with one or more limb reduction defects (RR=1.7, 95%CI=1.1-2.7).

Two ecological studies have used wheat or wheat/sugar-beets as a proxy indicator for chlorophenoxy herbicide exposure. Garry et al.[183] illustrated that the wheat/sugar-beets growing region demonstrated an increased risk of circulatory/respiratory (OR=1.9, 95% CI=1.4-2.6), urogenital (OR=2.3, 95% CI=1.7-3.0), and muscular/integumental anomalies (OR=1.8, 95% CI=1.4-2.2), and an increased risk of all birth defects (OR=1.48, 95% CI=1.3-1.7), compared to the forest and urban regions[183]. As well, infants conceived in the spring in areas of high fungicide and herbicide use showed a significant increase in birth defects compared to infants conceived in other seasons (OR=1.36, CI, 1.10-1.69). Another recent record linkage study[184] conducted in Montana, North Dakota, South Dakota and Minnesota counties utilized wheat acreage as a surrogate for chlorophenoxy herbicide exposure. Among 43 634 births, an increased risk of circulatory/respiratory, musculoskeletal/integument defects and poly/syn/adactyly was seen in births that occurred in high-wheat verses low-wheat regions. Moreover, male

offspring in high-wheat regions were almost twice as likely to have circulatory/respiratory defects compared to male offspring of low-wheat regions (OR=1.83, 95% CI=1.06-3.14). Similarly, female offspring had an elevated risk of musculoskeletal/integumental defects (OR=1.62, 95% CI=1.01-2.60).

A study in Arkansas, USA, looked at the total acres planted in rice as a proxy measure of 2,4,5-T exposure[130]. After stratifying their analysis by race, the authors found a significant increase in the prevalence of cleft lip and palate over time for black females. A significantly increasing trend was also seen in white females and cleft palate and white males and cleft lip with or without cleft palate (p=0.02).

Other ecological studies that have defined exposure in terms of regions with high pesticide use have found an increase in limb reduction defects[131], cryptorchidism[132], and cleft lip or palate[130;134]. Also, a study in Australia[135] found a linear association between Australia's annual usage rates of 2,4,5-T and neural tube defects, with the highest rates occurring in the summer months. However, no visible increase was seen for a variety of birth defects in Hungary, where the use of the active ingredient 2,4,5-T rose from 28 tonnes to 660 tonnes between 1969 and 1975[136].

b) Aerial Pesticide Spraying

Epidemiologic studies in New Zealand[126], the United States[125;179], Canada[127] and Vietnam[140;141] have explored the reproductive effects of pesticide spray drift after aerial pesticide application. Hanify et al.[126] compared the monthly incidence rates of birth anomalies with the density of monthly aerial spraying of 2,4,5-T that took place between 1972 to 1977. Their results showed an increased risk of all birth malformations, all heart

malformations, hypospadias and epispadias, and clubfoot in exposed births compared to unexposed births during the period 1960 and 1966.

In California[125] the prevalence of clubfoot, anomalies of the ear and bowed legs was increased among births exposed to malathion and organophosphates through aerial spraying applications in 1981 and 1982. However the design did not allow for control of potential confounding factors, and the authors estimated that misclassification of exposure occurred 10-15% of the time. In a parallel investigation, Thomas et al.[179] attempted to improve upon this by obtaining detailed information on exposure and controlling for potential confounders. A significant but imprecise association was seen for gastrointestinal anomalies and exposures in the second trimester of pregnancy (OR=4.14, 95% CI=1.01-17.0).

A Canadian study[127] examined the incidence of birth anomalies in an area of aerial forest spraying of various pesticides used to combat the spruce budworm. Distinctively, this study examined spraying which occurred during a critical exposure window, 2 weeks before and 13 weeks after conception. After stratifying by length of gestation, maternal and paternal age, and geographic location, the authors found an increased risk of a severe congenital anomaly in offspring of residents who lived within 5 kilometers of the spraying (SRR=2.49, $p<0.05$), and in residents in upper verses lower New Brunswick (SRR=1.97, $p<0.05$).

During the Vietnam War (1962 -1971), US military sprayed approximately 3.6 million hectares of forest and villages in Central and Southern Vietnam with the intention of killing all vegetation[185]. The herbicides were identified by the color bandings on their containers (green, orange, purple, white, pink and blue). Agent orange, a 50:50 mixture

of 2,4-D and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) plus the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), was the most widely used of these defoliants, with over 100 million pounds sprayed in a 10 year period[186;187]. It has been estimated that nearly 17 million people living in South Vietnam were directly exposed to Agent Orange during the spraying operations, and indirectly from possible contamination of food, water, plants, and soil for up to ten years after the end of spraying[141;185]. Most of the studies on south and north Vietnam residents have been summarized in two review articles[140;141] . Constable & Hatch[140] reported on 9 Vietnamese studies reported at the 1983 "Symposium on Herbicides and Defoliants in War: The long-term consequences on Man and Nature in Ho Chi City". Five of the studies involved residential exposure of couples living in South Vietnam[188-192]. The relative risk of birth anomalies in the offspring of women living in exposed villages in South Vietnam compared to unexposed villages ranged from 2.2 (95% CI=1.9-2.5) [192] to 2.5 (95% CI=1.6-3.8) [193]. One cohort study of 848 families found that the incidence of birth defects increased from 0.14% before spraying to 1.78% after spraying [190]. The Vietnamese studies were limited by subject recall, and the lack of control for time of pregnancy and other risk factors. As well, many of the studies had sample sizes that were too small to measure rare outcomes.

c) Contaminated Food and Water

Four studies have attempted to examine the effects of pesticide contaminated food and water on the reproductive outcomes of exposed residents. In a small Hungarian village, a cluster of birth defects was observed between 1989-1990. Of the 15 infants born, 11 had congenital anomalies. Coinciding with this, the local fish farms had been treating fish with the organophosphate pesticide tricholorfon to combat parasites between

March and May of 1988-90. Tests done in 1991 indicated that fish content of trichlorofon averaged between 0.15 to 0.26 mg/kg, depending on the type of fish. The authors ruled out consanguinity, and more case mothers had reported consuming fish, often when the fish were in a comatose state, than control mothers[194].

In Iowa State, elevated levels of atrazine in water supplied by the Rathbun reservoir was found to be associated with an excess of all birth defects (RR =2.6, CI=2.0-3.4), cardiac defects (RR=3.1, 95% CI=2.1-4.6) urogenital defects (RR=3.5, CI= 2.1=4.6) and limb-reduction defects (RR=6.9, 95 % CI=4.2-11.0) compared to other communities in Iowa[137].

In 1982, the entire milk supply of the island of Oahu, Hawaii, was found to be contaminated with the pesticide heptachlor[195]. The cause of the contaminations was traced back to heptachlor contaminated foliage of pineapple plants used to feed cattle on the island. Le Marchand et al.[138] found that cardiovascular malformations, hip dislocation, and ventricular septal defects were increased in both temporal and geographical analysis. However it was also noted that these increases began before the time of contamination.

In China, Li et al.[139] investigated the effects of N, N'-Methylene-bis-(2-Amino-1,3,4-Thiadiazole) (MATDA) contaminated rice on reproductive outcomes. Over 1,600 women who consumed MATDA contaminated rice between 1977 and 1983 were compared to pregnant women from an adjacent county where MATDA was never used, and to women who were pregnant before the introduction of MATDA. After accounting for maternal age and pregnancy order, the results did not show an increased risk of birth anomalies or any birth anomaly categories in the exposed group.

2.3.2.2 Occupational Studies

Over the past several decades, the risk of birth defects has been explored in a number of occupational groups potentially exposed to pesticides, including field workers, agricultural workers, gardeners, pesticide applicators, floriculture or greenhouse workers, and pesticide production plant staff.

a) Field Workers, Agriculture Workers and Gardeners

Initially, case studies of pesticide exposed migrant workers sparked concerns about the health risks of pesticides. A 1964 article published in the *Journal of the American Medical Association* described a child born with congenital absence of ears, facial paralysis, and cardiac anomalies, similar to that in thalidomide reports[196]. The infant was born to a migrant farm worker who had picked cotton in the first 2 months of her pregnancy. The anomalies were not associated with thalidomide, chromosomal diseases, family history, or other pathological syndromes. The similarities in the anomalies to those induced by thalidomide were thought to be due a teratogenic effect, presumably her pesticide exposure while picking cotton.

A later case report described 35 field workers who entered a cauliflower field which had been sprayed just 20 hours prior with 3 different organophosphate insecticides[151]. After one hour of work, all the workers felt ill and went to a nearby hospital. Thirty-three of the 35 workers had blood samples that revealed below normal red blood cell (RBC) cholinesterase activity. One woman who was 4 weeks pregnant at the time had RBC cholinesterase activity of 138 units (the normal range is 210-360 units). She later gave birth to a child with multiple heart, eye, and structural defects. Trisomy D was ruled out and the mother had no history of birth defects. Although these

case reports raised serious questions about the health risks of pesticides, case reports lack a comparison group, and are unable to account for other factors that may have been related to the exposure and the outcome. Nonetheless, astute physicians first identified most human teratogens in case reports.

Whereas many early studies used job title or census data to reflect pesticide exposure, some later studies have included more refined methods of exposure assessment. Specifically, a recent study in the Phillipines[180] classifed households into conventional pesticide users (CPUs) and those that used integrated pest management (IPM). IPM households utilized all suitable technologies and methods, with zero spraying or spot spraying only as a last resort; CPU households were those that applied pesticides at levels beyond the "spot spraying" method. Birth defect data were verified through a medical exam and through the records of rural health centers. The study found 1,374 brands of pesticides used in 345 households of CPU groups and only 399 brands in IPM group of 331 households. Birth defects were 4 times more likely in the CPU group as compared to the IPM group (OR=4.56, 95% CI=1.21-17.09). As well, paternal mixing and application of pesticides during the first trimester of pregnancy was associated with birth defects (p=0.05).

In Spain, Garcia et al.[162] found that agricultural work in the "acute risk period", one month prior to conception and 3 months after inception, increased the odds of any congenital anomaly (OR=3.16, 95% CI=1.11-9.01). Other studies have found that Finish mothers who lived on farms[197], or Canadian women who worked in agriculture or horticulture at conception[167;176] had elevated birth defect rates. Conversely, other occupational studies looking at parents who were agriculture workers[142;174;198;199] or

agriculture pilots[143] have not found a significant increase in the risk of birth anomalies in offspring.

Several agriculture studies chose to look at specific categories of birth defects when examining the impact of pesticides. Limb, neural tube, urogenital, and orofacil defects were often examined in this respect.

i) Limb Defects

A recent cross sectional study in Washington state by Engel et al.[200] found that mothers who worked in agriculture, as indicated on birth certificate records between 1980 and 1993 had a significantly increased odds of having offspring with limb defects (OR=2.8, 95% CI=1.2-6.3). In line with this, the prevalence of limb reduction defects in the progeny of California agriculture workers was 3 to 14 fold higher amongst the offspring of parents who were agriculture workers as compared to US rates[201].

Nevertheless, other studies have found no increase in the risk [131;142]. Schwartz et al.[131]conducted a population-based case control, which included all live offspring born between 1982 and 1984 with one or more shortened or missing limb(s). No increased risk was observed among parents involved in agricultural occupations; however no distinction was made between maternal or paternal occupation. An additional study in Norway used record-linkage methods to examine close to 200,000 farm births and over 60,000 non-farm births[142]. The authors found no increased risk in the offspring of farmers after adjusting for year of birth, maternal age, geographical region, and parental consanguinity.

ii) Neural Tube Defects

Some occupational studies have observed an increased rate of neural tube defects (NTDs) in the offspring of fathers who were farm workers[182] and mothers working in

agricultural occupations[175;202]. Approximately 95% of all neural tube defects are either spina bifida or anencephaly[50]. Spina Bifida is a neural tube defect in which the spinal column has closed imperfectly leaving part of the meninges or spinal cord protruding, while anencephaly is the congenital absence of most of the brain and spinal cord. Early studies observed an elevated rate of anencephaly among offspring of father's who were agricultural machinery drivers[203], or agriculture workers[204] but later studies have not been able to replicate this[161;182;205;206].

An elevated risk of spina bifida has been reported in children of fathers who were agricultural or farm workers[182;203], gardeners or groundsmen[203], as well as mothers who were agriculture workers or living on a farm[207]. Yet, other studies have shown no significant relationship between spina bifida[142;161;204;208], NTDs[182;205;205;208;209], or central nervous system (CNS) defects[142;197;210] among offspring of parents who were agricultural or forestry workers, gardeners, groundsmen or farmer's wives.

iii) Cryptorchidism and Hypospadias

Cryptorchidism, or undescended testes, was found to be increased in the sons of Norwegian mothers who were farmers or gardeners[161;211]. A record linkage study in Denmark[142] also found that the risk of cryptorchidism nearly doubled in the progeny of field vegetable farmers who had made a pesticide purchase (OR=1.85, CI=1.10-3.10). An elevated prevalence of hypospadias was observed in the offspring of grain farmers who owned tractor spraying equipment (OR=1.53, CI=1.07-2.20) [142] and fathers who were forestry workers or loggers[206]. Conversely, two cross-sectional studies found no difference in the prevalence of hypospadias in the sons of parents who worked in agriculture as indicated on their child's birth certificate[201] or the Census[205].

iv) Orofacial Clefts

An increased prevalence of orofacial clefts has been seen in Finish women who were involved in agriculture work during the first trimester of pregnancy [174] and British fathers who were farmers, farm manager, or market gardeners, agricultural workers, and agricultural machine drivers[203]. Conversely, no increased risk was seen in parents who worked in agriculture from Canada[206], Europe[212], Finland[213;214] or Britain[204], farm managers from the United States[161], or Norwegian farm holders[142].

b) Vietnam Veterans

During the Vietnam War military personnel who served on Air Force Operation Ranch Hand and the Army Chemical Corps were the most likely to have been exposed to Agent Orange[215]. The health risks to Vietnam veterans have been investigated through a handful of Vietnamese[216-219], Australian[220;221], and US.[222-229] studies.

Vietnamese studies reported in two review papers[140;141] have looked at pregnancies of women married to men who served in South Vietnam in comparision with pregnancies of women with unexposed men. An increased risk was observed for any congenital anomaly[216;218], cleft lip[216] and cleft palate[216]. In one case-control study[217], 61 birth defect cases were verified against local health records and those living with a birth defect were medically confirmed. Fathers who served in the Vietnam War were found to be 3 times as likely to have a child with a birth anomaly (OR=3.57, 95% CI=1.91-6.69). However, uncertainties in exposure assessment and lack of control for other parental risk factors may have limited these findings.

An Australian birth defect study found a non-significantly increased risk of any birth defect in the offspring of Vietnam veterans (OR=1.3, 95% CI=0.9-2.0)[220]. The

study involved 127 infant cases and 123 infant controls whose father served in Vietnam and 202 cases and 205 controls whose father did not serve in Vietnam. Field & Kerr[221] found results that indicated a pattern of association with congenital heart disease and anomalies of the CNS in offspring of fathers who were Vietnam veterans; however, no formal statistical analysis was conducted.

In the U.S., the Vietnam Veterans Experience Study by the Centers for Disease Control (CDC)[223] found more birth defects among Vietnam veterans compared to non-veterans (OR=1.3, CI=1.2-1.4). The risks of multiple, nervous system, and integument defects, as well as hydrocephalus, were elevated in this population. A later sub-study compared the hospital records of children of Vietnam veterans and non-veterans. Specifically, black Vietnam veterans were found to have a significant increase in the risk of birth defects among their offspring (OR=3.4, CI=1.5-7.6). Sample size constraints precluded more detailed analyses of specific categories of anomalies. The Air Force Health Study[224] determined that conceptions following U.S. military service in Southeast Asia had a two-fold increase in the odds of urinary system defects (OR=2.5, CI=1.3-5.0), and a moderate increase in risk of any birth anomaly (OR=1.4, CI=1.1-1.6). Yet, other U.S. State[226-228] and national surveys[229] reported in the Institute of Medicine Report, *Veterans and Agent Orange*[215], reported no relationship between Vietnam veteran status and abnormalities in offspring.

An important shortcoming of these studies was the use of veteran status as a surrogate for exposure to Agent Orange, regardless of the type of military service. One study by Erickson et al.[230] attempted to more accurately measure exposure by deriving an Exposure Opportunity Index (EOI). Using a specialist familiar with existing records of

herbicide applications, veterans were categorized into 5 EOIs with EOI-1 representing the lowest opportunity for exposure and EOI-5 the highest. Most categories of birth defects were not significantly elevated among offspring of the Vietnam veterans. Nevertheless, spina bifida and cleft lip displayed an increasing risk from EOI-1 to EOI-5. Unfortunately, the response rate for this study was low (52% for cases and 54% for controls) raising questions about the representativeness of this sample.

c) Chemical Plant and Saw Mill Workers

Chemical plant workers may come into contact with pesticides while breathing contaminated air or by direct skin contact with chemicals. An early case study by Dickson[148] reported that 3 out of 4 children born to men working in a herbicide production plant between the period of January 1975 and June 1976, had heart deformities. The chemical plant produced the herbicide Oryzalin, which is used on soy beans for weed control. Subsequently, two cohort studies based on chemical plant workers producing the phenoxy herbicide 2,4,5-T have found no association with birth anomalies in offspring of exposed workers[154;231]. However, both of these studies had small sample sizes and low response rates.

In a record linkage study, Dimich-Ward et al.[159] examined the birth outcomes of over 23 000 infants of father's who worked in BC sawmills and were exposed to the fungicide chlorophenate, used as a wood preservative. Over 90 different job titles within the sawmill industry were rated according to their average frequency and duration of exposure to chlorphenates, which was subsequently used to estimate total hours of exposure. When comparing the 75th percentile to the 25th percentile of estimated exposure, those fathers who were exposed during a particular time window had an

elevated risk of eye defects, congenital cataracts, genital organ defects, and undescended testes in their offspring. More specifically, an elevated but imprecise increase in risk was seen for congenital cataracts if the father was exposed in the 3 months prior to conception (OR=5.68, 95% CI=1.3-22.6) or during the entire pregnancy period (OR=4.34, 95% CI=1.3-13.8).

d) Greenhouse Workers

Greenhouse workers are a unique population because, unlike farmers, who are seasonally exposed to pesticides, they apply pesticides throughout the year. In addition, their dose is potentially greater than that delivered to outdoor agricultural workers because they work in more confined spaces where vapors can accumulate and contact with residue on plants is more likely[232].

Restrepo et al.[233] looked at birth anomalies in the offspring of nearly 9000 Columbian floriculture workers laboring in greenhouses. The authors found an increased risk of malformed offspring in female workers (OR=1.34, 95%CI=1.07-1.68), and the wives of male workers (OR=1.53, 95%CI=1.04-2.25) who had worked for one year or more in the floriculture industry. A subsequent case-control study by the same investigators[234] showed that parental work in the floriculture industry during pregnancy increased the odds of total congenital malformations (OR=1.8, $p<0.01$). However, subgroup analyses did not show an increased risk for any major birth defect as compared to a random set of children reported as normal at birth.

Kristensen et al.[142] linked birth registry data to the agricultural census and found that owners of orchards and greenhouses had over 3 times the odds of hydrocephaly in progeny (OR=3.26, CI=1.30-8.2). In addition, those owners who were also in the

possession of tractor spraying equipment had an elevated risk of spina bifida (OR=2.69, CI=1.08-6.71), while those who made a pesticide purchase had a higher risk of urinary system defects in their offspring (OR=2.68, CI=1.11-6.46).

In line with this, an ecological study[132] done along the Mediterranean coast of Grenada, Spain investigated municipal pesticide use and orchidiopexy rates. Orchidopexy is an operation done to mobilize a testis, bring it into the scrotum, and attach it so that it will not retract for individuals with cryptorchidism[235]. Within this region there is an extensive area devoted to farming in plastic greenhouses in which large amounts of pesticides are used. After adjusting for age and population of the municipality it was found that orchidopexy rates tended to increase in magnitude as pesticide use increased. Zones, with the highest use of pesticides demonstrating a significantly increased risk of orchidiopexy (OR= 2.32, CI= 1.26-4.29) in comparison with zones with the lowest pesticide use.

e) Pesticide Applicators

Epidemiologic studies in New Zealand[153;236], Minnesota[146;183] and India[22] have examined the risk of birth anomalies in the progeny of pesticide applicators. Importantly, these studies looked at populations that are more homogeneously exposed, often to higher doses, than other occupations. Specific studies have focused on male pesticide applicators who mixed organochlorinated pesticides with their bare hands[22] or were reportedly drenched with chemicals while spraying[153]. Other occupational groups such as farmers and gardeners are more likely to be exposed to a combination of chemicals, including fertilizers and petroleum products, and may be exposed less frequently throughout the year.

Studies of pesticide applicators have revealed a significant increase in the risk of any congenital anomaly[22;183;146], central nervous system anomalies[146], musculoskeletal anomalies[183], and circulatory/respiratory anomalies[183]. In a cross-sectional study, Garry et al.[146] found that applicators who applied fumigants had an increase risk of central nervous system defects or neurobehavioral problems (OR=2.5, 95% CI=1.2-5.1) and pesticide applicators were more likely to have a child with a birth defect if the child was conceived in the spring, when herbicides are routinely applied (p=0.02). Rupa et al.[22] found that male pesticide sprayers and mixers who worked in the cotton fields of India had over 4 times the risk of congenital defects in their offspring than unexposed couples from the same socioeconomic group. Conversely, Smith et al.[153;236] did not find an increase in the risk of congenital anomalies in the offspring of fathers who sprayed 2,4,5-T any time during the calendar year in which the preganancy occurred, nor in the previous calendar year. The power of this study may have been limited as the authors analyzed the birth outcomes of only 427 exposed men.

2.3.2.2 Pesticide Users

Many studies have gathered generic information on pesticide exposures at work or home. Often no specification was provided as to the type of work or type of pesticide in which the parent was exposed. Such studies have shown an increase in the risk in any congenital anomaly[177] and cardiovascular anomalies[237], as well as stillbirth or early neonatal death[173], due to occupational exposures to pesticides. Gibson et al.[177] found a pronounced increase in any birth defect in the offspring of public (OR=3.38, 95% CI=1.86-6.14) and private (OR=1.91, 95% CI=1.11-3.29) patients in Australia who were exposed to pesticides at the time of conception. Correa-villasenor et al.[238] examined 37

cases of a specific cardiovascular anomaly, Total Anomalous Pulmonary Venous Return (TAPVR), and found that exposure to pesticides in the mother's lifestyle, hobbies or work nearly tripled the odds of this anomaly in her offspring (OR=2.74, CI=1.17-6.44). Two studies that have examined the use of pesticides in gardening during a critical exposure window, observed an elevated odds of abdominal wall defects (OR=2.13, 95% CI=0.97-4.71)[166] , conotrunctal heart defects (OR=3.1, 95% CI=1.3-7.3), and neural tube defects (OR=2.9, 95%CI=1.3-7.3)[129]. Another study in Spain[149] found that father's exposed to pyridil derivatives during the 3 months prior to conception and one month after conception were almost 3 times as likely to have a child with any birth defect (OR=2.77, 95% CI=1.19-6.44).

A number of other studies looking at occupational or hobby exposures to pesticides have found no association with any type of congenital anomaly[144;162;169;172;178;239;240], cardiovascular anomalies[168;170;171], conotruncal heart defects, limb deficiencies or orofacial clefts[145], congenital diaphragmatic hernia[239], or central nervous system anomalies[129;165;210].

a) Herbicide Use

Several years after a report indicated that men producing the herbicide Oryzalin had an unusual incidence of heart deformities[148], Loffredo et al.[147] found that mothers who used weed killers in the period 3 months prior to conception or in the first trimester pregnancy were almost 4 times as likely (OR=3.6, 95% CI=1.6-8.2) to have offspring diagnosed with heart disease (specifically, transposition of the great arteries) in the first year of life. In addition, if exposures occurred exclusively in the period 4 to 6 months prior to pregnancy, the risk increased (OR=4.7, 95% CI=1.6-13.6). Yet, other studies

have shown no increase in birth defects for fathers occupational exposed to the active ingredients 2,4,5-T[153;154;236], MCPA[149] or the chemical family chlorophenoxy herbicides[149].

b) Insecticide Use

Some studies have looked specifically at the teratogenic risks of insecticides. Initial attention was sparked by a case study reported by Hall et al.[150] The authors described two cousins who were conceived within 8 days of each other, both born with coarctation of the aorta. Their parents went on a camping trip in the mountains when the mothers were between 6 and 8 weeks pregnant. Large amounts of insect repellents and insecticides containing n-octyl bicycloheptene dicarboximide, piperonyl butoxide, allethrin, pyrethrins, diethyl toluaide, 2-2 dichloroviyl dimethyl phosphate (OFF insect repellent, Raid Insect Spray, Raid Mosquito Coil, Shell Vapona Insect Strip) were used to combat insects. This was the only time that the mothers were together during their pregnancy, and there was no family history of this anomaly. Another case study described a woman working in Africa who applied 25% DEET to her arms and legs once or twice a day through the duration of her pregnancy. In the first month of life, her child was observed to have statomotor retardation, muscular hypotonia, central hearing loss, and strabismus[241].

Three case control studies have since looked specifically at home insecticide use[129;145;173]. The first study[173] observed that home pesticide application for insects such as ants and cockroaches in the first two months of pregnancy resulted in a slight increase in the risk of stillbirth or early neonatal death due to congenital anomalies (OR=1.7, 95% CI=1.0-2.9). This study controlled for several other risk factors, but there was a 2 to 4

year gap between the birth of the child and the questionnaire, increasing the likelihood of recall bias. The second study[129] investigated approximately 1,300 infants delivered to women living in California counties between 1987 and 1989. Using the California Birth Defects Monitoring System, cases of NTDs, conotruncal heart defects, limb defects and orofacial clefts were identified. Controls were defined as infants born alive in the same geographical area and time period as the cases. In an interview, the mother was asked to provide information on pesticide use one month prior to conception and 3 months after conception. No significant increase in risk was seen for any of the birth anomalies for mothers who carried out pesticide treatments in the home or pet flea treatments in the home during the defined window. A slight increase in risk was found for insect fogger use and cleft palate in the presence of other birth anomalies (OR=2.0, 85%CI=1.0-4.4), and insect repellent was related to an increased risk for conotruncal defects (OR=2.2, 95%CI=1.3-3.9). Conversely, Shaw et al.[145] found no association between a variety of birth defects and maternal exposure to insecticides at work during the month prior to conception and the first trimester of pregnancy including conotruncal heart defects, limb deficiencies, and orofacial clefts.

2.3.2.4 Biomarkers of Exposure

To date, only two studies have analyzed the association of serum or lipid pesticide levels and birth anomalies. Hosie et al.[123] measured organochlorine levels in fat samples from 18 patients undergoing orchidiopexy because of unilateral (n=8) or bilateral (n=10) cryptorchidism. These were compared to the levels found in 48 children undergoing other surgical procedures. Significantly increased levels of the pesticide heptachlor were seen in patients with cryptorchidism. Unfortunately, only the mean age of the control

group was reported, raising questions about their disease status, reason for surgery, and how they were chosen for the study.

The second study by Longnecker et al.[124] set out to determine if maternal serum DDE levels, the most common metabolite of DDT, were associated with male reproductive defects. Pregnant women were recruited between 1959 and 1966 as part of the Collaborative Perinatal Project. Using a nested case-control study design, maternal DDE serum levels were not found to be significantly association with cryptorchidism, hypospadias, or polythelia (extra nipples) in male offspring. However, there was a borderline association with polythelia in the highest exposure group (≥85.6 ug/litre) (OR=1.9, 95% CI=0.9-4.0).

2.3.3 Discussion

The literature surrounding birth defects and parental pesticide exposure does not reveal consistent results. The heterogeneity in research findings may in part be due to differences in subject characteristics and exposure levels (nature, modality and assessment). The most important limitation of most studies was the imprecise nature of the exposure assessment. Several studies did not specify the type of pesticide, the method of application, frequency of application, or the exposure time window. Other studies used an ecological indicator of exposure, severely limiting the interpretation of their findings. The degree of association observed at the group level may not necessarily reflect the individual level of association. Tremendous variation of exposure would have occurred among individuals, depending on factors such as whether they were outdoors during the time of spraying, and their length of residence in an "exposed" village or area.

Additionally, using surrogate measures of exposure may further distort the association and limit the degree of control over confounding variables[242].

Those studies that were the most refined in terms of their exposure assessment[123;124;145;147;149;155] showed some positive associations between pesticides and birth defects. Associations have been observed between any birth defect and paternal occupational exposure to pyridil derivatives[149], transposition of the great arteries and maternal exposure to rodenticides and herbicides[147], orchidiopexy rates and adipose tissue levels of heptachlor[123], and eye and genital defects with paternal exposure to chlorophenate wood preservatives.[159]. A borderline association was seen between polythelia and maternal serum DDE concentrations in the third trimester of pregnancy[124].

Another common problem in the literature was the measurement of health outcomes. A minority of studies used population based registries that carefully classify birth defects. Other studies utilized less accurate methods to identify cases, such as birth registries and birth certificates, or they relied on self-reports by the study subjects. Investigators have found that the accuracy of birth certificate data in reporting birth anomalies can range from 12 to 100%[243]. Other limitations were the vagueness of the outcome measures (i.e., "any birth defect) and the uncertainty surrounding the validity of using disease classifications. Using the category "any congenital anomaly" as an outcome measure has been criticized for its vagueness[244]. Olsen et al.[245] note that disease classification is based on certain principles, but not on principles associated with causal research. It is not known, for example, whether different anomalies such as Down's syndrome, hypospadias, and cleft lip have the same causal agents[244].

Other challenges in reproductive epidemiology involve missed birth defects. The prevalence of birth defects is derived usually from fetuses that survive until birth, and does not consider malformations that are part of syndromes incompatible with fetal life, or those electively aborted due to prenatal screening[245]. It is estimated that between one fifth and three quarters of all conceptus are naturally aborted, many of which possess chromosomal abnormalities[50].

Many of the studies had very small sample sizes, limiting their power to detect an association. Low response rates can also introduce selection bias, arising from systematic differences in characteristics between those who took part in a study and those who do not[246]. Those that agreed to participate may have been more concerned about their health or may have had more family health problems than those who did not participate.

The inconsistencies across studies may in part be due to the fact that many of the studies focused on acute pesticide exposures, ignoring the effects of persistent pesticides that can accumulate over time. As well, agricultural workers are exposed to a variety of other exposures such as dust, molds, mycotoxins, zoonoses which may have had an impact on the outcome of interest.

Finally, one cannot ignore the possible influence of publication bias. Publication bias has been described as a tendency for studies that report statistically significant results to be published[247]. However, given the large number negative findings found in this review, publication bias may be of less concern here than in other contexts..

CHAPTER 3: LITERATURE REVIEW PART II

3.0 *In utero* Pesticide Exposure & Child Health

There is growing evidence to suggest that fetal and early life events can affect health later in life[24]. A number of pesticides have shown both neurotoxic[8-11] and immunotoxic[12] effects in laboratory animals and humans. The effect of such exposures on the development of the human immune and nervous systems remains elusive.

3.1 Developmental Neurotoxicity

3.1.1 Neurodevelopment

Compared to other organ systems, the developing nervous system is more vulnerable to insults from toxic agents. CNS effects are seen with several known teratogens including rubella, methylmercury, lead, alcohol, retinoids (vitamin A) and thalidomide, often at lower does than required for the anomalies of other body parts[248].

The development of the human central nervous system involves the production of 100 billion nerve cells and 1 trillion glial cells[14]. After being generated, these neurons undergo migration, synaptogenesis, selective cell loss, and myelination in a uni-directional manner. Any alteration at one stage will cause changes at subsequent stages[14]. Rodier[248] explains that toxic agents have the ability to interfere with specific developmental processes including neuron proliferation, cell migration, synaptogenesis, cell death, transmitters and receptors, trimming of connections, myelination, and the development of the blood-brain barrier. Empirical evidence suggests that the vulnerable perod for toxic insults to the developing nervous system extends from early gestation to adolescence in humans and animals[249].

a) Neurotoxicity

A number of pesticides are known to cause neurotoxic effects in adults. Organophosphate pesticides inhibit the enzyme cholinesterase which inactivates the neurotransmitter acetylcholine. The buildup of acetylcholine at the cholinergic synapses causes symptoms related to the autonomic (abdominal cramps, nausea, diarrhea, salivation, miosis) and the central nervous (dizziness, tremor, anxiety, confusion)[11;250] systems. Studies of workers or individuals with suspected and confirmed organophophate poisonings have shown decreased performance on visual attention and mood-scale tests, intellectual functioning, academic skills, flexibility of thinking, abstraction, motor speed, and coordination[251;252].

Prenatal exposure to organophosphate pesticides has been associated with lowered acetylchloine in the neural tissue of rodents[253] . Moreover, Banerjee et al.[254] conducted an *in vitro* study of human fetal brain tissue, which demonstrated the ability of commercial organophosphates and carbamates to significantly alter acetylcholine activity. Experimental studies have suggested that the critical period of exposure to the organophosphate pesticide chlorpyrifos extends across the pre and postnatal periods[10]. Initially, chlorpyrifos acts by impairing the development of neurons, and later by affecting glia cells (astrocytes, oligodendrocytes, microglia), which are critical for brain development[255;256].

b) Hormonal Roles in Brain Development

Thyroid hormones are vital for homeostatic regulation and metabolism. The thyroid gland produces the hormones thyroxine (T4) and triodiothyronine (T3). Eighty percent of the production is T4, while 20% is T3[257]. When T3 and T4 levels are low, the pituitary gland produces thyroid stimulating hormone (TSH), which then stimulates the

thyroid gland to produce more T3 and T4. Once produced, thyroid hormones are transported through the blood by proteins (T4-binding globulin, TBG). The unbound T3 and T4 are referred to as "free T3 and T4", which are metabolically active. Karmaus[257] described 5 targets for thyroid hormone disruption: (1) the production of T3, T4; (2) the transport of T3 and T4; (3) the metabolism of T3 and T4; and (4) the feedback and production of TSH and; (5) blockage of the T3 and T4 cell receptors. Evidence has shown that non-toxic doses of environmental contaminants have the ability to mimic the action of the thyroid hormone[62]. In a literature review on halogenated organic compounds (HOCs) and thyroid disorders, Karmus[257] identified 13 reports that showed HOC-related increases or decreases in T3 or T4 levels.

Thyroid hormones are essential for normal brain development. It is the first endocrine gland to develop, starting around 24 days after fertilization[92]. Thyroid hormones control neuronal and glial proliferation in specific brain regions, regulate neuronal migration and differentiation, including the development of neuronal connectivity and myelination, and orchestrate the timing of specific developmental events and signals in the developing brain[258]. Subtle changes in thyroid function in pregnant woman can affect the neurological development of her offspring[259]. Cretinism and maternal hypothyroxemia are two pathological conditions that demonstrate the importance of thyroid hormones during fetal development. Endemic cretinism, a condition that is usually associated with severe iodine deficiency during fetal development, can result in severe mental retardation, spastic dysplasia, and problems with gross and fine motor control in offspring[258]. Other adverse outcomes include deaf-mutism, perceptive hearing loss, and speech problems[62]. Interestingly, the incidence of

mental retardation in children born to women with hypothyroidism can be reduced through early thyroid screening and replacement therapy with thyroxine[260].

3.1.2 Epidemiologic Studies

Few epidemiologic studies have addressed the neurotoxic effects of *in utero* or early childhood pesticide exposures. One study by Garry et al.[146] found an increased risk of neurodevelopmental effects in the offspring of pesticide applicators exposed to phosphine and glyphosphate.

In line with this, an anthropological study in Mexico found that aboriginal pre-school children exposed to pesticides under-performed on several cognitive and developmental tests[17]. The Yaqui have two populations that share economic, genetic, cultural, and social traits. The only difference is that the Yaqui who live in the foothills and ranch use little or no pesticides, while those who live in the valley engage in agriculture and use high volumes of pesticides. The farmers in the valley plant two crops a year, with pesticide application up to 45 times per crop between planting and harvesting. Guillette et al.[17] conducted a small ecological study on children aged 4-5 years living in Mexico and found that those living in an agricultural region (n=33) had lower scores on gross motor skills (p=0.034), fine eye-hand coordination (p=0.009), and 30 minute recall (p=0.027). However, given the small numbers of subjects and the absence of risk analyses in the repor, no conclusions can be drawn.

Others have postulated that organochlorines in breastmilk may have detrimental effects on the reflexes of suckling infants. Rogan et al.[261] reported that elevated levels of DDE in breast milk (>4ug/g lipid) was associated with suppression of reflexes in neonates. However, DDE was not confirmed to be the causative factor.

3.2 Developmental Immunotoxicity

It is well known that hormones affect immune function. Differences in immune function have been seen in pregnant and non-pregnant women, individuals exposed *in utero* to DES, and females are more susceptible to auto-immune diseases than males[262]. It has therefore been postulated that chemicals in the environment that mimic or block hormones could potentially alter immunity. Several suspected endocrine toxicants have been shown to alter immunity, although the mechanism by which this occurs remains unclear.

3.2.1 Animal Studies

In humans, immune development begins early in embryonic life and continues throughout the early postnatal period. A number of pesticides, including hexachlorocychohexane, chlordane, diazinon, DDT, carbofuran and hexachlorobenzene, have been observed to induce developmental immunotoxicity in mice [263]. *In utero* exposure to DDT has altered primary and secondary humoral immune response, immunoglobulin production, histamine concentrations, and mast cell numbers in animals[262]. Further, these adverse effects are sustained throughout life. Long-term depression of the immune system was seen in rodents exposed to the insecticide chlordane during the gestational period; such effects were either not observed or were reduced in exposed adult mice[263].

3.2.2 Epidemiologic Data

Few human studies have examined the effects of *in utero* or early postpartum exposures to pesticides and subsequent immune function. Vietnam veterans exposed to Agent Orange reported more child health conditions among their offspring (OR=1.3, 95%

CI=1.2-1.4)[223]. More than half of the reported childhood health problems were respiratory diseases (mostly asthma and pneumonia) and diseases of the ear (mostly otitis media). When children with serious health problems such as birth defects or cancer were excluded from the analysis, the overall crude odds ratio was 1.2 (95% CI=1.1-1.3). As well, elevated ORs were seen for anemias (OR=2.0, 95% CI=1.2-3.3), diseases of the skin (OR=1.5, 95% CI=1.1-1.9), rash (OR=2.3, 95% CI=1.1-4.9), and allergies (OR=1.6, 95% CI=1.2-2.1).

Dewailly et al.[264] measured organochlorine concentrations in breast milk fat of Inuit women as an index of *in utero* exposure to these substances. Their data showed a relationship between middle ear infections in children and prenatal exposure to organochlorines, specifically the pesticide metabolite DDE.

Other environmental contaminants have been shown to alter immune function in humans following *in utero* or postnatal exposures. Infants born to Taiwan women exposed to polychlorinated biphenyls and polychlorinated dibenzofurans through the consumption of contaminated rice oil had an increased prevalence of middle ear and pulmonary diseases[261;265].

3.4 Summary

The level and timing of exposure to potential endocrine toxicants are important determinants of the formatioin and function of many different tissues. According to the World Health Organization[98], human health research on endocrine disrupting compounds lacks exposure data during critical periods of development that influence later function in adult life. It is well documented in animal studies that *in utero* exposures to environmental toxicants can affect the immune and neurological system, but few human

studies have examined such effects. Birth defect studies are numerous but most lack adequate exposure assessment during distinct exposure windows.

The Ontario Farm Family Health Study (OFFHS) provides a unique opportunity to analyze these health outcomes and add to the current literature in this area. Data pertaining to direct and indirect farm exposures to pesticides is available. As well, 17 pesticide unit variables relating to specific pesticide classes, families, and active ingredients have been derived along with the month and year of use. With this data, we are able to evaluate the effects of exposures occurring during the pre-conception and *in utero* periods.

CHAPTER 4 - METHODS I: The Ontario Farm Family Health Study

4.0 General Design

The Ontario Farm Family Health Study (OFFHS) was established with the primary objective of retrospectively assessing the relationship between phenoxy herbicides and spontaneous abortion[25]. Ontario was chosen as the study area due to the amount and diversity of farms in this province. According to data from Statistics Canada, Ontario had the largest number of farms of any Canadian province (n=72 713) [25].

4.1 Sampling Method

The sampling frame consisted of all farm operations in Ontario as reported in the 1986 Census. Farms were restricted to family run farms with reported sales of agricultural products of $50 000 or greater in 1986 and were excluded if they were:

1. a legally constituted company with most of the shares owned by some other person(s) or business;
2. institutions;
3. community pastures;
4. land operated privately for an estate or trust company; or
5. cooperative farms.

Tobacco farms were also excluded due to their small numbers and the distinct types of pesticides that they use[25]. All farms meeting the criteria (below) were contacted in order to determine eligibility of the couples living on the farms.

Farms Identified from 1986 Census of Agriculture for Ontario for the OFFHS[25]	Pool available
Farms with 100 or more acres of grain (wheat, oats, barley, mixed grains, and/or rye) AND sprayed or dusted some farm land with chemicals to control weeds only.	2 612
Farms with 30 or more acres of potatoes, fruits and/or vegetables AND sprayed or dusted some of their farm land with chemicals to control insects or disease.	1 474
Farms that reportedly did not spray or dust any of their farm land with chemicals to control weeds, insects or disease.	3 293

4.2 Eligibility Criteria

A screening questionnaire was developed and administered by telephone to assess the eligibility of the farms[25]. To be eligible for inclusion in the study, couples had to be married or living as married, living year-round on the farm operation, and the wife had to be 44 years of age or younger. In total there were 2,946 eligible couples identified.

4.3 Study Questionnaires

Three questionnaires were mailed to each farm family in order to gather information on health, pesticide use, and farm activity exposures. Form A was addressed to the farm operator and collected information on farm operations, as well as present and former pesticide use on the farm. Form B was addressed to the husband and gathered information on basic demographic, socioeconomic, lifestyle, medical history, as well as his activities and chemical exposures on the farm. Finally, form C was completed by the wife and collected similar information to form B, but also included a complete reproductive history of her first 5 pregnancies (See Appendix H).

4.3.1 Pesticide Exposure Information

All three questionnaires collected detailed information on pesticides used on crops, livestock, pets, and around the farm yard and home. As well, detailed information on farm operation activities and the use of protective equipment was provided by the husband and wife.

4.3.1.1 Reported Pesticide Use

The farm operator (Form A) provided detailed information on agriculture chemicals used on the farm's six largest crops sown or harvested in 1991. The crop name, chemical name, reason for use, total area sprayed or dusted, total quantity used, method of application, months of application, and number of years of use was requested. In addition, the questionnaire asked for the following information on historical farm chemical use:

> *Q 22: Have there been any changes in the types of agricultural products grown or livestock raised since you started working on this farm?*
>
> - *If yes: please list the agricultural products or livestock that you used to have on the farm but don't have any more and the years that you had these animals or crops.*
>
> *Q23: Are there any chemicals that you regularly used in previous years, but have since stopped using?*
>
> - *If yes: Please supply the name of the chemical, years used, and crops used on.*
>
> *Q30: If you have ever used any of the following chemicals on your farm, please write beside that chemical the years in which you used it. List of 60 different chemicals and asked to provide the years of use.*
>
> *Q31: Are there any other chemicals that are used (or have been used) on this farm but have not been asked about in this questionnaire? Provide chemical name, reason for use, months used, years used.*

Forms B (husband) and C (wife) asked for information pertaining to chemical activities on the farm and around the home. For each chemical activity, the name of the chemical (up to two), reason for its use, months of use, and method of application was requested.

- *Do you use chemicals to spray or dust flowers, shrubs, vegetables or fruit in your family garden?*
- *Do you use chemicals to spray or dust family pets for insect or disease?*
- *Do you use chemicals to control weeds in your yard or lawn?*

4.3.1.2 Reported Farm Operation Activities

Both forms B and C asked the husband and wife to complete a checklist relating to their farm operation activities over the past five years. The frequency (number of days), intensity (never, occasionally, regularly), and months during which they were involved in these activities was requested. For the purposes of this analysis, the assumption will be made that the husband's reported activities extends beyond the 5 year interval and back to the time of the first pregnancy. For the wife, farm activity information was collected for each pregnancy.

- *Direct chemical activities:*

  Mixing or applying chemicals to crops for weed or brush control.
  Mixing or applying chemicals to crops for insect or disease control.
  Mixing or administering chemicals to livestock to control insects & disease.
  Mixing or applying chemicals around the yard and buildings to control weeds and brush.
  Mixing or applying chemicals around the farm buildings to control pests.

- *Other Farm Activities that do not necessarily involve pesticide exposure:*

  Milking cows, plowing, harrowing/disking, cultivating, planting, applying fertilizer, manure, harvesting crops, working with farm livestock, working in the family garden, working in dusty areas, heavy lifting, filling, servicing, and unloading silo.

4.3.2 Protective Equipment

In addition to providing information on pesticide-related activities, both the wife and husband self-reported on their use of protective equipment during pesticide mixing, loading, or application. Further to this, participants were asked to provide the year that they started using such equipment

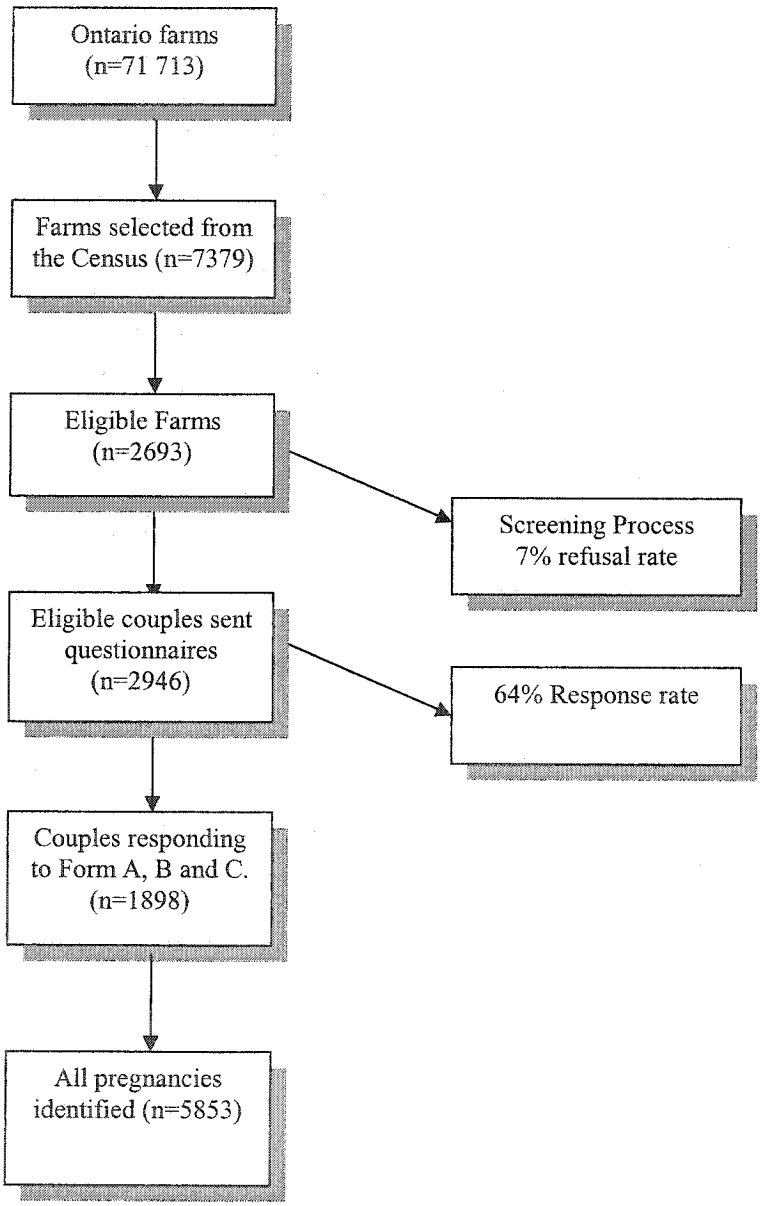
- *Do you mix, load or apply any pesticides (herbicides, insecticides, fungicides, rodenticides, etc) on this farm? If yes, please check the frequency (Never, Occasionally, Regularly) that you use each of the following types of protective equipment and indicate your best guess of the year that you started using it:*

    1. *tractor with a cab for crop spraying*
    2. *plastic, rubber or vinyl gloves*
    3. *face shield or goggles*
    4. *coveralls or overalls*
    5. *plastic or chemically resistant apron*
    6. *respirator or mask with pesticide*

4.4 Response Rate

Of the 2,964 eligible couples that met the eligibility criterion, 64% returned all three questionnaires. The responding couples identified 5853 pregnancies *(See Figure 1)*.

Figure 1: Summary of Recruitment Process



CHAPTER 5 - METHODS II

5.0 Summary of Methods

This thesis examined the effect of parental pesticide exposures during critical exposure windows on birth defects and other child health outcomes. There were 17 different types of pesticide examined. For some of the outcomes the husband's involvement in chemical activities was also considered. Logistic regression and generalized estimating equations were used to developed models linking pesticide exposures to health outcomes. To identify important covariates, several potential risk factors were independently tested for their effect on the outcome. Potential confounders were identified by individually adding those risk factors with crude odds ratios > 1.2 or < 0.8 to the crude (the effect of the exposure on the outcome) or base model (the effect of exposure plus *a priori* covariates on the outcome). If the exposure odds ratio changed by 10% or more, the covariate was retained in the final model *(See Appendix E)*. This chapter gives a detailed description of the eligibility criteria, outcomes, exposure variables, covariates, and analysis methods utilized in this study.

Dependent Variables:	*Definition*
Any birth defect	1=yes; 2=no
Musculoskeletal birth defects	1=yes; 2=no
Frequent ear infections in offspring	1=yes; 2=no
Persistent cough or bronchitis	1=yes; 2=no
Hearing problems in offspring	1=yes; 2=no
Childhood Epilepsy	1=yes; 2=no
Childhood Allergies or Hayfever	1=yes; 2=no
Childhood Asthma	1=yes; 2=no
	1=yes; 2=no
Independent Variables:	
Reported farm chemical use during a defined exposure window	1=yes; 2=no
Farm activities involving direct chemical exposure & reported farm chemical use during a defined exposure window	1=yes; 2=no
Maternal Risk Factors	Dichotomous, Categorical
Paternal Risk Factors	Dichotomous, Categorical

5.1 Dependent Variables

5.1.1 Birth Defects

As part of their reproductive histories, farm wives were asked to report on any pregnancies that resulted in a birth defect(s) diagnosed at birth, or since birth. If a pregnancy did result in a birth defect, the subjects were asked to describe the birth defect(s). A total of 118 birth defects were described and subsequently cataloged into appropriate ICD-9 codes by the author of this thesis (See appendix B). These codes were checked for accuracy by a practicing obstetrician. Analyses were conducted on pregnancies ending in one or more birth defect (n=108), as well as musculoskeletal defects (ICD-9: 754.0-756.9) (n=43).

5.1.1.1 Inclusion/Exclusion Criteria: Birth Defects

The following pregnancies were excluded from the analysis (see Figure 2):

- 110 pregnancies with missing data on outcome, delivery data and/or gestational age at delivery;
- 1649 pregnancies that occurred when the woman was not living on the study farm and had unknown exposure status;
- 27 pregnancies for which the study husband may not be the father (mother reported more than one marriage and the pregnancy occurred more than 1 year before the date of marriage to the husband); and
- 395 miscarriages, 31 stillbirths, 13 induced abortions, 36 ectopic pregnancies, 5 hydatidaform moles, 118 current pregnancies.

In addition, 15 pregnancies were ignored because the mother did not answer the question relating to birth defects, and did not describe any type of birth defect, leaving 3,412 pregnancies for the analysis. When analyzing musculoskeletal defects, the 65

pregnancies ending in other birth defects were excluded from the analysis leaving a total of 3,347 pregnancies.

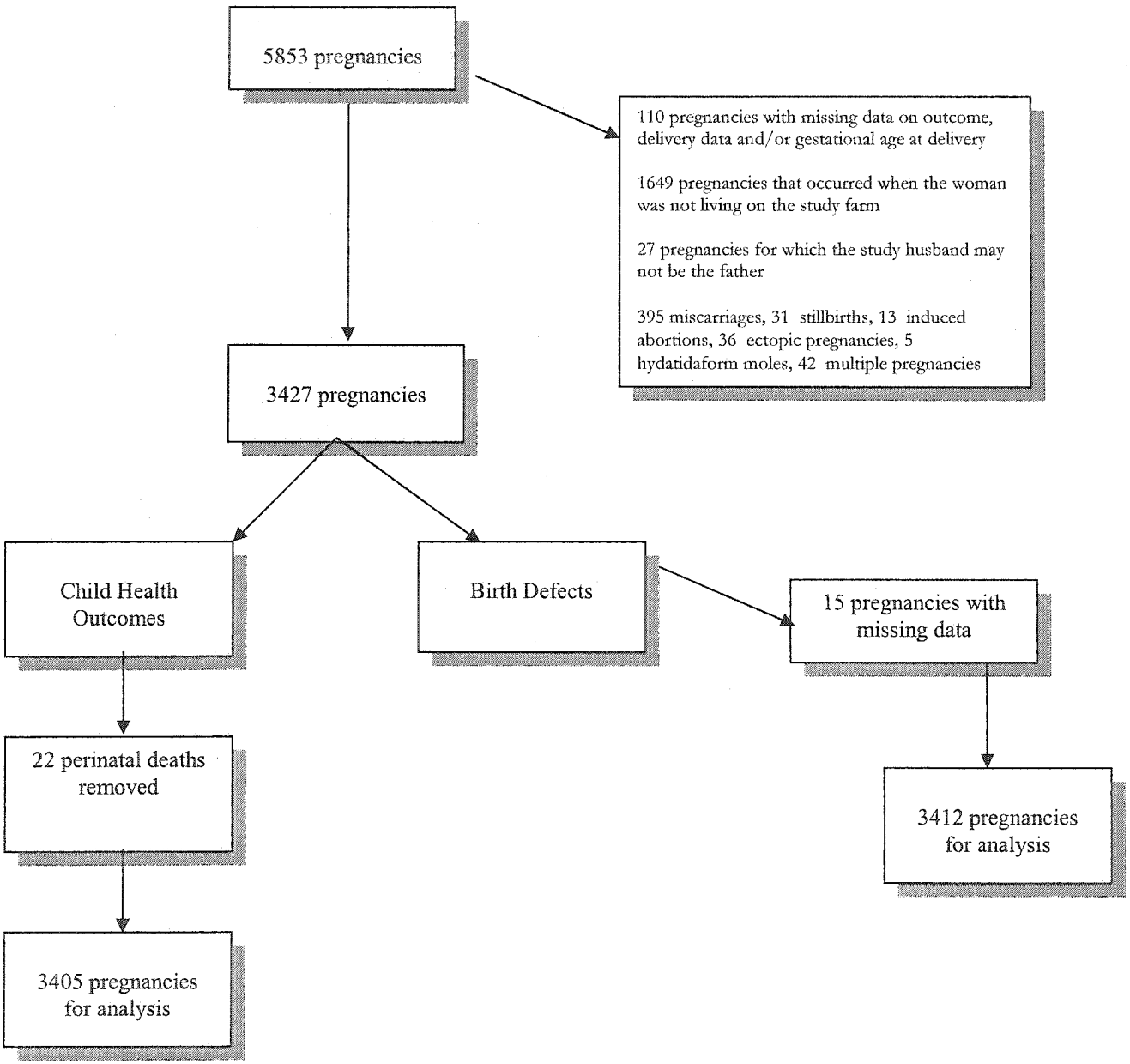
5.1.2 Other Child Health Outcomes

Farm wives were also asked to self report "if a doctor had ever told them" if their child had the following health problems: epilepsy, chronic bronchitis or cough, hearing problems, asthma, hayfever or allergies, and frequent ear infections.

5.1.2.1 Inclusion/Exclusion Criteria: Child Health Outcomes

A similar inclusion/exclusion criteria was used for the analysis of child health outcomes. However, perinatal deaths (children who died in the first year of life) were also excluded from the analysis.

Figure 2: Inclusion/Exclusion Criteria



5.2 Independent Variables

5.2.1 Pesticide Exposures

The exposure assessment strategy employed in this study was designed with the intention of capturing direct and indirect exposures during three different exposure windows: the preconception period (3 months prior to conception and the conception month), the post-conception period (the first trimester of pregnancy), and the entire pregnancy interval beginning at conception. Chemical exposures were derived from self-reported farm activities and reported farm pesticide use.

5.2.1.1 Data Set-up

In prior analyses all chemical data pertaining to pesticide use in forms A, B and C, and dates of use were extracted into a pesticide history file. In this file, each observation corresponded to a pesticide product used on a farm. If the product was reported more than once in forms A, B or C, it contributed more than one observation. The active ingredient was then identified for each pesticide product using a database of registered pesticide products in Canada. The active ingredient and chemical families were identified for those pesticides that were most frequently used on the farm and those that had reported reproductive effects according to the literature[26]. Subsequently, the active ingredients were categorized into chemical families and four major classes of use: herbicides, insecticides, fungicides, and other miscellaneous products. In total, 17 pesticide exposure variables were developed (see below).

Table 4: 17 Pesticide Exposure Variables

Active Ingredients (AI)			Chemical Families	Chemical Classes
AI	Chemical Class/ Family	Some Other Common Names where AI found		
1. Atrazine	Herbicide Triazine derivative		10. Phenoxy Acetic Acid Herbicides	14. Herbicides
2. Captan	Fungicide N-trihalomethylthio		11. Triazine Herbicides	15. Insecticides
3. Carbaryl	Insecticide Carbamate		12. Organophospate Insecticides & Herbicides	16. Fungicides
4. Cyanazine	Herbicide Triazine derivative		13. Thiocarbamate Herbicides & Fungicides	17. Other Pesticides
5. 2,4-D	Herbicide Phenoxyacetic acid derivative			
6. 2,4-DB	Herbicide Phenoxyacetic acid derivative			
7. Dicamba	Herbicide Benzoic Acid	Divel, Killex, Weed-away		
8. Glyphosate	Herbicide	Round-up		
9. MCPA	Herbicide Phenoxyacetic acid derivative			

5.2.1.2 Imputation Method

An imputation process was used to deal with chemical exposures with missing dates (either months, years, or both). During data setup, if the month or year of a particular application of a pesticide was not reported, it was imputed that the exposure occurred in a particular calendar month or year if at least 75% of all the applications of that pesticide, in the study population, reported use in that particular month or year.

5.2.1.3 Critical Exposure Windows

Previously, variables were created that matched the months of chemical use on the farm to the months leading up to and during each pregnancy that occurred on the

farm. Similarly, variables relating to farm chemical activities during the months prior to and after conception had previously been derived.

i) Pre-conception and Post-conception Window

For the analysis of birth defects, SAS array statements were used to create 17 pesticide exposure variables that identified pregnancies with reported farm chemical use during the pre-conception and the post-conception period. Unexposed pregnancies were those in which the farm did not report using the pesticide during the same time window. Similar methods were used to create exposure variables for fathers also involved in farm chemical activities during these same time periods *(See Table 5)*.

ii) Entire Pregnancy Interval

Pesticide exposures during the entire pregnancy period were considered in the analysis of the child health outcomes (frequent ear infections, persistent cough or bronchitis, hearing problems, epilepsy, allergies or hayfever and asthma). Using SAS array statements, an exposed pregnancy was defined as those that had reported pesticide use anytime during the pregnancy interval including the conception month. Unexposed pregnancies were those with no reported pesticide use during this time period *(See Table 5)*.

Table 5: Exposure Groups

Exposure Groups	Time Window	Comparison Group	Outcomes
Reported pesticide use on the farm	Pre-conception	No reported use of that type of pesticide during the time window	1. Any birth defect 2. Musculoskeltal defects
	1st trimester	No reported use of that type of pesticide during the time window	1. Any birth defect 2. Musculoskeltal defects
Reported pesticide use on the farm and chemical activities by husband	Pre-conception	No reported use of that type of pesticide or chemical activities by the husband	1. Any birth defect
	1st trimester	No reported use of that type of pesticide or chemical activities by the husband	1. Any birth defect
Reported pesticide use on the farm	Pregnancy	No reported use of any pesticide during pregnancy	1. Frequent Ear Infections 2. Persistent Cough or Bronchitis 3. Hearing Problems 4. Allergies 5. Asthma
		No Reported use of that type of pesticide during pregnancy	1. Epilepsy

5.2.2 Other Covariates: Birth Defects

A number of other factors known or suspected to be related with birth defects were considered separately for their impact on the outcome. They included:

a) demographic factors (income, education, parental age, and ethnicity);

b) pregnancy factors (weight gain, caffeine, and alcohol consumption, parental smoking during pregnancy, maternal hyperthermia, medical problems during pregnancy, and parity);

c) other factors (maternal age at menarche, child's gender, number of years the couple had lived on the farm, other hazardous jobs off the farm as discussed n Appendix D., and the number of years of recall).

The following variables were derived for use in the analysis.

Income

Total income, including yearly net farm income plus other sources of income, was collapsed into three categories using the SAS procedure PROC rank.

Education

Maternal and paternal education was collapsed into two categories: less than grade 12 and greater than or equal to grade 12.

Ethnicity

Due to low numbers, ethnicity was collapsed from 13 different ethnic groups into 2 categories: one group which included European descendants and the other which including Chinese, Black and other ethnic groups.

Parental age at time of conception

Originally, maternal and paternal age at the time of conception, were continuous variables. These were stratified into 3 categories: less than 25 years, 25 to 29 and greater than or equal to 30.

Lifestyle factors during pregnancy

In prior analyses, two variables had been created for the consumption of 3 or more cups of tea or coffee during the first trimester of pregnancy. A new dichotomous variable was created to describe the consumption of 3 or more cups of caffeinated beverages during the first trimester. Other variables had also been previously derived for alcohol, smoking, crack, and marijuana use during the first trimester. When cell

frequencies were adequate (≥5 cases per cell) these covariates were considered in the analysis.

Maternal medical problems during pregnancy

Specific medical problems during pregnancy are known to increase the risk of birth defects including thyroid disorders and diabetes. Mothers provided the year of diagnosis of several different health outcomes. A dichotomous variable was created indicating those mothers who were diagnosed with the illness prior to the conception year. In addition, maternal hyperthermia has been found to be associated with adverse birth outcomes. Originally maternal fever during pregnancy was defined by trimester. Due to the limited numbers in the data set, this variable was collapsed to include fever anytime during pregnancy verses no fever.

Parity

The birth number of the child was analyzed for its effect on the outcome. The women recorded information on their first 5 pregnancies. Given that few women had more than 3 pregnancies, parity was collapsed into 3 categories: 1, 2, and 3 or higher.

Weight gain and body mass index (BMI)

Weight gain during pregnancy was originally a continuous variable. This was subsequently categorized into 3 categories: <20, 20 to 40, and >40 lbs gained during pregnancy. Several studies have shown that maternal obesity (≥30 kg/m^2) increases the risk of several types of birth defects[266]. The National Institute of Health has defined underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (≥30 kg/m^2) according to body mass index[267]. A body mass index was calculated for each woman using her usual height and usual weight. Due to small

numbers, only three BMI categories were created (<20, 20-29, >29) identifying underweight and obese women.

Other jobs off the farm

Variables had previously been derived for maternal and paternal employment at a job site off the farm. The kind of work, product produced, and years of employment were subsequently categorized into pesticide-related jobs and other hazardous jobs (see appendix D). The years of work were used to determine if the parent worked at the job during a year in which the couple was trying to conceive or was pregnant: 0 = no job during the interval, 1 = pesticide exposure job during the interval, 2 = hazardous, non-pesticide job during the interval, 3 = other job, non-hazardous and non-pesticide, during the interval, and 9 = indeterminate (hazardous or pesticide job, but indeterminate time period). For the purpose of this analysis, indeterminate values (value = 9) were considered to be missing values.

Protective equipment

The use of protective equipment (see section 4.4.1.3) would have modified the subject's exposure to pesticides during these activities. The regular use of any protective equipment prior to the year of conception was considered in the analysis for its effect on the exposure odds ratio.

Other potential covariates

Other derived covariates included: the year the mother attained menarche, the year the couple moved on the farm and the numbers of years of recall since the child's conception. These continuous variables were categorized into tertiles using the SAS procedure PROC RANK.

5.2.3 Other Covariates: Child Health Outcomes

The same covariates were considered in the analysis of child health outcomes, but other factors at birth and during the first year of life were also considered.

Child's age at the time of the questionnaire

The age of the child at the time of the questionnaire was considered as a potential covariate. Children were grouped according to developmental stage: infancy (0 to 2 years of age), early childhood (3 to 7 years), pre-adolescence (8 to 12 years), and 12 years and older. If the child died after 1 year of age, the age of the child was determined by subtracting the questionnaire year of death from the the year of birth. It is important to note that this variable does not reflect the child's age at the time of diagnosis.

Breastfeeding

Breastfeeding was originally asked in two questions: did you breastfeed this child; if yes, how any months. A new variable was created to combine this information: 0 = no breastfeeding; 1 = less than a month to 3 months of breastfeeding (neonatal period); 2 = 4 to 6 months of breastfeeding; 3 = more than 6 months of breastfeeding.

Parental history of asthma, allergies, epilepsy

Maternal and paternal history of asthma, allergies, and epilepsy were derived and used as covariates in the analyses of childhood asthma, allergies and epilepsy.

Low birth weight and preterm delivery

Low birth weight was defined as children born weighing less than 2,500 grams verses those born weighing greater than 2,500 grams. Preterm delivery was indicated if the gestational age was less than 37 weeks.

Smoking during the child's first year of life

Parental smoking during the child's first year of life was indicated if current smokers started smoking prior to the delivery year, or if former smokers were smoking during the delivery year.

Other potential allergens

Allergens present in maternal blood have been found to be present in fetal blood circulation giving direct evidence for transplacental materno-fetal allergen transfer[268]. In the analysis of the outcome "allergies or hayfever", crop acreage (grains, hay and fodder, oil seeds, other field crops, fruit trees, vegetables), and livestock (cattle, poultry, and pigs) was used to indicate other potential allergen sources such as dust, pollen, molds that the child may have been exposed to during pregnancy. Additional variables were created if the parent worked with livestock during pregnancy, or if he/she was involved in field work that did not involve pesticide exposure during the pregnancy interval (i.e. plowing, harrowing or disking, cultivating, planting, applying fertilizer, manure, harvesting crops, working in the family garden, or working in dusty areas.

5.2.4 Missing Values

Missing values were handled by using complete-subject analysis[242]. This approach is considered to be valid whenever subjects with complete data are a random sample of all the subjects in the study, and within levels of stratification. It should be noted that this approach can be inefficient if many subjects have missing values because it simply deletes such records from the analysis[242]. Most explanatory variables had fewer than 5% missing values. Exceptions included income (15%), paternal education (6.5%), and paternal smoking during the pregnancy interval (10.6%).

5.3 Statistical Analysis

5.3.1 Overview of Generalized estimating equations

The generalized estimating equation (GEE) method is often used to analyze correlated response data, especially when responses are binary[269]. In general, repeated observations on the same individual at different points in time (different pregnancies from the same mother) tend to be correlated. If the correlation among pregnancies from the same mother is ignored, the analysis would assume there is more information in the data than there is, potentially underestimating the standards errors of the estimated coefficients.

Briefly, the method of maximum likelihood provides values for the unknown parameters that maximize the probability of obtaining the observed set of data. In order to do this the likelihood function must be constructed. This function expresses the probability of the observed data as a function of unknown parameters. The maximum likelihood estimators of these unknown parameters are those values that maximize this function – those that agree most closely with the observed data. Likelihood equations are used to obtain the maximum likelihood estimates[270].

GEE is an iterative procedure using quasi-likelihood to estimate the regression coefficients[271]. GEE use a set of equations that appear to be weighted versions of the likelihood equations. The weights involve an approximation of the underlying covariance matrix* of the correlated within cluster (in the present context, within mother) observations[270]. When observations are uncorrelated, the off diagonal elements, ρ, in a

* the variance-covariance matrix consists of the variances of the variables along the main diagonal and the covariances between each pair of variables in the other matrix positions

covariance matrix are equal to zero. If observations are positively correlated, the variance of weighted combinations involves the 1's on the diagonal and the pairwise nonzero off-diagonal elements in the correlation matrix, making the standard deviations larger[272].

	Child 1	Child 2	Child 3	Child 4	Child 5
Child 1	1	ρ	ρ	ρ	ρ
Child 2	ρ	1	ρ	ρ	ρ
Child 3	ρ	ρ	1	ρ	ρ
Child 4	ρ	ρ	ρ	1	ρ
Child 5	ρ	ρ	ρ	ρ	1

Different "working correlation structures" can be used with GEE. In our analysis we chose the "exchangeable" structure. This structure assumes that the correlation between subsequent pregnancies to be the same, irrespective of the length of time between pregnancies[273]. We felt that this correlation structure would be the most appropriate given that birth defects and child health conditions such as asthma and allergies have genetic risk factors, and it is assumed that the risk would be the same for each offspring. Other correlation structures such as independent (assumes no correlation among subsequent pregnancies) or the first order autoregressive (observations closer in time are more correlated than those farther apart) did not seem appropriate for this study. Especially given that the time interval between pregnancies was not fixed.

There are a few assumption with the GEE method that may be violated in our analysis and should be noted:

1. In our dataset the number of pregnancies per mother was random and the GEE method assumes that they are fixed by design[271]. Therefore, if the number of children per woman is highly correlated with the exposure, even after controlling for the other covariates, some bias could result.

2. When the pattern of missing data at a given time depends on the previous outcomes, the robustness to the choice of the correlation structure does not hold true [271]. In our dataset the maximum cluster size is 5 pregnancies. If the outcome of the first pregnancy influenced whether a woman decided to have more children the number of pregnancies within a cluster would be non-random. For example, if the first born child developed severe asthma, the parents may be less likely to have more children. If this is suspected, Zeger suggests that "if your results when using the independence working model with robust variance estimate are qualitatively different than when you use a particular correlation model, (it is better) to trust the independence result more"[274].

5.3.2 Analysis of Birth Defects

Initially, a brief descriptive analysis was conducted to understand the basic characteristics of the data. A base model was derived that included the primary exposure variable of interest, along with the following known risk factors for birth defects: maternal fever during pregnancy, sex of the offspring, maternal age at conception, and parity. Following this, other potential covariates were identified and their crude odds ratios were calculated with the outcome using logistic regression models fit by maximum likelihood. Those covariates with odds ratios greater than 1.2 or less than 0.8 were added to the base model individually. If the addition of the covariate changed the exposure odds ratio by 10% or more, it was retained and added to the final model[275] (see Appendix E for an example).

Generalized estimating equations were not used in the parameter estimation of birth defects given that the correlation among mothers was minimal (<0.05). When a subset of the birth defect analysis was done using GEEs there was less than a 5% change

in the risk estimates, indicating that the GEE and maximum likelihood estimation (MLE) estimates are approximately equivalent in this case. In addition, the differences in the width of the confidence intervals between the GEE and MLE estimates was often less than 5% (See Appendix G for Sensitivity Analysis).

5.3.3 Analysis of Child Health Outcomes

A similar approach was used for the analysis of child health outcomes. However, generalized estimated equations (GEE) were applied in order to account for the correlation among pregnancies from the same mother. After the final models were constructed gender-specific, and age specific (according to the child's age at the time of the questionnaire) results were calculated for those health outcomes that had sufficient numbers.

CHAPTER 6 - Results I: Birth Defects

6.1 Descriptive Analyses

There were 5,853 pregnancies identified by the responding couples, of which 3,412 were included in the analysis of birth defects. A total of 118 birth defects were identified from 108 pregnanices (3.17%), with 10 pregnancies (0.28%) ending in multiple birth defects. The prevalence of frequent ear infections (14.4%), persistent cough or bronchitis (3.0%), hearing problems (3.6%), epilepsy (0.78%), and allergies or hayfever (9.9%) was estimated from self-reports by mothers on the basis of 3,405 pregnancies. . Few children developed cancer (0.15%) and neurological disorders (0.09%). Previous analyses showed childhood injury rates to be 16 per 1,000, with rates being twice as high in boys than girls[276] .

The percentages of male (50.4%) and female (49.6%) offspring included in the study were nearly equal. The mean age of women was 26.3 years (median age 26 years) at the time of conception; men were, on average, slightly older (mean age 29.0 years, median age 28 years). More women (48.7%) than men (36.1%) had some form of post-secondary education, most mothers (90.4%) and fathers (98.4%) were of European descent, and the median family income was $35 000. Women in the study had lived on the farm for a median of 3 years prior to the conception year, with a range of 0 to 36 years. The median number of years since the pregnancy, at the time of the questionniare, was 8 years, with a range of 0 to 27 years.

The bulk of the chemical data (89%) utilized for the exposure assessment in this study came from the Farm Operator Survey (see Appendix A). The majority of men (81.7%) and most women (62.9%) did not work off the farm during the pregnancy

period. Approximately 53% of the husbands and 5.9% of the wives indicated that they were the farm operators. For most of the pregnancies there was reported use of some type of pesticide on the farm during the pre- or post-conception periods (57.9%). Over half of the fathers reported direct chemical activity (see section 4.3.1.2) during both the pre- (59.1%) and post-conception (52.3%) windows. Conversely, only 2.5% of the women reported being involved in chemical activites duirng these same time windows. In the pre-conception period, the most frequently reported pesticide class was herbicides (27%), while in the post-conception period insecticides were most often reported (22%). Phenoxy herbicides were the most common pesticide family used in both the pre- and post-conception windows (15% and 11%, respectively), and 2,4-D was the most common active ingredient (9% and 6%).

6.2 Assessment of Other Potential Risk Factors

The distribution of other potential risk factors is given in Table 6. The crude risk of self-reported birth defects was found to be increased in women who drank 3 or more cups of tea or coffee in the first trimester, and among those who had a fever during pregnancy. An increased risk was also seen for the first pregnancy (parity=1), male offspring, and women who lived 0 - 1 or 1 - 4 years on the farm, as compared to women who had lived on the farm for more than 4 years. No significant increase in the crude risk of birth defects was associated with parental age, education, income, alcohol intake, or smoking.

Table 6: Birth Defect Odds Ratios in relation to Sociodemographic, Pregnancy and Other Factors

RISK FACTOR	BIRTH DEFECT CASES	TOTAL PREGNANCIES	% PREGNANCIES	CRUDE OR	95% CI
Maternal Age					
<25.0	42	1183	(34.7)	1.00	
25-29	48	1526	(44.7)	0.88	0.58, 1.34
>30.0	18	703	(20.6)	0.71	0.41, 1.25
Paternal Age					
<25.0	20	705	(20.7)	1.00	
25-29	50	1417	(41.5)	1.25	0.74, 2.12
>30.0	38	1290	(37.8)	1.04	0.6, 1.80
Maternal Education					
< Highschool	10	473	(13.9)	0.63	0.32, 1.21
≥Highschool	98	2936	(86.1)	1.00	
Paternal Education					
< Highschool	28	996	(31.2)	0.81	0.52, 1.25
≥Highschool	76	2195	(68.8)	1.00	
Maternal Ethnicity					
Chinese, Black or Other	14	322	(9.56)	0.7	0.40, 1.24
European	94	3047	(90.4)	1.00	
Income					
≤$25 000	47	1280	(44.1)	1.17	0.72, 1.89
$25 000.01 to $45 000	26	767	(26.4)	1.08	0.62, 1.86
>$45 000	27	856	(29.5)	1.00	
Drank 3+ cups of tea or coffee or both in first trimester of pregnancy					
yes	45	1150	(33.7)	1.42	0.96, 2.10
no	63	2262	(66.3)	1.00	
Drank 3 or more alcoholic drinks, any occasion in 1st trimester of pregnancy					
yes	8	213	(6.2)	1.21	0.58, 2.52
no	100	3199	(94.8)	1.00	
Smoked 1+ cigarettes per day in 1st trimester					
yes	13	516	(15.1)	0.76	0.42, 1.37
no	95	2896	(84.9)	1.00	
Father smoked during the time the couple started trying to get pregnant through the post conception interval					
yes	28	796	(26.1)	1.09	0.70, 1.70
no	73	2255	(73.9)	1.00	
Maternal fever during pregnancy verses no fever					
yes	9	158	(4.7)	1.91	0.95, 3.85
no	98	3192	(95.3)	1.00	
Medical Problem during pregnancy					
yes	22	651	(19.2)	1.08	0.67, 1.74
no	86	2748	(80.8)	1.00	
Parity					
Parity=1	41	964	(28.3)	1.70	1.07, 2.69
Parity=2	32	1074	(31.5)	1.18	0.72, 1.91
Parity=>3	35	1374	(40.3)	1.00	
Weight gain during pregnancy (in pounds)					
<20	11	362	(11.2)	1.00	
20 to 40	64	2239	(69.0)	0.76	(0.47, 1.23)
>40	24	646	(19.9)	0.81	(0.39, 1.68)
Maternal BMI (kg/m^2) at time of questionnaire					
<20	9	350	(12.4)	1.00	
20-29	86	2600	(77.2)	1.07	(0.43, 2.67)
>29	10	416	(12.4)	1.39	(0.72, 2.69)

Table 6: Birth Defect Odds Ratios in relation to Sociodemographic, Pregnancy and Other Factors

RISK FACTOR	BIRTH DEFECT CASES	TOTAL PREGNANCIES	% PREGNANCIES	CRUDE OR	95% CI
Maternal age at Menarche					
<12 years	12	468	(13.7)	0.78	0.43, 1.43
>=12 years	96	2944	(86.3)	1.00	
Child's Gender					
Male	64	1719	(50.4)	1.45	0.98, 2.14
Female	44	1693	(49.6)	1.00	
Number of years mother lived on the farm before conception (Year moved on farm - conception year)					
0 to 1 year	39	902	(26.4)	**2.03**	1.21, 3.40
>1 to 4 years	45	1408	(41.3)	1.48	0.90, 2.45
>4 years	24	1102	(32.3)	1.00	
Length of recall since delivery (year of questionnaire – delivery year)					
0 to 5 years	38	1233	(36.1)	0.93	0.59, 1.48
>5 to 10 years	33	1053	(30.9)	0.95	0.59, 1.53
>10 years	36	1090	(31.9)	1.00	

6.3 Reported Farm Chemical Use & Any Birth Defect

6.3.1 Pre-conception Exposures

6.3.1.1 All offspring

No statistically significant associations were observed between reported pesticide use anytime during the pre-conception period and birth defects in offspring. However, some risk estimates were numerically elevated, including: fungicides (OR=1.33, 95% CI=0.75-2.34), dicamba (OR=1.67, 95% CI=0.79-3.53), and cyanazine (OR=2.31, 95% CI=0.81-6.57) (see Table 7).

6.3.1.2 Stratification by gender

The stratum specific results for male and female offspring (see Table 8 and 9) showed a significant elevation in the adjusted odds ratios for male offspring in relation to reported use of dicamba (OR=2.42, 95% CI=1.06-5.53) and cyanazine (OR=4.99, 95% CI=1.63-15.27) in the pre-conception period. No such relationships were seen in female offspring. In fact, for female births, herbicide exposure in the pre-conception period was associated with a reduced risks of any birth defect (OR=0.36, 95% CI=0.14-0.93). However, this finding may be attributable to the small number of subjects reporting use of this pesticide. Only 3/17 pesticide variables had adequate numbers (>5 cases exposed) for the analysis of birth defects in female offspring.

6.3.2 Post-conception Exposures

6.3.2.1 All offspring

In the post-conception period, there were no statistically significant associations between reported pesticide use and birth defects (see Table 7). Reported use of fungicides was of borderline significant in the base model (OR=1.70, 95% CI=0.99-2.90). However, the association was reduced after adjustment for family income (OR=1.52, 95% CI=0.86-2.69).

6.3.2.2 Stratification by gender

For male offspring, no significant associations between pesticide exposures in the first trimester and birth defects were observed (see Table 8 and 9). Yet, reported use of fungicides, thiocarbamate, and organophosphates in this time period all had point estimates in excess of 1.60. Female offspring showed no significant increases in risk, althougth fungicide and miscellaneous pesticide exposure in first trimester had point estimates above 1.40.

6.4 Direct Chemical Activity by Father and Any Birth Defect

An additional exposure group was created to examine couples who lived on farms where the father had reported direct chemical activity during an exposure window, and there was reported use of a particular pesticide class, family, or active ingredient during the same time period. It should be noted that this combination of chemical activity and reported farm chemical use of a particular pesticide in the same exposure time window does not necessarily mean that the father mixed or applied that type of pesticide. This

method of exposure assessment was chosen because there was no direct linkage in the questionnaire between farm chemical activities and the type of pesticide used.

6.4.1 Pre-conception exposures

In the pre-conception period, no association was observed between a father's involvement in chemical activities and birth defects. There was a non-significant elevation in risk in offspring whose fathers' were involved in chemical activities and there was reported use of cyanazine (OR=2.26, 95% CI=0.75-6.77). Other combinations of exposures were either non-significant or significantly protective (as for phenoxy herbicides and herbicides) (see Table 10).

6.4.2 Post-conception exposures

In this dataset, a father's involvement in a chemical activity, coupled with the reported use of pesticides in the post-conception period, did not show any associations with birth defects in offspring (see Table 10).

6.5 Reported Farm Chemical Use and Musculoskeletal Defects

The risk of musculoskeletal defects (ICD-9: 754.0-756.9) in relation to parental pesticide exposure during critical windows was also explored. Overall, no association between reported farm chemical use in the pre- or post-conception periods and musculoskeletal defects was observed. However, reported use of fungicides (OR=2.29, 95% CI=0.89-5.93) in the post-conception period did have numerically elevated risk estimates, but with wider confidence intervals (see Table 11).

Table 7: Reported Farm Chemical Use & Any Birth Defect (all offspring)

PESTICIDE[1]	Type	# Defects	# Exposed	# Defects	# Unexposed	Crude OR	95% CI	Base[2] OR	95% CI	Adjusted OR	95% CI	Adjustment[4]
Pre-conception												
Herbicides	class	24	917	84	2495	0.77	0.49, 1.22	0.72	0.45, 1.16	0.65	0.40, 1.07	*income*
Fungicides	class	18	403	90	3009	1.52	0.90, 2.54	1.61	0.95, 2.71	1.33	0.75, 2.34	*income*
Insecticides	class	26	899	82	2513	0.88	0.56, 1.38	0.86	0.54, 1.36	0.73	0.45, 1.19	*income*
Other Pesticides	misc.	8	272	100	3140	0.92	0.44, 1.91	0.93	0.44, 1.93	0.58	0.23, 1.47	*recall, maternal weight gain during pregnancy*
Phenoxy	family	12	522	96	2890	0.69	0.37, 1.26	0.60	0.32, 1.13	0.60	0.32, 1.13	-
Triazines	family	9	381	99	3031	0.72	0.36, 1.43	0.63	0.30, 1.31	0.63	0.30, 1.31	-
Organophosphates	family	12	347	96	3065	1.11	0.60, 2.04	1.16	0.63, 2.14	0.94	0.48, 1.82	*income*
Thiocarbamates	family	7	201	101	3211	1.11	0.51, 2.42	1.25	0.56, 2.79	1.02	0.44, 2.38	*income*
Carbaryl	AI	7	285	101	3127	0.76	0.35, 1.64	0.76	0.35, 1.66	0.65	0.28, 1.51	*income*
Cyanazine	AI	5	71	103	3341	2.38	0.94, 6.04	1.95	0.70, 5.48	2.31	0.81, 6.57	*income*
2,4-D	AI	10	296	108	3116	1.08	0.56, 2.09	1.07	0.55, 2.08	1.07	0.55, 2.08	-
Dicamba	AI	8	158	100	3254	1.68	0.81, 3.52	1.67	0.79, 3.53	1.67	0.79, 3.53	-
FUNG/INSC	mixture[3]	15	334	67	2003	1.36	0.77, 2.41	1.46	0.82, 2.61	1.14	0.60, 2.16	*income*
HERB/INSC	mixture	12	450	67	2003	0.79	0.43, 1.48	0.75	0.39, 1.44	0.59	0.29, 1.22	*income*
HERB/FUNG	mixture	8	220	67	2003	1.09	0.52, 2.30	1.15	0.54, 2.45	0.85	0.36, 2.01	*income*
Post-conception												
Herbicides	class	7	395	101	3017	0.52	0.24, 1.13	0.53	0.24, 1.15	0.53	0.24, 1.15	-
Fungicides	class	17	355	91	3057	1.64	0.97, 2.79	1.70	0.99, 2.90	1.52	0.86, 2.69	*income*
Insecticides	class	22	751	86	2661	0.90	0.56, 1.45	0.87	0.53, 1.41	0.76	0.45, 1.28	*income, BMI*
Other Pesticides	misc.	10	253	98	3159	1.29	0.66, 2.50	1.31	0.67, 2.55	1.10	0.53, 2.31	*maternal weight gain during pregnancy*
Phenoxy	family	9	376	99	3036	0.73	0.37, 1.45	0.77	0.39, 1.54	0.77	0.39, 1.54	-
Triazines	family	9	282	99	3130	1.01	0.50, 2.02	0.99	0.50, 2.00	0.99	0.50, 2.00	-
Organophosphates	family	12	285	96	3127	1.39	0.75, 2.56	1.41	0.76, 2.62	1.14	0.58, 2.23	*income*
Thiocarbamates	family	7	167	101	3245	1.36	0.62, 2.98	1.37	0.62, 3.00	1.37	0.62, 3.00	-
2,4-D	AI	7	210	101	3202	1.06	0.49, 2.31	1.12	0.51, 2.45	0.97	0.42, 2.25	*income*
FUNG/INSC	mixture	13	303	80	2451	1.33	0.73, 2.42	1.36	0.74, 2.49	1.11	0.58, 2.14	*income*

1. All offspring exposed to that particular pesticide in the exposure window compared to pregnancies not exposed to that pesticide.
2. All models contain an a priori variables including: Mother's age at conception, maternal fever during pregnancy, child's gender and parity
3. Mixture means exposure to both pesticide classes during the exposure window compared to pregnancies not exposed to herbicides, insecticides, or fungicides in the time window.
4. Additional covariates added that change the exposure odds ratio by 10% or more when added to the base model.

Table 8: Reported Farm Chemical Use & Any Birth Defect (Male offspring)

Pesticide[1]	Type	No. Cases	No. Exposed	No. Cases	No. unexposed	Crude OR	95% CI	Base[2] OR	95% CI	Adjusted OR	95% CI	Adjustment[3]
Pre-conception												
Fungicides	Class	13	192	51	1527	**2.10**	**1.12, 3.94**	**2.15**	**1.14, 4.06**	1.55	0.77, 3.14	*income*
Insecticides	Class	20	447	44	1272	1.31	0.76, 2.24	1.25	0.72, 2.18	0.96	0.53, 1.73	*income*
Herbicides	Class	19	470	45	1249	1.13	0.65, 1.95	1.05	0.60, 1.84	0.88	0.49, 1.59	*income*
Phenoxy Herbicides	Family	9	259	55	1460	0.92	0.45, 1.89	0.78	0.36, 1.67	0.78	0.36, 1.67	~
Triazine	Family	7	191	57	1528	0.98	0.44, 2.19	0.83	0.35, 1.97	0.83	0.35, 1.97	~
Thiocarbamate	Family	6	100	58	1619	1.72	0.72, 4.08	1.74	0.73, 4.15	1.47	0.57, 3.81	*income*
Organophosphates	Family	10	172	54	1547	1.71	0.85, 3.42	1.77	0.88, 3.57	1.32	0.61, 2.86	*income*
2,4-D	AI	7	153	57	1566	1.27	0.57, 2.83	1.25	0.56, 2.81	1.25	0.56, 2.81	~
Dicamba	AI	7	87	57	1632	**2.42**	1.07, 5.47	**2.42**	1.06, 5.53	**2.42**	1.06, 5.53	~
Cyanazine	AI	5	36	59	1683	**4.44**	1.68, 11.83	**3.66**	1.24, 10.78	**4.99**	1.63, 15.27	*income*
Post-conception												
Fungicides	Class	11	168	53	1551	1.98	1.01, 3.87	2.01	1.02, 3.94	1.61	0.77, 3.38	*income*
Insecticides	Class	15	365	49	1354	1.14	0.63, 2.06	1.06	0.58, 1.94	0.91	0.47, 1.75	*income, BMI*
Other Pesticides	Misc.	5	133	59	1586	1.01	0.40, 2.56	1.02	0.40, 2.60	0.88	0.31, 2.48	*maternal weight gain during pregnancy*
Triazine	Family	6	155	58	1564	1.05	0.44, 2.46	1.04	0.44, 2.46	1.04	0.44, 2.46	~
Thiocarbamate	Family	5	82	59	1637	1.74	0.68, 4.45	1.71	0.67, 4.41	1.71	0.67, 4.41	~
Organophosphates	Family	9	140	55	1579	1.90	0.92, 3.94	1.91	0.92, 3.98	1.62	0.74, 3.52	*income*

1. Male offspring exposed to that particular pesticide in the exposure window compared to pregnancies not exposed to that pesticide.
2. All models contain an a priori variables including: Mother's age at conception, maternal fever during pregnancy, and parity
3. Additional covariates added that change the exposure odds ratio by 10% or more when added to the base model.

Table 9: *Reported Chemical Use & Any Birth Defect (Females)*

Pesticide[1]	Type	No. Cases	No. Exposed	No. Cases	No. unexposed	Crude OR	95% CI	Base[2] OR	95% CI	Adjusted OR	95% CI	Adjustment[3]
Pre-conception												
Fungicides	Class	5	211	39	1482	0.90	0.35, 2.31	0.97	0.37, 2.50	1.00	0.38, 2.62	*income*
Insecticides	Class	6	452	38	1241	0.43	0.18, 1.01	0.42	0.17, 1.01	0.44	0.18, 1.07	*income*
Herbicides	Class	5	447	39	1246	0.35	0.14, 0.89	0.34	0.13, 0.88	**0.36**	**0.14, 0.93**	*income*
Post-conception												
Fungicides	Class	6	187	38	1506	1.28	0.53, 3.07	1.34	0.55, 3.26	1.50	0.61, 3.71	*income*
Insecticides	Class	7	386	37	1307	0.63	0.28, 1.43	0.65	0.29, 1.48	0.58	0.24, 1.42	*income, BMI*
Other Pesticides	Misc.	5	120	39	1573	1.71	0.66, 4.42	1.78	0.67, 4.70	1.46	0.50, 4.25	*maternal weight gain during pregnancy*
Phenoxy	Family	5	195	39	1459	0.99	0.38, 2.53	1.12	0.43, 2.92	1.12	0.43, 2.92	~

1. Female offspring exposed to that particular pesticide in the exposure window compared to pregnancies not exposed to that pesticide.
2. All models contain an a priori variables including: Mother's age at conception, maternal fever during pregnancy, and parity
3. Additional covariates added that change the exposure odds ratio in the base model by 10% or more when added to the base model.

Table 10: *Direct Chemical Activity & Any Birth Defect (all offspring)*

Pesticide[1]	Type	Cases Exposed	Total Exposed	Cases Unexposed	Total Unexposed	Crude OR	95% CI	Base[3] Model	95% CI	Adjusted Model	95% CI	Adjustment[4]
Pre-conception												
Chemical Activity[2]	Any	61	2018	47	1394	0.89	0.61, 1.32	0.85	0.57, 1.25	0.70	0.46, 1.05	*income, father's education*
Fungicides	Class	13	337	42	1328	1.23	0.65, 2.32	1.26	0.66, 2.39	0.86	0.42, 1.76	*income, father's education*
Insecticides	Class	20	711	41	1206	0.82	0.48, 1.42	0.78	0.45, 1.37	0.57	0.31, 1.05	*income, father's education*
Herbicides	Class	19	785	42	1262	0.72	0.42, 1.25	0.67	0.38, 1.19	0.53	0.29, 0.96	*income, father's education*
Triazine	Family	8	342	47	1592	0.68	0.32, 1.46	0.56	0.25, 1.26	0.48	0.21, 1.11	*income, father's education*
Phenoxy Herbicides	Family	8	458	43	1330	0.53	0.25, 1.14	0.47	0.21, 1.05	0.42	0.18, 0.94	*father's education*
Organophosphates	Family	10	294	45	1341	1.01	0.51, 2.04	1.01	0.50, 2.04	0.65	0.29, 1.42	*income, father's age at conception, father's education*
2,4-D	AI	6	256	43	1354	0.73	0.31, 1.74	0.72	0.30, 1.72	0.60	0.25, 1.46	*income, father's age at conception*
Cyanazine	AI	5	63	47	1386	2.46	0.94, 6.41	1.98	0.68, 5.76	2.26	0.75, 6.77	*income, father's age at conception*
Thiocarbamate	AI	6	167	46	1360	1.07	0.45, 2.53	1.10	0.46, 2.64	0.84	0.32, 2.18	*income, father's education*
Post-conception												
Chemical Activity	Any	58	1783	50	1629	1.06	0.72, 1.56	1.06	0.72, 1.56	0.84	0.55, 1.29	*maternal weight gain during pregnancy*
Fungicides	Class	12	305	45	1579	1.40	0.73, 105	1.36	0.70, 2.62	1.00	0.47, 2.13	*income, maternal weight gain during pregnancy*
Insecticides	Class	14	583	42	1461	0.83	0.45, 1.53	0.79	0.43, 1.47	0.59	0.30, 1.18	*income, maternal weight gain during pregnancy*
Herbicides	Class	6	329	49	1563	0.57	0.24, 1.35	0.55	0.23, 1.31	0.48	0.19, 1.23	*maternal weight gain during pregnancy*
Triazine	Family	6	245	46	1355	0.83	0.35, 1.95	0.80	0.33, 1.89	0.77	0.30, 1.99	*year wife moved on farm, maternal weight gain during pregnancy*
Phenoxy Herbicides	Family	6	314	47	1567	0.63	0.27, 1.49	0.65	0.27, 1.53	0.50	0.19, 1.28	*income, maternal weight gain during pregnancy*
Organophosphates	Family	9	250	47	1594	1.23	0.60, 2.54	1.15	0.55, 2.40	0.83	0.36, 1.88	*income, maternal weight gain during pregnancy*

1. Fathers who had direct exposure (ie: mixing or applying chemicals on the farm.(see section Methods: 1.4.1.2) during the acute risk period and Reported Farm Chemical Use compared to pregnancies where the father was not involved in chemical activities and there was no reported use of that type of chemical
2. Any chemical activity vs. no chemical activity in the exposure window.
3. All models contain an a priori variables including: Mother's age at conception, maternal fever during pregnancy, and parity
4. Additional covariates added to the base mdoel that change the exposure odds ratio (pesticide) by 10% or more when added to the base model.

Table 11: Reported Chemical Use & Musculoskeletal Defects (all offspring)[2]

PESTICIDE[1]	# Defects	Total Exposed	# Defects	Total Unexposed	Crude OR	95% CI	Adjusted[3] OR	95% CI	Adjustment[4]
Pre-conception									
Herbicides	8	901	35	2411	0.62	0.29, 1.33	0.49	0.20, 1.18	*maternal weight gain during pregnancy, income, father smoked during pregnancy*
Fungicides	5	385	38	2919	1.00	0.40, 2.52	0.90	0.32, 2.58	*maternal weight gain during pregnancy, income*
Insecticides	8	881	35	2431	0.64	0.30, 1.37	0.50	0.21, 1.22	*maternal weight gain during pregnancy, income, father smoked during pregnancy*
Other Pesticides	5	264	38	3040	1.51	0.60, 3.79	0.55	0.13, 2.37	*maternal weight gain during pregnancy, number of years of recall*
Post-conception									
Fungicides	8	346	35	2966	1.98	0.93, 4.24	2.29	0.89, 5.93	*maternal weight gain during pregnancy, income, father smoked during pregnancy*
Insecticides	10	739	33	2575	1.07	0.53, 2.16	0.98	0.44, 2.19	*maternal weight gain during pregnancy, income, father smoked during pregnancy*
Other Pesticides	5	243	38	3061	1.64	0.65, 4.14	1.02	0.31, 3.38	*maternal weight gain during pregnancy, income*
Organophosphates	5	278	38	3069	1.46	0.57, 3.74	1.42	0.49, 4.13	*maternal weight gain during pregnancy, father smoked during pregnancy, number of years of recall*

1. Pregnancies with reported farm chemical use of a particular pesticide compared to pregnancies not exposed to that pesticide.
2. Those 65 pregnancies ending in other birth defects were ignored in the analysis.
3. Each model also contains a priori variables: mothers age at conception, maternal fever during pregnancy, parity, child's sex
4. Additional covariates added to the base model that change the exposure odds ratio by 10% or more when added to the base model.

6.6 Chapter Summary

Overall, there did not appear to be an association between parental pesticide exposure in the pre- and post-conception periods and birth defects. There was some evidence that male offspring may be differentially susceptible to the active ingredients dicamba and cyanazine used in pesticides when exposure occurs in the pre-conception period. However, the possibility that this may be a chance finding cannot be ruled out in light of the large number of associations examined.

CHAPTER 7 - RESULTS II: Child Health Outcomes

7.1 Assessment of Other Potential Risk Factors

The distribution of other potential risk factors for frequent ear infections, persistent cough or bronchitis, hearing problems, epilepsy, allergies or hayfever and asthma is summarized in Table 12.

Frequent Ear Infections

The diagnosis of frequent ear infections was signficantly less in offspring of parents who were over 30 years of age at the time of conception as compared to younger parents, and in parents with less than a grade 12 education as compared to parents of higher educational attainment. Women who reported working off the farm during pregnancy at a hazardous job were more likely to report offspring with frequent ear infections.

Persistent Cough or Bronchitis

Similarly, the development of a persistent cough or bronchitis was lower in the offspring of mothers who were 30 years of age or older at the time of conception and higher in mothers who reported to have medical problems during pregnancy.

Hearing Problems

There was a highly significant association between frequent ear infections diagnosed by a doctor and hearing problems in the offspring (OR=9.59, 95% CI=6.31-14.57). As well, significantly more male than female offspring had hearing problems, and children aged 8 to 11 years of age at the time of the questionnaire were most likely to have hearing problems.

Epilepsy

Epilepsy was more likely in children who were born by caesarian section, and whose mother's had labor or delivery problems.

Allergies or Hayfever

Allergies or hayfever tended to be lower in the offspring of fathers with less than a grade 12 education, and mothers who were older than 25 at the time of conception. Allergies tended to be more likely when the child was the first or second pregnancy, as compared to the third or higher pregnancy. A notable increase in risk was seen if the mother reported having allergies (OR=4.15, 95% CI=3.15-5.49). The development of allergies or hayfever was more likely in male offspring and children over 12 years of age at the time of the questionnaire.

Crop acreage and the presence of livestock on a farm were used as proxy measures of other potential allergens being present during the perinatal period. The presence of such allergens may have confounded the association between allergy and pesticides as there is evidence for transplacental materno-fetal allergen transfer[268] (see Table 22). Farms with poultry and pigs were less likely to have children with allergies. High crop acreage of grains, hay and fodder crops, oilseeds and other field crops did not show any association with childhood allergies or hayfever. Nor was parental field or livestock work during the pregnancy interval significantly associated with this outcome. For completeness, farms with fruit trees or vegetables were tested for possible association with allergies in offspring: both showed significant associations. Women living on farms with one or more acreas of fruit or berries (OR=1.70, 95% CI=1.11-2.62) and vegetables (OR=1.54, 95% CI=1.06-2.24) were more likely to have children with

allergies than those farms with zero acreage of these same crops. It was assumed that fruit trees and vegetable crops were more likely associated with pesticides, and not allergens, because fruit and vegetable farmers usually have less crop acreage than grain farmers, and the pollen or dust from these crops would be much less than that generated by grains or hay. Therefore, they were not considered for the final model.

Asthma

Asthma was more likely to occur in offspring of parents earning $25 000 to $45 000 per year compared to those in the highest income tertile. As well, asthma was more likely to occur in offspring born to women who had reported medical problems during pregnancy or who had labor and delivery problems, women who had a history of asthma, and those that delivered by cesarean section. Finally, low birth weight and male infants were more likely to later develop asthma in this study population than were normal birth weight and female infants, respectively.

Table 12: *Odds Ratios for Child Health Outcomes in Relation to Sociodemographic, Pregnancy and Other Factors*

RISK FACTOR	*Ear Cases*	*Cough Cases*	*Hear Cases*	*Epil Cases*	*Allerg Cases*	*Asthma Cases*	Total	Ear		Cough		Hear		Epilepsy		Allergies		Asthma	
								OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SOCIODEMOGRAPHIC FACTORS																			
Maternal Age at Conception																			
<25.0	84	10	22	5	45	55	705	1.00		1.00		1.00		1.00		1.00		1.00	
25-29	226	52	63	11	150	94	1523	0.94	0.77, 1.14	0.98	0.66, 1.46	1.35	0.89, 2.06	0.76	0.34, 1.69	0.74	0.59, 0.92	1.31	0.93, 1.86
>30.0	185	42	36	11	146	24	1177	0.77	0.58, 1.01	0.41	0.21, 0.82	0.97	0.55, 1.74	0.75	0.26, 2.18	0.44	0.30, 0.64	0.65	0.39, 1.09
Paternal Age at Conception																			
<25.0	166	29	44	12	91	48	1299	1.00		1.00		1.00		-		1.00		1.00	
25-29	210	55	50	12	155	88	1413	0.85	0.67, 1.08	1.38	0.79, 2.43	0.90	0.56, 1.46	-	-	0.82	0.62, 1.07	1.26	0.84, 1.89
>30.0	119	20	27	3	95	37	703	0.74	0.57, 0.96	0.82	0.45, 1.52	0.86	0.51, 1.43	-	-	0.47	0.34, 0.65	0.70	0.43, 1.11
Maternal Education																			
< Highschool	50	13	13	4	37	18	477	0.68	0.47, 0.98	0.91	0.48, 1.72	0.67	0.36, 1.27	-	-	0.73	0.48, 1.10	0.69	0.42, 1.14
≥Highschool	445	91	109	23	304	155	2925	1.00		1.00		1.00		-	-	1.00		1.00	
Paternal Education																			
< Highschool	117	28	28	9	68	36	998	0.73	0.56, 0.95	0.91	0.55, 1.50	0.73	0.46, 1.16	1.07	0.48, 2.40	**0.59**	**0.43, 0.80**	0.69	0.42, 1.14
≥Highschool	334	69	83	18	249	122	2186	1.00		1.00		1.00		1.00		1.00		1.00	
Maternal Ethnicity																			
Chinese, Black or Other	50	14	14	5	43	20	322	1.04	0.72, 1.51	1.44	0.81, 2.55	1.21	0.64, 2.28	2.24	0.73, 6.83	1.40	0.94, 2.08	1.24	0.76, 2.03
European	441	90	107	21	298	151	3040	1.00		1.00		1.00		1.00		1.00		1.00	
Income																			
≤25 000	155	37	36	10	107	44	1273	0.76	0.56, 1.03	0.98	0.56, 1.70	0.91	0.52, 1.59	0.94	0.36, 2.47	0.77	0.54, 1.09	0.73	0.45, 1.18
> 25 000 to ≥45 000	130	28	37	8	93	57	768	1.12	0.81, 1.53	1.21	0.66, 2.22	1.47	0.84, 2.57	1.28	0.44, 3.73	1.16	0.80, 1.68	1.65	1.03, 2.65
> 45 000	131	25	27	7	88	40	852	1.00		1.00		1.00		1.00		1.00		1.00	
PREGNANCY FACTORS																			
Drank 3+ cups of tea or coffee or both in 1st trimester of pregnancy																			
yes	181	36	46	7	106	63	1146	1.14	0.90, 1.44	1.10	0.69, 1.76	1.18	0.77, 1.81	0.70	0.29, 1.67	0.93	0.70, 1.23	1.17	0.83, 1.65
No	314	68	75	20	235	110	2259	1.00		1.00		1.00		1.00		1.00		1.00	

RISK FACTOR	*Ear Cases*	*Cough Cases*	*Hear Cases*	*Epil Cases*	*Allerg Cases*	*Asthma Cases*	Total	Ear		Cough		Hear		Epilepsy		Allergies		Asthma	
								OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Drank 3 or more alcoholic drinks, in 1st trimester of pregnancy																			
yes	25	6	7	1	19	9	212	0.78	0.49 1.23	0.87	0.34, 2.26	0.97	0.46, 2.05	-	-	0.91	0.55, 1.49	0.85	0.44, 1.65
no	470	98	114	26	322	164	3193	1.00		1.00		1.00		-		1.00		1.00	
Smoked 1+ cigarettes per day in 1st trimester																			
yes	85	16	23	4	46	31	515	1.18	0.89, 1.57	1.12	0.66, 1.90	1.35	0.82, 2.23	-	-	0.87	0.61, 1.26	1.30	0.84, 2.02
no	410	88	98	23	295	142	2890	1.00		1.00		1.00		-		1.00		1.00	
Father smoked during the pregnancy interval																			
yes	120	21	33	5	87	47	798	1.12	0.86, 1.46	0.79	0.46, 1.37	1.27	0.81, 2.09	0.68	0.22, 2.08	1.13	0.83, 1.54	1.30	0.88, 1.92
no	312	74	74	20	221	152	2248	1.00		1.00		1.00		1.00		1.00		1.00	
Maternal fever during pregnancy																			
yes	35	8	10	3	21	9	154	1.72	0.85, 2.52	1.65	0.72, 3.79	1.89	0.96, 3.74	-	-	1.38	0.82, 2.31	1.16	0.56, 2.42
no	452	95	108	24	311	159	3189	1.00		1.00		1.00		-	-	1.00		1.00	
Maternal medical problem during pregnancy																			
yes	116	33	33	7	85	49	644	1.33	0.96, 1.70	**1.84**	**1.21, 2.80**	1.59	0.98, 2.46	1.44	0.55, 3.78	1.30	0.97, 1.74	**1.68**	**1.16, 2.41**
no	379	71	88	20	256	124	2748	1.00		1.00		1.00		1.00		1.00		1.00	
Weight Gain during pregnancy (in lbs)																			
0 to 15	32	12	11	-	19	9	239	0.81	0.50, 1.31	0.97	0.45, 2.10	1.00	0.40, 2.49	-	-	1.03	0.50, 2.12	1.24	0.44, 3.48
16 to 30	269	59	71	-	212	103	1942	0.80	0.55, 1.16	0.56	0.31, 1.01	0.79	0.38, 1.64	-	-	1.44	0.85, 2.45	1.72	0.79, 3.78
31 to 45	131	17	23	-	76	47	838	0.93	0.63, 1.38	**0.39**	**0.19, 0.80**	0.64	0.29, 1.40	-	-	1.15	0.65, 2.01	1.76	0.79, 3.92
>45	43	13	12	-	21	8	246	1.00		1.00		1.00		-	-	1.00		1.00	
<20	-	-	-	6	-	-	362	-	-	-	-	-	-	2.00	0.55, 7.34	-	-	-	-
20 to 40	-	-	-	15	-	-	2251	-	-	-	-	-	-	0.87	0.28, 2.72	-	-	-	-
>40	-	-	-	5	-	-	648	-	-	-	-	-	-	1.00		-	-	-	-
Season of Conception:																			
fall	99	28	20	8	85	30	829	0.87	0.66, 1.14	1.17	0.60, 1.72	0.63	0.37, 1.07	1.16	0.42, 3.22	1.02	0.75, 1.39	0.70	0.44, 1.11
summer	143	24	38	7	84	48	887	1.26	0.99, 1.61	0.80	0.47, 1.36	1.04	0.66, 1.65	0.46	0.32, 2.68	0.89	0.66, 1.21	1.05	0.71, 1.54
spring	134	24	28	5	89	52	848	1.13	0.88, 1.45	0.83	0.48, 1.44	0.76	0.46, 1.26	0.71	0.23, 2.17	1.00	0.74, 1.34	1.19	0.78, 1.82
winter	119	28	35	7	83	43	841	1.00		1.00		1.00		1.00		1.00		1.00	

RISK FACTOR	*Ear Cases*	*Cough Cases*	*Hear Cases*	*Epil Cases*	*Allerg Cases*	*Asthma Cases*	Total	Ear		Cough		Hear		Epilepsy		Allergies		Asthma	
Fertility Drugs Taken prior to pregnancy																			
yes	10	3	1	0	12	6	63	1.04	0.55, 1.97	-	-	-	-	-	-	1.75	0.84, 3.68	1.84	0.78, 4.39
no	482	99	119	26	328	166	3317	1.00		-	-	-	-	-	-	1.00		1.00	
Parity:																			
Parity=1	154	27	25	10	123	48	961	1.19	0.98, 1.46	0.91	0.58, 1.42	0.70	0.44, 1.12	1.75	0.68, 4.50	**1.79**	**1.37, 2.33**	0.99	0.72, 1.45
Parity=2	151	33	45	9	111	55	1071	1.00	0.81, 1.22	0.99	0.65, 1.51	1.11	0.74, 1.66	1.44	0.56, 3.71	**1.35**	**1.04, 1.76**	1.02	0.72, 1.45
Parity=>3	190	44	51	8	107	70	1373	1.00		1.00		1.00		1.00		1.00		1.00	
OTHER FACTORS Child was diagnosed with frequent ear infections																			
yes	-	-	70	-	-	-	495	-	-	-	-	9.59	6.31, 14.57	-	-	-	-	-	-
no	-	-	51	-	-	-	2932	-	-	-	-	1.00		-	-	-	-	-	-
Parental History of Epilepsy																			
yes	-	-	-	0	-	-	31	-	-	-	-	-	-	-	-	-	-	-	-
no	-	-	-	27	-	-	3374	-	-	-	-	-	-	-	-	-	-	-	-
Maternal History of Allergies																			
yes	-	-	-	-	142	-	599	-	-	-	-	-	-	-	-	**4.15**	**3.14, 5.49**	-	-
no	-	-	-	-	199	-	2806	-	-	-	-	-	-	-	-	1.00		-	-
Paternal history of allergies																			
yes	-	-	-	-	14	-	164	-	-	-	-	-	-	-	-	0.96	0.60, 1.54	-	-
no	-	-	-	-	327	-	3241	-	-	-	-	-	-	-	-	1.00		-	-
Maternal history of asthma																			
yes	-	-	-	-	-	19	162	-	-	-	-	-	-	-	-	-	-	**2.58**	**1.45, 4.61**
no	-	-	-	-	-	154	3243	-	-	-	-	-	-	-	-	-	-	1.00	
Paternal history of Asthma																			
yes	-	-	-	-	-	3	44	-	-	-	-	-	-	-	-	-	-	-	-
no	-	-	-	-	-	170	3361	-	-	-	-	-	-	-	-	-	-	-	-
Child's age at time of questionnaire																			
0 to 2 years	70	11	6	4	19	14	607	**0.73**	**0.53, 0.99**	0.50	0.23, 1.05	**0.22**	**0.09, 0.56**	0.73	0.22, 2.41	**0.17**	**0.10, 0.27**	**0.45**	**0.24, 0.79**
3 to 7 years	131	31	15	8	47	58	901	0.96	0.74, 1.24	1.05	0.61, 1.81	**0.46**	**0.25, 0.85**	0.98	0.37, 2.61	**0.25**	**0.17, 0.36**	1.20	0.80, 1.80
8 to 11 years	154	32	66	7	123	56	993	0.97	0.76, 1.25	1.03	0.61, 1.74	**1.83**	**1.18, 2.82**	0.79	0.29, 2.12	**0.65**	**0.50, 0.83**	1.05	0.72, 1.54
>=12 years of age	140	30	34	8	152	45	904	1.00		1.00		1.00		1.00		1.00		1.00	

RISK FACTOR	*Ear Cases*	*Cough Cases*	*Hear Cases*	*Epil Cases*	*Allerg Cases*	*Asthma Cases*	Total	Ear		Cough		Hear		Epilepsy		Allergies		Asthma	
Child's Sex:																			
Male	303	61	83	11	191	118	1718	1.59	0.76, 1.90	1.41	0.96, 2.07	**2.28**	**1.54, 3.39**	0.68	0.31, 1.50	1.24	0.99, 1.54	**2.12**	**1.54, 2.93**
Female	192	43	38	16	150	55	1687	1.00		1.00		1.00		1.00		1.00		1.00	
C-section																			
yes	79	14	15	7	35	33	438	1.33	0.99, 1.79	1.03	0.56, 1.90	0.93	0.51, 1.71	**2.42**	**1.00, 5.82**	0.73	0.49, 1.10	**1.62**	**1.07, 2.45**
no	416	90	106	20	306	140	2967	1.00		1.00		1.00		1.00		1.00		1.00	
Labor or Delivery Problems																			
yes	174	42	43	14	120	38	1056	1.17	0.95, 1.44	1.36	0.88, 2.12	1.17	0.80, 1.71	2.42	0.91, 5.32	1.14	0.89, 1.46	**1.40**	**1.02, 1.91**
no	321	62	78	13	221	105	2345	1.00		1.00		1.17		1.00		1.00		1.00	
Low Birth weight (<2500g):																			
yes	17	2	2	0	9	11	99	1.42	0.88, 2.30	-	-	-	-	-	-	0.93	0.53, 1.63	**2.33**	**1.21, 4.49**
no	478	102	119	27	332	162	3306	1.00		-		-		-		1.00		1.00	
Preterm birth (<37 weeks):																			
yes	2	0	0	1	5	1	21	-	-	-	-	-	-	-	-	2.79	0.78, 9.92	-	-
no	493	104	121	26	336	172	3384	-		-		-		-		1.00		-	-
Breastfed:																			
yes	361	67	79	18	249	126	2435	1.12	0.88, 1.43	0.75	0.49, 1.14	0.77	0.51, 1.17	0.79	0.35, 1.79	1.10	0.84, 1.45	1.05	0.73, 1.50
no	134	37	42	9	92	47	970	1.00		1.00				1.00		1.00		1.00	
If yes, breastfeeding length																			
no breastfeeding	134	37	42	9	92	47	970	1.02	0.75, 1.39	1.40	0.78, 2.52	1.66	0.89, 3.09	1.52	0.47, 4.95	0.96	0.67, 1.37	0.96	0.61, 1.54
0 to 3 months	133	29	31	6	103	43	798	1.28	0.94, 1.72	1.46	0.81, 2.61	1.54	0.82, 2.92	1.22	0.35, 4.32	1.33	0.95, 1.88	1.08	0.68, 1.70
4 to 6 months	133	19	29	8	80	47	862	1.22	0.93, 1.61	0.75	0.39, 1.43	1.36	0.72, 2.56	1.53	0.46, 5.04	0.95	0.67, 1.33	1.03	0.65, 1.61
> 6 months	87	17	18	4	64	33	660			1.00		1.00		1.00		1.00		1.00	
Mother was a smoker during the child's first year of life																			
yes	92	18	25	5	52	29	577	1.13	0.86, 1.49	1.09	0.63, 1.88	1.30	0.79, 2.14	1.08	0.42, 2.73	0.88	0.63, 1.24	1.03	0.66, 1.60
no	403	86	96	22	289	144	2828	1.00		1.00		1.00		1.00		1.00		1.00	
Father was a smoker during the child's first year of life																			
yes	120	19	33	5	85	48	806	1.04	0.81, 1.34	0.71	0.40, 1.23	1.22	0.77, 1.96	0.72	0.24, 2.21	1.06	0.79, 1.43	1.27	0.86, 1.86
no	375	85	88	22	256	125	2599	1.00		1.00		1.00		1.00		1.00		1.00	

RISK FACTOR	*Ear Cases*	*Cough Cases*	*Hear Cases*	*Epil Cases*	*Allerg Cases*	*Asthma Cases*	Total	Ear		Cough		Hear		Epilepsy		Allergies		Asthma	
Number of years mother lived on the farm before conception																			
0 to 1 year	144	28	28	8	99	43	899	1.21	0.97, 1.51	1.11	0.68, 1.81	0.88	0.52, 1.48	1.10	0.45, 2.72	1.60	1.18, 2.18	1.06	0.71, 1.58
>1 to 4 years	196	44	56	10	151	78	1401	1.03	0.84, 1.27	1.13	0.72, 3.72	1.22	0.81, 1.82	0.79	0.36, 2.20	1.51	1.15, 1.97	1.23	0.88, 1.73
>4 years	155	32	37	9	91	52	1105	1.00		1.00		1.00		1.00		1.00		1.00	
Mother worked off farm during pregnancy interval																			
Hazardous job with potential pesticide exposure	5	2	0	2	0	1	24	1.79	0.75, 4.26	-	-	-	-	-	-	-	-	-	-
Hazardous job without pesticide exposure	22	3	4	0	14	5	82	2.34	1.33, 4.10	-	-	-	-	-	-	-	-	-	-
Other job non-hazardous	180	31	45	12	114	61	1164	1.19	0.96, 1.47	-	-	-	-	-	-	-	-	-	-
Did not work off farm during pregnancy interval	287	67	71	13	213	106	2155	1.00		-	-	-	-	-	-	-	-	-	-
Father worked off farm during pregnancy interval:																			
Hazardous job with potential pesticide exposure	0	2	1	0	4	1	37	-	-	-	-	-	-	-	-	-	-	-	-
Hazardous job without pesticide exposure	3	0	1	1	6	3	47	-	-	-	-	-	-	-	-	-	-	-	-
Other job non-hazardous	75	13	18	3	52	33	502	-	-	-	-	-	-	-	-	-	-	-	-
Did not work off farm during pregnancy interval	372	81	91	23	254	121	2613	-	-	-	-	-	-	-	-	-	-	-	-

NOTE: OR=crude odds ratio estimated using Generalized Estimating Equations

7.2 In utero Pesticide Exposure and Child Health Outcomes

7.2.1 Frequent Ear Infections

There did not appear to be any association between reported pesticide use during pregnancy and the development of frequent ear infections in offspring (see Table 13). Most point estimates were near the null value except for the pesticides carbaryl, which appeared to be protective (OR=0.68, 95% CI=0.49-0.94), and captan, which exhibited a numerically, but non-significantly, elevated odds ratio (OR=1.26, 95% CI=0.80-1.98). The gender (see Table 14) and age (see Table 25) stratified results were similar, with most point estimates near the null value of unity.

7.2.2 Persistent Cough or Bronchitis

Persistent cough or bronchitis in children was not signficantly associated with reported pesticide use during pregnancy (see Table 15). However, reported use of dicamba and carbaryl did have numerical elevations above 1.6. Borderline signficant associations were also seen for female offspring when any pesticide (OR=1.80, 95% CI=0.90-3.59) or insecticides (OR=2.29, 95% CI=0.95-5.53) were reported to be used during the pregnancy period (see Table 16).

7.2.3 Hearing Problems

There were no significant associations between reported pesticide use during pregnancy and the subsequent diagnosis of hearing problems in all offspring. Numerically elevated odds ratios were observed for herbicides, phenoxy herbicides, and the active ingredients 2,4-DB, 2,4-D, and MCPA, from the phenoxy herbicide family (see Table 17). The gender-specific results showed significant associations between hearing

problems in male offspring and reported farm use of phenoxy herbicides (OR=2.15, 95% CI=1.12-4.12), 2,4-D (OR=2.58, 95% CI=1.19-5.62) and MCPA (OR=2.30, 95% CI=1.05, 5.05) during the pregnancy period (see Table 18). No such associations swere apparent in female offspring.

7.2.4 Epilepsy

No significant associations were found between reported farm chemical use during the pregnancy period and the development of epilepsy in offspring *(See Table 19).* However, the point estimates of the odds ratios were above 1.2 for exposure to herbicides, organophosphates, 2,4-D, and any pesticide. There were insufficient numbers available for stratum specific analyses of these data.

7.2.5 Allergies or Hayfever

Any pesticide use and reported use of all three major pesticide classes (herbicides, insecticides and fungicides) during the pregnancy interval exhibited significant associations with the development of allergies or hayfever in offspring (see Table 20). Furthermore, the pesticide families comprised of phenoxy herbicides (OR=1.43, 95% CI=1.03-1.99) and organophosphates (OR=1.55, 95% CI=1.02-2.36), and the active ingredient 2,4-D (OR=1.66, 95 % CI=1.11-2.49) also showed significant associations with allergies or hayfever. When examining the gender specific results, male offspring had significant elevations in allergies and hayfever when there was reported farm use of any pesticide, fungicides, insecticides, herbicides, phenoxy herbicides and 2,4-D during the pregnancy period. No such associations existed for female offspring alone, excluding exposure to any pesticide, which showed borderline significance (see Table 21). The age

stratified analysis suggested that perinatal pesticide exposures increased the risk of allergies in children who were 12 years of age and older at the time of the questionnaire. Children aged 12 and over had nearly double the odds of having allergies or hayfever if they were exposed to herbicides (OR=1.98, 95 % CI=1.30-3.01), insecticides (OR=1.70, 95% CI=1.07-2.70), fungicides (OR=1.63, 95% CI=0.90-2.96) and any pesticide (OR=1.82, 95% CI=1.24-2.67) *in utero* (see Table 25).

7.2.6 Asthma

There was no evidence to suggest that asthma was associated with reported farm chemical use during the pregnancy interval in the crude, adjusted or gender or age-specific analysis (see Table 23 - 25).

Table 13: Reported Farm Chemical Use during Pregnancy & Frequent Ear Infections (all offspring)

PESTICIDE[1]	Cases Exposed	Total Exposed	Crude OR[2]	95% CI	Adjusted OR	95% CI	Adjustment[3]
Any Pesticide	312	2243	0.85	0.69, 1.05	0.85	0.69, 1.05	-
Insecticides	191	725	0.81	0.63, 1.02	0.81	0.63, 1.02	-
Fungicides	100	1444	0.78	0.58, 1.06	0.78	0.58, 1.06	-
Herbicides	250	1697	0.90	0.72, 1.13	0.90	0.72, 1.13	-
Other Pesticides	49	391	0.76	0.54, 1.08	0.90	0.60, 1.37	*child's age*
Phenoxy	145	1052	0.89	0.69, 1.15	0.89	0.69, 1.15	-
Triazine	127	786	1.01	0.76, 1.34	1.01	0.76, 1.34	-
Thiocarbamate	57	405	0.84	0.59, 1.22	0.84	0.59, 1.22	-
Organophosphates	87	613	0.85	0.62, 1.16	0.85	0.62, 1.16	-
Dicamba	36	282	0.82	0.53, 1.27	0.86	0.55, 1.36	*child's age*
Glyphosphate	55	384	0.95	0.66, 1.35	1.03	0.67, 1.60	*child's age*
2,4 DB	30	219	0.96	0.62, 1.49	1.06	0.67, 1.68	*child's age*
2,4-D	75	571	0.84	0.61, 1.15	0.97	0.69, 1.37	*child's age, father's age at conception*
MCPA	77	519	0.99	0.73, 1.36	0.99	0.73, 1.36	-
Atrazine	87	578	0.94	0.68, 1.28	0.94	0.68, 1.28	-
Cyanazine	25	161	0.99	0.59, 1.66	0.99	0.59, 1.66	-
Carbaryl	67	568	0.68	0.49, 0.94	**0.68**	**0.49, 0.94**	-
Captan	35	189	1.26	0.80, 1.98	1.26	0.80, 1.98	-
No Pesticide	**183**	**1162**	**1.00**		**1.00**		

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios.
3. Additional covariates that when added to the crude exposure model changed the exposure odds ratio by 10% or more.

Table 14: Reported Farm Chemical Use during Pregnancy & Frequent Ear Infections (Stratified by Gender)

	MALE OFFPSRING								FEMALE OFFSPRING							
PESTICIDE[1]	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI
Any Pesticide	194	1128	109	593	303	1727	0.90	0.68, 1.17	118	1115	75	572	193	1700	0.82	0.59, 1.14
Fungicides	62	364	109	593	171	958	0.88	0.61, 1.26	35	361	75	572	110	939	0.67	0.43, 1.06
Insecticides	128	730	109	593	236	1324	0.92	0.68, 1.24	63	714	75	572	138	1295	0.65	0.45, 0.94
Herbicides	152	854	109	593	261	1453	0.93	0.70, 1.24	98	843	75	572	173	1424	0.92	0.65, 1.29
Other Pesticides	28	192	109	593	143	785	0.98	0.56, 1.71	21	187	75	572	96	775	0.94	0.51, 1.72
Phenoxy	83	511	109	593	192	1108	0.87	0.63, 1.20	62	541	75	572	137	1118	0.90	0.61, 1.33
Triazine	78	394	109	593	187	990	1.08	0.77, 1.52	49	392	75	572	124	970	0.96	0.62, 1.48
Thiocarbamate	38	207	109	593	146	804	0.93	0.61, 1.44	19	198	75	572	94	773	0.69	0.40, 1.18
Organophosphate	50	308	109	593	159	902	0.82	0.52, 1.29	34	305	75	572	109	881	0.82	0.52, 1.29
Dicamba	22	152	109	593	131	746	0.79	0.46, 1.35	14	130	75	572	89	706	0.97	0.48, 1.95
Glyphosphate	32	199	109	593	131	792	0.94	0.54, 1.63	23	185	75	572	98	761	1.30	0.63, 2.68
2,4-DB	19	111	109	593	128	706	1.04	0.60, 1.82	11	106	75	572	86	681	0.97	0.45, 2.09
2,4-D	40	275	109	593	149	869	0.81	0.53, 1.22	35	296	75	572	110	872	1.29	0.76, 2.19
MCPA	45	248	109	593	154	842	1.01	0.69, 1.51	32	271	75	572	107	847	0.93	0.58, 1.49
Atrazine	52	282	109	593	151	876	0.99	0.68, 1.44	35	296	75	572	110	873	0.89	0.55, 1.45
Cyanazine	12	77	109	593	111	672	0.81	0.40, 1.63	13	84	75	572	88	661	1.21	0.58, 2.51
Carbaryl	45	281	109	593	144	875	0.81	0.55, 1.21	23	287	75	572	97	864	**0.56**	**0.33, 0.93**
Captan	20	95	109	593	129	688	1.20	0.67, 2.15	15	94	75	572	90	671	1.25	0.64, 2.43

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios. Same adjustment as models with all offspring.

Table 15: Reported Farm Chemical Use during Pregnancy & Persistent Cough or Bronchitis (all offspring)

PESTICIDE[1]	*No. Cases*	*No. Exposed*	*Crude OR*[2]	*95% CI*	*Adj. OR*[2]	*95% CI*	*Adjustment*[3]
Any Pesticide	70	2243	1.10	0.70, 1.73	1.21	0.77, 1.90	*child's age*
Fungicides	17	725	0.77	0.41, 1.44	1.27	0.61, 2.67	*child's age, income, maternal weight gain during pregnancy*
Insecticides	41	1444	1.04	0.63, 1.73	1.45	0.81, 2.60	*child's age, income*
Herbicides	47	1697	0.97	0.59, 1.57	1.05	0.65, 1.70	*child's age*
Other Pesticides	10	391	0.95	0.47, 1.90	1.39	0.59, 3.28	*child's age, breastfeeding, income*
Phenoxy	33	1052	1.12	0.66, 1.88	1.27	0.73, 2.21	*income*
Triazine	20	786	0.91	0.48, 1.72	0.91	0.48, 1.72	-
Thiocarbamate	6	405	0.52	0.22, 1.24	0.52	0.20, 1.35	*father's age at conception, child's age*
Organophosphates	16	613	1.03	0.55, 1.94	1.35	0.66, 2.78	*child's age, weight gain during pregnancy*
Dicamba	9	282	1.20	0.52, 2.79	1.66	0.58, 4.80	*child;s age, income, father's age at conception*
Glyphosphate	6	384	0.43	0.14, 1.33	0.71	0.21, 2.35	*mother's and father's age at conception, income, child's age, child's sex, breastfeeding, father smoked during pregnancy*
2,4-DB	3	219	-	-	-	-	-
2,4-D	21	571	1.39	0.77, 2.51	1.46	0.80, 2.66	*child's age*
MCPA	12	519	0.85	0.44, 1.64	0.91	0.46, 1.82	-
Atrazine	12	578	0.73	0.35, 1.50	0.69	0.35, 1.36	-
Cyanazine	5	161	-	-	-	-	-
Carbaryl	16	568	1.02	0.51, 2.02	1.69	0.75, 3.81	*breastfeeding, child's age, mother's age at conception, income*
Captan	3	189	-	-	-	-	-
No Pesticide	**34**	**1162**	**1.00**	~	~	~	

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios.
3. Additional covariates that when added to the crude exposure model changed the exposure odds ratio by 10% or more.

Table 16: Reported Farm Chemical Use during Pregnancy & Persistent Cough or Bronchitis (Stratified by gender)

	MALE OFFSPRING								FEMALE OFFSPRING							
PESTICIDE[1]	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI
Any Pesticide	38	1128	23	593	61	1727	0.81	0.46, 1.43	32	1115	11	572	43	1700	1.80	0.90, 3.59
Fungicides	10	364	23	593	33	958	0.88	0.32, 2.43	7	361	11	572	18	939	1.61	0.55, 4.75
Insecticides	21	730	23	593	44	1324	0.99	0.46, 2.15	20	714	11	572	31	1295	2.29	0.95 5.53
Herbicides	26	854	23	593	49	1453	0.75	0.40, 1.41	21	843	11	572	32	1424	1.51	0.74, 3.08
Other Pesticides	5	192	23	593	28	785	0.99	0.28, 3.28	5	187	11	572	16	775	2.15	0.69, 6.72
Phenoxy	19	511	23	593	42	1108	1.14	0.57, 2.21	14	541	11	572	25	1118	1.45	0.61, 3.45
Triazine	14	394	23	593	37	990	0.88	0.42, 1.81	6	392	11	572	17	970	0.81	0.30, 2.20
Thiocarbamate	3	207	23	593	26	804	~	~	3	198	11	572	14	773	~	~
Organophosphates	7	308	23	593	30	902	0.68	0.25, 1.83	9	305	11	572	20	881	2.67	0.93, 7.66
Dicamba	5	152	23	593	28	746	~	~	4	130	11	572	15	706	~	~
Glyphosphate	2	199	23	593	25	792	~	~	4	185	11	572	15	761	~	~
2,4-DB	2	111	23	593	25	706	~	~	1	106	11	572	12	681	~	~
2,4-D	11	275	23	593	34	869	0.99	0.44,2.19	10	296	11	572	21	872	2.25	0.94, 5.38
MCPA	8	248	23	593	31	842	0.79	0.35, 1.79	4	271	11	572	15	847	~	~
Atrazine	8	282	23	593	31	876	0.71	0.30, 1.66	4	296	11	572	15	873	~	~
Cyanazine	2	77	23	593	25	672	~	~	3	84	11	572	14	661	~	~
Carbaryl	6	281	23	593	29	875	**	**	10	287	11	572	21	864	**	**
Captan	1	95	23	593	24	688	~	~	2	94	11	572	13	671	~	~

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios. Same adjustment as models with all offspring

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Table 17: *Reported Farm Chemical Use during Pregnancy & Hearing Problems in Offspring*

PESTICIDE[1]	*Exposed Cases*	*Total Exposed*	*Crude OR*[2]	*95% CI*	*Base OR*[2]	*95% CI*	*Adj. OR*[2]	*95% CI*	*Adjustment*[3]
Any Pesticide	75	2243	0.80	0.53, 1.21	0.88	0.34, 1.43	1.30	0.78, 2.15	*child's age, breastfeeding, father's education, father smoked during pregnancy*
Fungicides	24	725	0.71	0.39, 1.29	0.81	0.56, 1.39	1.13	0.59, 2.16	*income, breastfeeding, child's age, father smoked during pregnancy*
Insecticides	39	1444	0.64	0.40, 1.02	0.70	0.67, 1.74	0.95	0.52, 1.71	*income, child's age, father smoked during pregnancy*
Herbicides	57	1697	0.81	0.52, 1.25	0.88	0.35, 1.14	1.31	0.76, 2.26	*child's age, breastfeeding, father's education, father smoked during pregnancy*
Other Pesticides	10	391	0.62	0.31, 1.25	0.69	0.43, 1.14	1.07	0.44, 2.68	*breastfeeding, child's age*
Phenoxy	43	1052	0.96	0.60, 1.51	1.08	0.67, 1.74	1.65	0.94, 2.89	*breastfeeding, child's age, father's education*
Triazine	21	786	0.63	0.36, 1.12	0.63	0.29, 1.06	0.60	0.31, 1.19	*income, father smoked during pregnancy*
Thiocarbamate	7	405	0.41	0.18, 0.94	0.43	0.32, 1.77	0.52	0.21, 1.25	*child's sex, income, father's education, father smoked during pregnancy*
Organophosphates	13	613	0.53	0.28, 0.99	0.56	0.10, 0.93	0.64	0.30, 1.36	*breastfeeding, mother's age at conception, income, father smoked during pregnancy*
Dicamba	8	282	0.69	0.30, 1.58	0.75	0.42, 2.66	1.10	0.39, 3.11	*mother's age at conception, breastfeeding, child's age*
Glyphosphate	5	384	0.30	0.10, 0.88	0.84	0.51, 1.67	0.86	0.18, 4.06	*income, maternal age at conception, child's age, breastfeeding*
2,4-DB	9	219	1.01	0.41, 2.44	1.08	0.20, 1.13	1.74	0.60, 5.07	*income, child's age*
2,4-D	23	571	1.07	0.54, 1.62	1.08	0.61, 1.92	1.75	0.91, 3.38	*father's education, child's age, breastfeeding*
MCPA	19	519	0.90	0.51, 1.60	0.92	0.29, 2.66	1.39	0.68, 2.81	*income, father's education, child's age, breastfeeding*
Atrazine	10	578	0.41	0.19, 0.85	0.43	0.30, 1.30	0.42	0.18, 0.94	*father's age, father smoked during pregnancy*
Cyanazine	6	161	0.82	0.28, 2.50	0.88	0.22, 1.52	0.49	0.10, 2.51	*income, mother's age at conception, father's education, father smoked during pregnancy*
Carbaryl	13	568	0.50	0.24, 1.04	0.63	0.30, 1.30	0.96	0.42, 2.18	*father's education, child's age at conception, income, breastfeeding*
Captan	5	189	0.64	0.26, 1.61	0.58	0.22,1.52	0.89	0.31, 2.56	*income, child's age, father smoked during pregnancy*
No Pesticide	**46**	**1162**	**1.00**	~	~	~	~	~	

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Base Model contains both the pesticide exposure & persistent ear infections. Generalized Estimating Equations used to calculate crude, base and adjusted odds ratios.
3. Adjustment: additional covariates that when added to the base model change the exposure odds ratio by 10% or more.

Note: child's age means the child's age at the time of the questionnaire

Table 18: Reported Farm Chemical Use during Pregnancy & Hearing Problems (stratified by gender)

	MALE OFFSPRING								FEMALE OFFSPRING							
PESTICIDE[1]	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI
Any Pesticide	54	1128	29	593	83	1727	1.45	0.80, 2.61	21	1115	17	572	38	1700	1.06	0.46, 2.41
Fungicides	16	364	29	593	45	958	1.32	0.57, 3.04	8	361	17	572	25	939	**	**
Insecticides	29	730	29	593	58	1324	1.28	0.62, 2.62	10	714	17	572	27	1295	**	**
Herbicides	42	854	29	593	71	1453	1.47	0.78, 2.76	15	843	17	572	32	1424	1.05	0.43, 2.56
Other Pesticides	6	192	29	593	35	785	1.26	0.44, 3.63	4	187	17	572	21	775	~	~
Phenoxy	30	511	29	593	59	1108	**2.15**	**1.12, 4.12**	13	541	17	572	30	1118	1.20	0.48, 2.99
Triazine	13	394	29	593	42	990	0.64	0.28, 1.45	8	392	17	572	25	970	0.52	0.18, 1.47
Thiocarbamate	5	207	29	593	34	804	0.60	0.20, 1.78	2	198	17	572	19	773	~	~
Organophosphates	11	308	29	593	40	902	1.04	0.42, 2.57	2	305	17	572	19	881	~	~
Dicamba	6	152	29	593	35	746	1.69	0.49, 5.81	2	130	17	572	19	706	~	~
Glyphosphate	4	199	29	593	33	792	~	~	1	185	17	572	18	761	~	~
2,4-DB	6	111	29	593	35	706	2.36	0.77, 7.18	3	106	17	572	20	681	~	~
2,4-D	16	275	29	593	45	869	**2.58**	**1.19, 5.62**	7	296	17	572	24	872	1.20	0.40, 3.58
MCPA	15	248	29	593	44	842	**2.30**	**1.05, 5.05**	4	271	17	572	21	847	~	~
Atrazine	4	282	29	593	33	876	~	~	6	296	17	572	23	873	0.76	0.24, 2.40
Cyanazine	2	77	29	593	31	672	~	~	4	84	17	572	21	661	~	~
Carbaryl	9	281	29	593	38	875	1.31	0.51, 3.36	5	287	17	572	22	864	**	**
Captan	4	95	29	593	33	688	~	~	1	94	17	572	18	671	~	~

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios. Same adjustment as models with all offspring

** unable to compute due to zero cells

Table 19: Reported Farm Chemical Use during Pregnancy & Epilepsy (all offspring)

PESTICIDE[1]	*No. Cases*	*No. Exposed*	*No. Cases*	*No. Unexposed*	*TOTAL*	*Crude OR*[2]	*95% CI*	*Adj. OR*[2]	*95% CI*	*Adjustment*[3]
Insecticides	13	1444	14	1961	3427	1.22	0.56, 2.67	1.08	0.46, 2.53	*income, maternal ethnicity, father smoked during pregnancy*
Herbicides	15	1697	12	1708	3427	1.29	0.59, 2.80	1.50	0.65, 3.47	*income, maternal ethnicity & weight gain during pregnancy*
Phenoxy	9	1052	18	2353	3427	1.12	0.48, 2.63	1.12	0.48, 2.63	~
Organophosphates	7	613	20	2792	3427	1.52	0.65, 3.54	1.27	0.52, 3.12	*income*
2,4-D	5	571	22	2834	3427	1.09	0.35, 3.37	1.20	0.38, 3.75	*maternal ethnicity*
Any Pesticide	19	2243	8	1162	3427	1.22	0.53, 2.81	1.46	0.56, 3.79	*father's age at conception, maternal ethnicity & weight gain during pregnancy*

1. Comparison Group is pregnancies not exposed to that type of pesticide during the pregnancy interval
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios.
3. Adjustment: additional covariates that when added to the crude model changed the exposure odds ratio by 10% or more.

Table 20: Reported Farm Chemical Use during Pregnancy & Hayfever or Allergies (all offspring)

PESTICIDE[1]	Exposed Cases	Total Exposed	Crude OR[2]	95% CI	Adj. OR[2]	95% CI	Adjustment[3]
Fungicides	76	725	0.96	0.68, 1.35	**1.69**	1.15, 2.47	*child's age, mother's & father's age at conception*
Insecticides	126	1444	0.84	0.63, 1.12	**1.48**	1.07, 2.03	*child's age, mother's & father's age at conception*
Herbicides	158	1697	0.94	0.72, 1.24	**1.56**	1.15, 2.11	*child's age, mother's & father's age at conception*
Other Pesticides	27	391	0.66	0.41, 1.08	1.25	0.68, 2.31	*child's age, mother's age & father's age at conception, father's education*
Any Pesticide	221	2243	1.00	0.77, 1.28	**1.58**	1.19, 2.08	*child's age, mother's & father's age at conception*
Phenoxy	95	1052	0.88	0.65, 1.20	**1.43**	1.03, 1.99	*child's age, mother's & father's age at conception*
Triazine	68	786	0.88	0.62, 1.23	1.32	0.89, 1.94	*child's age, mother's age & father's age at conception, father's education*
Thiocarbamate	36	405	0.81	0.52, 1.26	1.26	0.74, 2.16	*child's age, mother's age & father's age at conception, father's education*
Organophosphates	58	613	0.93	0.65, 1.32	**1.55**	1.02, 2.36	*child's age, mother's age & father's age at conception, father's education*
Dicamba	19	282	0.67	0.39, 1.14	1.51	0.77, 2.93	*child's age, mother's & father's age at conception*
Glyphosphate	19	384	0.49	0.29, 0.83	0.98	0.46, 2.10	*child's age, mother's age & father's age at conception, father's education*
2,4-DB	12	219	0.53	0.29, 0.98	1.03	0.51, 2.07	*child's age, mother's & father's age at conception*
2,4-D	52	571	0.90	0.63, 1.29	**1.66**	1.11, 2.49	*child's age, mother's & father's age at conception*
MCPA	43	519	0.83	0.55, 1.25	1.10	0.70, 1.71	*child's age, mother's age & father's age at conception, father's education*
Atrazine	44	578	0.77	0.52, 1.13	1.19	0.79, 1.79	*child's age, father's age at conception*
Cyanazine	15	161	0.82	0.40, 1.69	0.64	0.24, 1.71	*child's age, father's age at conception, father's education, income, maternal weight gain during pregnancy*
Carbaryl	46	568	0.75	0.50, 1.12	1.23	0.80, 1.90	*child's age, mother's & father's age at conception*
Captan	18	189	0.90	0.51, 1.60	1.18	0.59, 2.33	*child's age, mother's age & father's age at conception, income, maternal weight gain during pregnancy*
No pesticide	**120**	**1162**	**1.00**	~	~	~	~

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios.
3. Additional covariates that when added to the crude exposure model change the exposure odds ratio by 10% or more.

Table 21: Reported Farm Chemical Use during Pregnancy & Hayfever or Allergies (Stratified by Gender)

	MALE OFFSPRING								FEMALE OFFSPRING							
PESTICIDE[1]	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total preg	GEE OR[2]	95% CI
Any Pesticide	127	1128	64	590	191	1727	**1.63**	1.13, 2.34	94	1115	56	572	150	1700	1.35	0.90, 2.01
Fungicides	47	364	64	590	111	958	**2.12**	1.20, 3.76	29	361	56	572	85	939	1.14	0.56, 2.30
Insecticides	70	730	64	590	134	1324	**1.55**	1.02, 2.36	56	714	56	572	112	1295	1.30	0.82, 2.07
Herbicides	92	854	64	590	156	1453	**1.64**	1.10, 2.46	66	843	56	572	122	1424	1.29	0.83, 2.00
Other Pesticides	15	192	64	590	79	785	1.22	0.57, 2.61	12	187	56	572	68	775	1.13	0.45, 2.84
Phenoxy	60	511	64	590	124	1108	**1.73**	1.12, 2.62	35	541	56	572	91	1118	0.98	0.60, 1.62
Triazine	40	394	64	590	104	990	1.36	0.81, 2.26	28	392	56	572	84	970	1.10	0.63, 1.93
Thiocarbamate	22	207	64	590	86	804	1.26	0.62, 2.55	14	198	56	572	70	773	0.84	0.36, 1.96
Organophosphates	32	308	64	590	96	902	1.66	0.96, 2.86	26	305	56	572	82	881	1.33	0.72, 2.44
Dicamba	12	152	64	590	76	746	1.74	0.74, 4.11	7	130	56	572	63	706	1.04	0.35, 3.09
Glyphosphate	11	199	64	590	75	792	1.06	0.41, 2.68	8	185	56	572	64	761	0.70	0.20, 2.44
2,4-DB	6	111	64	590	70	706	0.84	0.34, 2.07	6	106	56	572	62	681	1.20	0.45, 3.23
2,4-D	30	275	64	590	94	869	**1.84**	1.08, 3.14	22	296	56	572	78	872	1.26	0.70, 2.28
MCPA	34	248	64	590	98	842	1.71	0.99, 2.95	9	271	56	572	65	847	0.42	0.19, 0.91
Atrazine	23	282	64	590	87	876	1.13	0.63, 2.03	21	296	56	572	77	873	1.08	0.61, 1.89
Cyanazine	10	77	64	590	74	672	0.84	0.21, 3.34	5	84	56	572	61	661	0.36	0.08, 1.59
Carbaryl	25	281	64	590	89	875	1.38	0.78, 2.44	21	287	56	572	77	864	1.08	0.59, 1.98
Captan	13	95	64	590	77	688	1.53	0.55, 4.23	5	94	56	572	61	671	0.44	0.11, 1.78

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios. Same adjustment as models with all offspring

Table 22: Other Farm Exposures

Farm Crops		Allergy Cases	Total Exposed	Crude OR	95% CI
Crop Acreage:					
Grains					
	low acreage	109	1033	1.02	0.72, 1.45
	high acreage	116	1209	0.95	0.67, 1.34
	zero acreage	89	876	1.00	
Hay and Fodder Crops					
	low acreage	57	616	0.81	0.56, 1.16
	high acreage	107	1174	0.78	0.58, 1.07
	zero acreage	150	1328	1.00	
Oilseeds					
	>0 acre	103	974	1.13	0.84, 1.51
	Zero	211	2144	1.00	
Other Field Crops					
	>0 acres	40	401	0.98	0.64, 1.49
	Zero	274	2717	1.00	
Fruit Trees or berries					
	Yes	40	260	**1.70**	1.11, 2.62
	No	274	2858	1.00	
Vegetables					
	Yes	59	406	**1.54**	1.06, 2.24
	no	255	2712	1.00	
Livestock:					
Cattle	(Beef or Dairy)				
	1 to 70 cows	55	532	0.90	0.62, 1.30
	>70 cows	101	1201	0.72	0.53, 0.98
	no cattle	158	1384	1.00	
Poultry					
	1 or more chickens	53	727	**0.66**	0.46, 0.95
	no poultry	261	2390	1.00	
Pigs					
	1 or more pigs	47	599	**0.72**	0.49, 1.06
	no pigs	267	2518	1.00	
Other animals (horses, sheep, goats, fox, rabbit, mink, other):					
	Yes	54	506	1.07	0.74, 1.55
	No	263	2611	1.00	
Mother worked with livestock during pregnancy interval: milking cows, or working with farm livestock					
	Yes	42	493	0.86	0.60, 1.23
	No	299	2912	1.00	
Mother was involved in field work during pregnancy*					
	Yes	124	1100	1.18	0.90, 1.56
	No	217	2305	1.00	
Father worked with livestock during pregnancy interval: milking cows, or working with farm livestock					
	Yes	27	282	0.93	0.56, 1.54
	No	314	3123	1.00	
Father was involved in field work during pregnancy*					
	Yes	233	2222	**1.22**	0.92, 1.62
	no	108	1183	1.00	

Table 23: Reported Farm Chemical Use during Pregnancy & Asthma (all offspring)

PESTICIDE[1]	No. Cases Exposed	Total Exposed	Crude OR[2]	95% CI	Adj. OR[2]	95% CI	Adjustment[3]
Fungicides	42	725	1.09	0.69, 1.70	1.25	0.74, 2.12	*father's age at conception, father's education, child's age at time of questionnaire*
Insecticides	78	1444	1.06	0.73, 1.54	1.06	0.73, 1.54	-
Herbicides	75	1697	0.87	0.60, 1.27	0.84	0.55, 1.30	*father's age at conception, income*
Other Pesticides	12	391	0.54	0.27, 1.10	0.55	0.23, 1.31	*income, father's education, child's age at time of questionnaire*
Any Pesticide	114	2243	1.00	0.71, 1.40	1.00	0.71, 1.40	-
Phenoxy	48	1052	0.88	0.58, 1.33	0.83	0.53, 1.32	*father's age at conception, father's education*
Triazine	36	786	0.93	0.58, 1.47	0.89	0.54, 1.48	*father's age at conception, father's education*
Thiocarbamate	22	405	1.04	0.63, 1.73	1.02	0.52, 2.00	*father's age at conception, father's education, child's age at time of questionnaire, income*
Organophosphates	30	613	0.95	0.59, 1.54	0.95	0.55, 1.65	*father's education, child's age at time of questionnaire*
Dicamba	10	282	0.70	0.35, 1.40	0.82	0.39, 1.71	*child's age at time of questionnaire*
Glyphosphate	21	384	1.07	0.61, 1.86	0.82	0.35, 1.90	*child's age at the time of questionnaire, income, father's education*
2,4-DB	11	219	1.04	0.53, 2.02	1.15	0.58, 2.30	*child's age at time of questionnaire*
2,4-D	24	571	0.78	0.45, 1.35	0.74	0.38, 1.43	*father's age at conception, father's education, income, father was smoker during pregnancy*
MCPA	23	519	0.89	0.54, 1.48	0.89	0.54, 1.48	-
Atrazine	23	578	0.79	0.47, 1.34	0.66	0.38, 1.17	*father's education, income*
Cyanazine	10	161	1.23	0.55, 2.76	0.98	0.38, 2.59	*income, father's education, maternal weight gain during pregnancy, child's age at time of questionnaire, father was smoker during pregnancy*
Carbaryl	28	568	0.97	0.59, 1.60	1.08	0.65, 1.82	*child's age at time of questionnaire*
Captan	8	189	0.83	0.35, 1.96	0.99	0.39, 2.52	*father's age at conception, child's age at time of questionnaire*
No Pesticide**	**59**	**1162**	**1.00**	~	~	~	

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios.
3. Additional covariates that when added to the crude exposure model change the exposure odds ratio by 10% or more.

Table 24: Reported Farm Chemical Use during Pregnancy & Asthma (Stratified by Gender)

	MALE OFFSPRING								FEMALE OFFSPRING							
PESTICIDE[1]	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total Preg	GEE OR[2]	95% CI	Exposed Cases	Total Exposed	Unexposed Cases	Total Unexposed	Total Cases	Total Preg	GEE OR[2]	95% CI
Any Pesticide	80	1128	38	593	128	1727	1.07	0.70, 1.64	34	1115	21	572	55	1700	0.83	0.48, 1.44
Fungicides	31	364	38	593	69	958	1.28	0.72, 2.27	11	361	21	572	32	939	**	**
Insecticides	50	730	38	593	88	1324	1.06	0.67, 1.67	28	714	21	572	49	1295	1.08	0.60, 1.95
Herbicides	56	854	38	593	94	1453	0.93	0.55, 1.56	19	843	21	572	30	1424	0.64	0.29, 1.42
Other Pesticides	10	192	38	593	48	785	0.71	0.24, 2.10	2	187	21	572	23	775	-	-
Phenoxy	34	511	38	593	72	1108	0.91	0.52, 1.61	14	541	21	572	35	1118	0.63	0.30, 1.31
Triazine	29	394	38	593	67	990	1.05	0.58, 1.89	7	392	21	572	28	970	0.47	0.16, 1.33
Thiocarbamate	16	207	38	593	53	804	1.19	0.56, 2.54	6	198	21	572	27	773	**	**
Organophosphates	20	308	38	593	58	902	0.93	0.49, 1.76	10	305	21	572	31	881	1.11	0.44, 2.75
Dicamba	8	152	38	593	46	746	0.91	0.41, 2.05	2	130	21	572	23	706	-	-
Glyphosphate	17	199	38	593	55	792	1.05	0.38, 2.91	4	185	21	572	25	761	-	-
2,4-DB	9	111	38	593	47	706	1.24	0.54, 2.82	2	106	21	572	23	681	-	-
2,4-D	16	275	38	593	54	869	0.75	0.35, 1.61	8	296	21	572	29	872	**	**
MCPA	18	248	38	593	56	842	1.13	0.61, 2.09	5	271	21	572	26	847	0.48	0.18, 1.28
Atrazine	18	282	38	593	56	876	0.76	0.39, 1.47	5	296	21	572	26	873	0.45	0.14, 1.48
Cyanazine	8	77	38	593	46	672	1.47	0.56, 3.89	2	84	21	572	23	661	-	-
Carbaryl	15	281	38	593	53	875	0.91	0.46, 1.79	13	287	21	572	34	864	1.48	0.69, 3.15
Captan	7	95	38	593	45	688	1.41	0.55, 3.61	1	94	21	572	22	671	-	-

1. Comparison Group is pregnancies with no reported pesticide use during the pregnancy period
2. Generalized Estimating Equations used to calculate crude and adjusted odds ratios. Same adjustment as models with all offspring

** unable to compute

Table 25: *Child Health Outcomes Age Stratified*

	ALLERGIES			ASTHMA			PERSISTENT COUGH/BRONCHITIS			FREQUENT EAR INFECTIONS			HEARING PROBLEMS		
Pesticide Exposure & Age Group	*Exposed Cases / Total Exposed*	*Adjusted OR*	*95% CI*	*Exposed Cases / Total Exposed*	*Adjusted OR*	*95% CI*	*Exposed Cases / Total Exposed*	*Adjusted OR*	*95% CI*	*Exposed Cases / Total Exposed*	*Adjusted OR*	*95% CI*	*Exposed Cases / Total Exposed*	*Adjusted OR*	*95% CI*
HERBICIDES															
0 to 2 years	12 / 414	0.77	0.21, 2.83	10 / 414	1.06	0.23, 4.78	7 / 414	0.55	0.17, 2.15	48 / 414	0.94	0.47, 1.87	2 / 414	–	–
3 to 7 years	37 / 557	2.05	0.82, 5.15	35 / 557	0.84	0.38, 1.85	20 / 557	1.42	0.53, 3.82	88 / 557	1.19	0.75, 1.88	10 / 557	–	–
8 to 11 years	47 / 443	1.17	0.76, 1.82	19 / 443	0.92	0.41, 2.10	11 / 443	1.03	0.42, 2.50	64 / 443	0.82	0.57, 1.22	30 / 443	–	–
>=12 years	**62 / 283**	**1.98**	**1.30, 3.01**	11 / 283	0.68	0.30, 1.55	9 / 283	0.87	0.39, 1.96	50 / 283	1.16	0.79, 1.71	15 / 283	–	–
INSECTICIDES															
0 to 2 years	8 / 363	0.55	0.15, 2.00	7 / 363	unable to compute		6 / 363	0.78	0.15, 4.04	42 / 363	0.91	0.45, 1.84	2 / 363	–	–
3 to 7 years	25 / 480	1.53	0.57, 4.08	36 / 480	1.32	0.65, 2.66	12 / 480	1.19	0.74, 1.91	75 / 480	1.19	0.74, 1391	8 / 480	–	–
8 to 11 years	52 / 388	1.46	0.94, 2.28	25 / 388	1.29	0.69, 2.41	13 / 388	0.72	0.48, 1.10	51 / 388	0.72	0.48, 1.10	22 / 388	–	–
>=12 years	**41 / 213**	**1.70**	**1.07, 2.70**	10 / 213	0.89	0.42, 1.87	10 / 213	0.66	0.41, 1.06	23 / 213	0.66	0.41, 1.06	7 / 213	–	–
FUNGICIDES															
0 to 2 years	7 / 176	1.24	0.21, 7.46	3 / 176	–	–	2 / 176	–	–	23 / 176	1.04	0.48, 2.24	2/ 176	–	–
3 to 7 years	15 / 251	1.21	0.45, 3.25	17 / 251	–	–	4 / 251	–	–	36 / 251	1.07	0.61, 1.85	6 / 251	–	–
8 to 11 years	29 / 188	1.76	0.95, 3.26	13 / 188	–	–	8 / 188	–	–	22 / 188	0.63	0.36, 1.10	11 / 188	–	–
>=12 years	25 / 110	1.63	0.90, 2.96	9 / 110	–	–	3 / 110	–	–	16 / 110	0.83	0.44, 1.56	5 / 110	–	–
ANY PESTICIDE															
0 to 2 years	14/ 508	0.73	0.21, 2.48	12 / 508	0.73	0.21, 2.48	8 / 508	0.51	0.13, 1.95	58 / 508	0.92	0.47, 1.81	3 / 508	–	–
3 to 7 years	40 / 705	1.65	0.69, 3.95	46 / 705	0.99	0.46, 2.11	26 / 705	1.46	0.56, 3.84	104/ 705	1.10	0.70, 1.72	11 / 705	–	–
8 to 11 years	9 / 62	1.47	0.98, 2.22	37 / 620	1.16	0.62, 2.17	23 / 620	1.53	0.71, 3.29	92 / 620	0.85	0.59, 1.21	42 / 620	–	–
>=12 years	**84 / 410**	**1.82**	**1.24, 2.67**	19 / 410	0.90	0.47, 1.74	13 / 410	1.24	0.56, 2.75	58 / 410	0.90	0.62, 1.30	19 / 410	–	–

Comparison Group is pregnancies with no reported pesticide use during the pregnancy period.
Generalized Estimating Equations used to calculate crude and adjusted odds ratios. Same adjustment as models with all offspring.
Strata were only analyzed if all cells had >5 exposed cases.

7.3 Chapter Summary

Overall, there was no clear indication of an association between reported use of pesticides during the pregnancy period and the development of frequent ear infections, persistent cough, epilepsy, or asthma in offspring. There was some indication that phenoxy herbicide exposure during pregnancy may have increased the susceptibility of male offspring to hearing problems. Furthermore, the results suggest a possible association between the development of allergies or hayfever and reported farm chemical use of some pesticides during the pregnancy period, especially in male offspring, the strongest association being with reported use of fungicides during pregnancy in male offspring (OR= 2.12, 95% CI=1.20-3.76). Phenoxy herbicides and the active ingredient 2,4-D were significantly associated with both hearing problems and allergies or hayfever in male offspring.

CHAPTER 8: DISCUSSION

There is an increasing body of scientific evidence suggesting that there are critical windows extending from conception to puberty when chemical insults may be more harmful to the development of the reproductive[277], immune[278], nervous[249], and endocrine[279] systems in children. A major strength of this study was its ability to evaluate the use of specific pesticide classes, families, and active ingredients during a defined time window (pre-conception, post-conception, and pregnancy). Furthermore, this investigation adds to the sparse literature examining the effects of *in utero* pesticide exposures and the development of childhood disease.

8.1 Birth Defects

8.1.1 Covariates

Previous research has suggested that male infants are at greater risk for a number of birth defects[280]. Our study suggested similar results when comparing male to female offspring (Crude OR=1.45, 95% CI=0.98-2.14). Maternal hyperthermia is a known risk factor for birth defects[63-66]. In our study population, women who reported having a fever during pregnancy were found to have an increased odds of birth defects in offspring. There was a near significant association between birth defects and the consumption of tea or coffee in the first trimester of pregnancy (crude OR=1.42, 95% CI=0.96-2.10), but not with cigarette smoking. This may reflect the tendency of women to underreport socially undesirable behaviors such as smoking, while more accurately reporting socially neutral behavior such as coffee and caffeine consumption[281]. We also found that the first born child was more likely to have a birth defect compared to later born children. In contrast,

several other studies have shown that children with a higher birth order are more likely to have oral clefts[282], congenital heart disease[283], and neural tube defects[283].

8.1.2 Parental Pesticide Exposures and Birth Defects

There were no statistically significant associations between reported pesticide use in the pre-conception or post-conception periods and birth defects in male and female offspring combined. However, reported use of cyanazine (OR = 4.44, 95% CI=3.66-4.99) and dicamba (OR=2.42, 95% CI=1.07-5.47) in the pre-conception period was associated with a significant increase in birth defects among male offspring.

Pre-conception Exposures

Exposures occurring in the pre-conception period (3 months prior to conception) are most likely acting on spermatogenesis in the father. Studies on workers occupationally exposed to a mixture of pesticides, including cyanazine, have shown some evidence of genotoxic effects[284;285]. Furthermore, experimental studies indicate that spermatozoa with DNA damage are still able to fertilize the oocyte, providing a mechanism for male-mediated reproductive effects[114]. Other epidemiologic studies examining the effect of paternal pesticide exposures during the pre-conception period have shown an increased risk among the offspring of fathers exposed to pyridil derivatives[149] and chlorophenate wood preservatives[159]. As well, fathers who worked in agriculture during this time period had an increased prevalence of cleft lip or palate[161], neural tube[182], developmental[160], limb-reduction[142], central nervous system, and urogenital defects in their offspring.

Herbicides

Both cyanazine and dicamba are herbicides. Cyanazine is a herbicide active ingredient from the triazine chemical family[286] and is used for early pre-plant, pre-emergence or post-emergence weed control of corn, cotton, grain, sorghum and fallow cropland[287]. Experimental studies have observed an increase in eye malformations (microphthalmia, anophthalmia) among rats exposed to cyanazine during gestation. These effects may be a result of direct toxicity to the fetus, and not simply a consequence of maternal toxicity[287]. Dicamba is a broad spectrum benzoic acid herbicide used for general weed control on grain crops, seed crops, pastures and non-crop areas[286]. Cavieres et al.[288] did not observe fetotoxicity among the pups of mice exposed to a common commercial herbicide formulation containing a mixture if 2,4-D, mecoprop, dicamba, and inactive ingredients. No epidemiological studies have looked specifically at the effects of cyanazine or dicamba on pregnancy outcomes however some have shown increases in birth defects among the offspring of parents with potential unspecified herbicide exposures[140;141;147]. In contrast others have observed no effect for fathers who were occupational exposed to 2,4,5-T[153;154;236], MCPA[149], and chlorophenoxy herbicides[149].

Post-conception Exposures

Our study found some numerical elevations for post-conception pesticide exposures and birth defects. In male offspring, the reported use of fungicides, thiocarbamates and organophosphates on the farm during the first trimester of pregnancy exhibited non-significant elevations in risk, with odds ratios exceeding 1.6. Exposures occurring during this period are presumed to be acting on organogenesis through the mother. Studies exploring potential maternal exposures to pesticides during a critical time window that includes the period of organogenesis have shown increases in any birth

defect[162], total anomalous pulmonary venous return[289], transposition of the great arteries[147], abdominal wall defects[166], orofacial clefts[174], and developmental and musculoskeletal defects[176]. Conversely, other studies have shown no association with birth defects with potential pesticide exposures within this exposure window [164;169-172;290].

Organophosphates

Our study showed a numerically elevated risk of any birth defect among male offspring exposed to organophosphate pesticides in the post-conception period (OR=1.62, 95% CI=0.74-3.52). Previous studies have found significant elevations in the prevalence of clubfoot, anomalies of the ear, bowed legs[125] and gastrointestinal anomalies[179] among California births potentially exposed to malathion and organophosphates through aerial spraying applications during pregnancy. As well, Bell et al.[133] found that the application of phosphates in the same township, range or section during organogenesis increased the risk of fetal death due to congenital anomalies (OR=2.9, 95 % CI=1.3-6.6). Conversely, other studies have shown no increase in risk for parents exposed to organophosphates[149;155], or the active ingredients malathion[149], or glyphosphate[149] during a critical exposure window.

Fungicides

The reported use of fungicides in both the pre- and post-conception periods was numerically elevated, with odds ratios above 1.50 in male offspring. Dimich-ward *et al.*[159] found a significant increase in eye defects (OR=1.47, 95% CI=1.1-2.0) amongst the offspring of fathers exposed to the fungicide chlorophenate while working in British Columbia sawmills. Garry et al.[183] observed that infants conceived in the spring in areas

of high fungicide and herbicide use showed a significant increase in birth defects as compared to infants conceived in other seasons (OR=1.36, CI, 1.10-1.69).

Direct Chemical Activity

There was no evidence that a father's involvement in a chemical activity, coupled with the reported use of pesticides in the post-conception period, had any association with birth defects in offspring. Chemical activities included mixing or applying chemicals to crops for weed, brush, insect or disease control, applying chemicals to livestock for insects and disease, or applying chemicals around the yard and buildings to control weeds, brush or pests. This combined exposure measure is considered to be a more accurate measure of exposure for this dataset. Most risk estimates remained insignificant or moved closer towards the null, suggesting no association with paternal pesticide exposure and birth defects, or that this was not an improved exposure measure.

Male Susceptibility

No increase in risk was observed in female offspring from reported use of pesticides in the pre-conception and post-conception periods. In fact, herbicide use in the pre-conception period appeared to be protective against birth defects (OR=0.36, 95% CI=0.14-0.93). However this may have been due to low numbers as there were only 5 exposed cases. Alternatively, it may suggest that male offspring are differentially susceptible to *in utero* exposures. Bradley et al.[291] found an increase in craniosynostosis (premature fusion of cranial sutures) in male offspring when fathers worked in agriculture or forestry for at least 10 hours a week during the 3 months prior to conception (OR=10.4, 95% CI=2.3-46.5). Schreinemachers[184] observed an increase in circulatory/respiratory (OR=1.83, 95% CI=1.06-3.14), "other" circulatory/respiratory

(OR=2.05, 95% CI=1.02-4.09) and all circulatory/respiratory defects (OR=1.83, 95% CI=1.06-3.14) in male offspring in areas of high as compared to low wheat acreage. Other studies have shown an increase in the risk of specifically male birth defects among parents potentially exposed to pesticides including hypospadias and cryptorchidism[142;211].

Musculoskeletal Defects

No significant associations were observed between reported pesticide use in the pre- or post-conception periods and musculoskeletal defects. However, the odds ratio for musculoskeletal defects in relation to fungicide exposure in the post-conception period was numerically elevated (OR=2.29, 95% CI=0.89-5.93). Other research has shown significant elevations in musculoskeletal defects among women employed in agriculture or horticulture for 15 or more hours a week at the time of conception[176]. Also, an increased risk of musculoskeletal/integument defects (ICD-9: 754-757) was observed among families living in high verse low wheat regions (OR=1.50, 95% CI=1.06-2.12)[184], and in the wheat/sugar beets region (OR=1.75, 95% CI=1.4-2.2) [183] relative to urban regions in Minnesota. The wheat/sugar beets/potatoes region was considered to be a high pesticide use region based on poundage of fungicides and chlorophenoxy herbicides.

8.2 Child Health Outcomes

There are few human studies that have examined potential child health effects, excluding pregnancy outcomes, of *in utero* pesticide exposures. Vietnam veterans exposed to Agent Orange reported more child health conditions among their offspring (OR=1.3, 95% 95% CI=1.2-1.4)[223] than did the general US population. More than half of the reported childhood health problems were respiratory diseases and diseases of the ear. Elevated odds ratios were also seen for anemia (OR=2.0, 95% CI=1.2-3.3), diseases

of the skin (OR=1.5, 95% CI=1.1-1.9), rash (OR=2.3, 95% CI=1.1-4.9), and allergies (OR=1.6, 95% CI=1.2-2.1). Dewailly et al.[264] found an association between middle ear infections in Inuit children and prenatal exposure to organochlorines, specifically the pesticide metabolite DDE. Studies examining the effects of *in utero* exposures to other environmental contaminants have shown increases in the prevalence of middle ear and pulmonary diseases among infants born to Taiwan women exposed to polychlorinated biphenyls and polychlorinated dibenzofurans through the consumption of contaminated rice oil[261;265]. Dutch children were found to have a decrease in immune parameters after prenatal exposure to background levels of PCBs and dioxins. However, prenatal exposures were not significantly associated with infectious or allergic disease within the first few years of life[292;293].

8.2.1 Covariate analysis

The crude covariate analysis showed some strong associations with specific child health outcomes (see Table 12). For example, maternal history of allergies and asthma was significantly associated with the development of allergies or hayfever (OR=4.15, 95% CI=3.14-5.49) and asthma (OR=2.58, 95% CI=1.45-4.61) in children. Studies on families with allergic disease have suggested that there are strong genetic factors responsible for atopic disease (asthma, allergic rhinitis, and atopic dermatititis)[294]. A moderate association was also observed between low birthweight and asthma (OR=2.33, 95%CI=1.21-4.49). Other studies have observed low birthweight[295] and pregnancy complications[296] to be associated with an increased risk of asthma. Also, a strong association was observed between frequent ear infections and hearing problems (OR=9.59, 95% CI=6.31-14.57) in this study populaton. Otitis media with effusion has

been suggested as one of the most common causes of acquired hearing loss in children[297]. Male offspring had an increased odds of persistent cough or bronchitis (OR=1.41, 95% CI=0.96-2.07), hearing problems (OR=2.28, 95%CI=1.54-3.39), allergies or hayfever (OR=1.24, 95%CI= 0.99-1.54), and asthma (OR=2.12, 95% CI=1.54-2.93). Other studies have confirmed a higher prevalence of atopy and pre-adolescent asthma in male children [298]. Finally, younger children (aged 0 to 2 at the time of the questionnaire) were less likely to develop frequent ear infections, hearing problems, allergies or hayfever, and asthma. These finding may simply reflect the fact that younger children have less time to develop these conditions, or they are much harder to recognize and/or diagnose at this age.

8.2.2 Potential *in utero* Pesticide Exposure and Child Health Outcomes

Our study did not reveal any significant associations between potential parental pesticide exposures during pregnancy and the development of asthma, frequent ear infections, epilepsy, persistent cough, or bronchitis in offspring. There was some indication that reported use of phenoxy herbicides during the pregnancy interval may have increased the susceptibility of male offspring to hearing problems. In addition, the development of allergies or hayfever appeared to be more common in children who had been potentially exposed to pesticides during the pregnancy period, especially in male offspring.

Allergies or Hayfever

Interestingly, a number of studies have shown farm children to have a reduced risk of allergies[299-301]. In our study population, the prevalence of developing allergies or hayfever in offspring was close to 10%. However, the odds of allergies or hayfever was

significantly elevated in children who lived on farms with reported use of any pesticide (OR=1.58, 95% CI=1.19-2.08), fungicides (OR=1.69, 95% CI=1.15-2.47), insecticides (OR=1.48, 95% CI=1.07-2.03), herbicides (OR=1.56, 95% CI=1.15-2.11), organophosphates (OR=1.55, 95% CI=1.03-1.99), phenoxy herbicides (OR=1.43, 95% CI=1.03-1.99), and 2,4-D (OR=1.66, 95% CI=1.11-2.49) during the pregnancy period, compared to children living on farms with no reported use of any pesticide use during this same time period. Also, "season of conception" was not found to be associated with the development of allergies, and was therefore not a counfounding factor (see Table 12).

When restricting the analysis to male offspring, most of the estimates remained significant, with the highest risk estimate for allergies or hayfever being associated with fungicide use (OR=2.12, 95 % CI=1.20-3.76) during the pregnancy period. No such effects were seen when the analysis was restricted to female offspring.

The age-stratified analysis suggested that *in utero* pesticide exposures increased the risk of allergies, most notably in children who were 12 years of age and over at the time of the questionnaire (see Table 25). Children aged 12 and over had nearly double the odds of having allergies or hayfever if they were exposed *in utero* to herbicides (OR=1.98, 95 % CI=1.30-3.01), insecticides (OR=1.70, 95% CI=1.07-2.70), or any pesticide (OR=1.82, 95% CI=1.24-2.67) in comparison to unexposed children of the same age. The elevated odds ratio seen in this age category, but not in younger children, may simply reflect the fact that allergies increase with age (either due to later development or later recognition).

It has been suggested that approximately 40% of the world's population is atopic[294]. The principal biological feature of atopic individuals is the enhanced ability of

their B-lymphocytes to produce IgE antibodies that activate the immune system in response to otherwise "innocuous" environmental antigens after inhalation, ingestion, or penetration through the skin[302]. In humans, immune development begins early in embryonic life and continues through the early postnatal period. Risk factors for allergic disease include genetic predisposition, early childhood infections, maternal cigarette smoking during pregnancy, early allergen sensitization, poor diet, lack of breast-feeding, prematurity and low birth weight, air pollution, and frequent immunizations in childhood[294]. As well, the risk of immune system impairment or modulation from some environmental contaminants has been shown to be increased if the exposure occurs *in utero* or during early infancy[263].

Few epidemiologic studies have examined the association between prenatal pesticide or other environmental exposures and the subsequent development of atopic disease in children. Reichrtov et al.[303] found a positive correlation between *p,p'*-DDE concentrations in placental tissue and cord serum levels of IgE (r=0.3294, p=0.01). Higher IgE levels in cord blood have been suggested by some as a good predictive test for atopy[303]. As well, Vietnam veterans exposed to Agent Orange prior to their wives becoming pregnant reported more offspring with diseases of the skin (OR=1.5, 95% CI=1.1-1.9), rash (OR=2.3, 95% CI=1.1-4.9), and allergies (OR=1.6, 95% CI=1.2-2.1). Yet another study has shown no increase in allergies among children prenatally exposed to background levels of PCBs and dioxins[293].

Hearing Problems

After controlling for frequent ear infections, there was a moderate increase in the odds of hearing problems among male offspring potentially exposed to phenoxy

herbicides (OR=2.15, 95% CI=1.12-4.12), 2,4-D (OR=2.58, 95% CI=1.19-5.62) and MCPA (OR=2.30, 95% CI=1.05, 5.05) during pregnancy. Other studies have shown that congenital cytomegalovirus, herpes, toxoplasmosis, syphilis, rubella, as well as certain ototoxic medications taken during pregnancy, have been associated with hearing loss in offspring[304]. Developmental ototoxicity has been observed among rats gestationally exposed to the PCB mixture Aroclor 1254[305;306]. Low frequency deficits were seen among 18 month old rats who received 6 mg/kg Aroclor 1254 in corn oil from gestation day 6 to lactational day 21[305]. As well, a human case study described a woman working in Africa who applied 25% DEET to her arms and legs once or twice a day through the duration of her pregnancy. In the first month of life, her child was observed to have statomotor retardation, muscular hypotonia, central hearing loss, and strabismus[241].

8.3 Study Observations

Interestingly, phenoxy herbicides and the active ingredient 2,4-D were both moderately associated with hearing problems and allergies or hayfever in male offspring. Previous work on this same farm population has shown phenoxy herbicide use in the pre-conception period to be associated with early spontaneous abortions (<12 weeks)[26]. As well in a subsequent biomonitoring study on a subset of this population, approximately 50% of Ontario farmers who reported using phenoxy herbicides in 1991-1992 had detectable levels of 2,4-D in their semen[307].

8.4 Study Limitations

8.4.1 Reliability of the Exposure Assessment

The reliability* of the exposure assessment may have been affected by the retrospective nature of this study, and the fact that the recall period of pesticide use often exceeded 10 years (approximately 30% of pregnancies). As well, more than 10% of the values were imputed for some pesticide groupings (see Appendix F for the percentage imputed, and section 5.2.1.2 for details on the imputation method). The reliability of self-reported exposure information from pesticide applicators was recently examined by Garry et al.[146] They found that the relative frequency of commonly applied pesticides was nearly identical for pesticide usage reported in a phone survey and that reported in a subsequent self-reported written survey carried out 6 months later.

The validity† of the exposure assessment is also uncertain due to a number of factors that were not measured including quantity of pesticides used, and time spent applying pesticides, which would have modified acutal exposures. Also, we did not account for pesticide half-lives, so the unexposed group may have been inadvertently exposed due to the persistence of the pesticides in the farm environment after application. In a study conducted by Arbuckle et al.[308] the sensitivity and specificity of self-reported herbicide exposures against urinary measures of exposure depended on the type of active ingredient measured. The questionnaire-based prediction of exposure had a sensitivity of 56.7% and specificity of 86.4% for 2,4-D, while MCPA had a sensitivity and specificity of 91.6% and 67.4%, respectively. Another recent study[309] found that only 60% of

* "..the degree to which the results obtained by a measurement, procedure can be replicated. Lack of reliability may arise from divergences between observers or instrument of measurement or instability of the attribute being measured". Last, JM. 2001. A dictionary of Epidemiology. Oxford University Press.

† "..the degree to which a measurement measures what it purports to measure". Last, JM. 2001. A dictionary of Epidemiology. Oxford University Press.

farmers had detectable levels of glyphosate in their urine on the day of its application. In addition, farmers who did not use rubber gloves had a higher geometric mean urinary concentrations of glyphosate as compared to those who did (10 ppb versus 2.0 ppb). Also, in the analysis of birth defects, an additional exposure group was created to look at couples who lived on farms where the father had reported direct chemical activity during an exposure window, in which there was reported use of a particular pesticide class, family or active ingredient during the same time period.

Although pesticide active ingredients were identified, it is unknown if these groupings are relevant to reproductive toxicity. Most pesticides also contain carrier substances added to the active ingredients in order to improve absorption. These so-called inert substances, or contaminants introduced during processing, may be more harmful than the active ingredients[2]. Moreover, the effect of mixtures may be more important due to possible synergistic or additive effects than the active ingredients themselves.

We were also unable to completely separate the effects of maternal and paternal exposures. For birth defects, we assumed that exposures occurring in the pre-conception period were acting on spermatogenesis, while maternal exposures were more relevant in the first trimester of pregnancy. Pesticide residues have been measured in human semen[307;310], and may have been passed to the woman during intercourse. Therefore, paternal exposures in the post-conception period may have been relevant. Also, depending on the half-life of the pesticide, maternal exposures occurring in the pre-conception period may have been of importance.

8.4.2 Recall Bias

Differential recall bias would have occurred if mothers of malformed infants or children with health problems recalled their exposures more thoroughly than mother's of healthy infants or children[242]. It is unlikely that there was differential exposure misclassification in this study because the majority of exposure information came from the farm operator, and women reported on reproductive outcomes (see Appendix A). Furthermore, the farm operator reported on the years and months of use of farm chemicals, and was not made aware of relevant "time window" of exposure to the fetus.

8.4.3 Limitations to the Outcome Assessment

Birth Defects

Although birth defects had the advantage of being reported by the mother and not the father, self-reported outcomes may introduce bias due to erroneous recall. However, pregnancy is a major life event for most people, and Olsen[245] suggests that the events that occurred during pregnancy are often accurately recalled even several years afterwards.

Other limitations included the vagueness of the outcome measures (i.e., any birth defect), and the uncertainty surrounding the validity of using disease classifications (i.e., musculoskeletal defects). Use of the category "any congenital anomaly" as an outcome measure has been criticized for its vagueness[244]. Furthermore, Olsen et al.[245] suggest that disease classification is based on certain principles, but not on principles associated with causal research[244].

Other challenges relate to missed birth defects. Since the prevalence of birth defects was derived from fetuses that survived until birth, malformations that were part of syndromes incompatible with fetal life, or those electively aborted due to prenatal

screening, are not represented in this analysis[245]. Consequently, the true incidence of birth anomalies may be much higher than the prevalence of such anomalies at birth.

Child Health Outcomes

A major limitation in the present investigation of child health outcomes was the fact that the child's age at diagnosis was not provided. Children were grouped according to developmental stages at the time of the questionnaire, but their actual age at the time of diagnosis was unknown. Given this limitation, the analyses of child health outcomes should be interpreted with caution. Moreover, the outcome measures were self-reported, further limiting their precision due to possible erroneous recall.

8.4.4 Other Limitations

Other factors such as unmeasured confounders or selection bias[‡] may have affected the findings. Although the participation rate was fairly high, those that agreed to participate may have been more concerned about their health, or may have had more family health problems than those who did not participate. Finally, given the modest sample size the power to detect an association was low for rare outcomes such as birth defects and epilepsy.

8.5 Weight of Evidence

In general, our study did not find strong evidence for an association between parental pesticide exposure during the pre-conception or post-conception windows and birth defects among the offspring of Ontario farm families. There was some indication that pre-conception exposure to cyanazine and dicamba increased the risk of birth defects in male offspring. However, given the large number of parameters estimated and the low

number of pregnancies exposed in these two categories, it is possible that this association was due to chance. Nevertheless, since animal studies have shown cyanazine to induce birth defects, this association should be investigated further.

The analysis of the child health outcomes did not reveal any strong associations between pesticide exposures during pregnancy and frequent ear infections, persistent cough or bronchitis, asthma, or epilepsy. There was suggestive evidence that hearing problems were more common in male children, who were exposed to pesticides during pregnancy. Specifically, phenoxy herbicides (OR=2.15, 95% CI=1.12-4.12) and the active ingredients 2,4-D (OR=2.58, 95% CI=1.19-5.62), and MCPA (OR=2.30, 95% CI=1.05-5.05) all exhibited moderate increases in the risk of hearing problems. As well, allergies and hayfever appeared to be more common in offspring, especially male offspring, exposed to pesticides during the pregnancy period. The most prominent association between pesticides and allergies and hayfever was with fungicides (OR=2.12, 95% CI=1.20-3.76). Nevertheless, given the lack of research examining *in utero* exposures on the development of allergies and other child health outcomes, these findings can only serve to generate hypotheses for future research.

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‡ "Selection bias results in errors due to systematic differences in characteristics between those who took part in a study and those who do not is known as selection bias". Last, JM. 2001. A dictionary of Epidemiology. Oxford University Press.

8.6 Conclusions

Several environmental chemicals with known adverse health effects have been found in umbilical cord blood[311], amniotic fluid [312;313], and meconium[314]. At the same time, scientists are increasingly recognizing the impact of the *in utero* environment on the later health of the child and adult[23;24]. In light of this, and the suggestive findings of this thesis, there is a need for a large well-designed prospective longitudinal study to examine the effect of environmental contaminants on Canada's children. A number of recent review articles have been written that address methods for improving the assessment of early life exposures in preparation for the U.S. National Children's Study[315-318]. Ideally, such a study would span the pre-conception period through to adolescence or even adulthood, with repeated biological sampling to measure background and intermittent exposures to non-persistent pesticides and other contaminants. Utilizing biomarkers such as concurrent measurements of maternal serum during pregnancy, as well as umbilical cord blood, meconium, and amniotic fluid at birth, would increase the sensitivity, specificity and power of the study[157]. Meconium and amniotic fluid collected at birth would represent cumulative exposures during pregnancy. Also, evidence suggests that the half-life of xenobiotics in meconium can be prolonged[315].

In conclusion, this study is one of only a few to examine the human health effects of specific pesticide exposures during the pre-concepton and pregnancy period. Some suggestive findings were found linking some pesticide exposures and birth defects, hearing problems, and allergies or hayfever in male offspring. Future better designed studies are needed to elucidate these findings.

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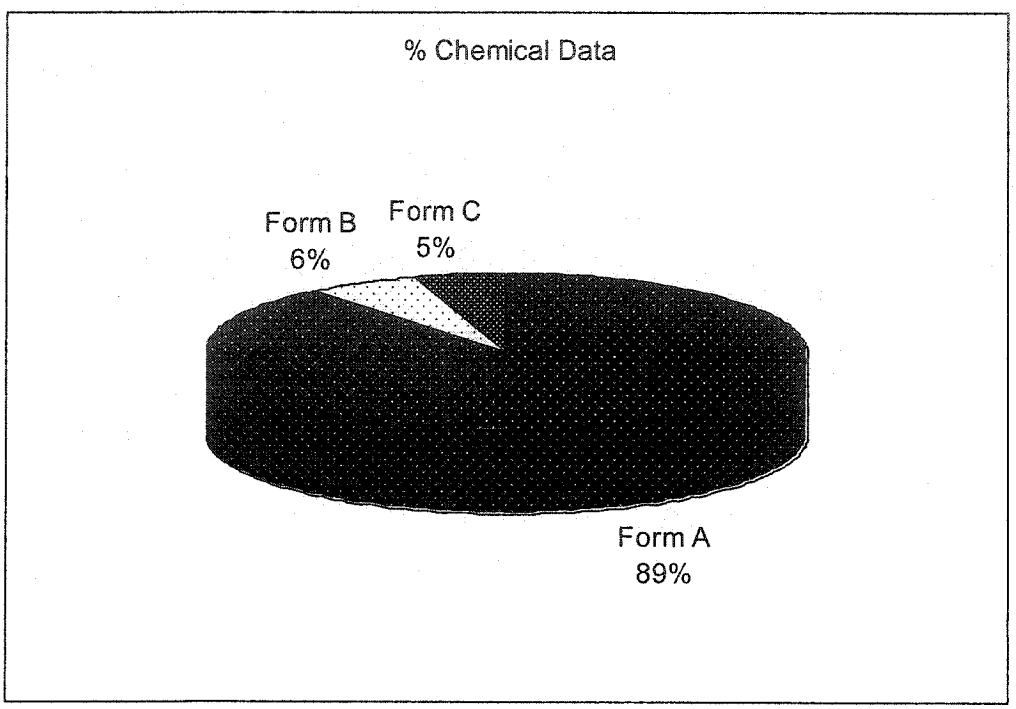
Appendixes

Appendix A: Chemical Data

All chemical data pertaining to pesticide use in forms A, B and C, and their dates of use were extracted into a pesticide history file (from HISTUSE file).



Appendix B: Summarized ICD-9 Codes for Birth Defects

Frequency of Birth Defects

Variable	ICD-9 Codes	Freq ANOMALY 1	Freq ANOMALY 2	Total	Percent of Pregnancies
Face and neck	744.0-744.9		1	1	
Chromosomal	758.0-758.8	4		4	
Digestive	750.0.-751.9	14	1	15	
CNS	740.0-742.9	4	2	6	
Cleft lip/palate	749.0-749.2	4	2	6	
Urogenital	752.6-753.9	9		9	
Heart	745.0-746.9	12	1	13	
Musculoskeletal	754.0-756.9	39	5	44	
Integument	757.0-757.9	20		20	
Total Birth Defects	All	106	12	118	
Pregnancies ending with multiple birth defects				10	0.29
Pregnancies that resulted in a single birth defect				98	2.87
Pregnancies with one or more birth defects				108	3.17
Pregnancies resulting in one or more musculoskeletal defects				43	1.26
Pregnancies ending in a musculoskeletal and/or Integumental defect				63	1.85

Appendix C: Detailed ICD-9 Codes

Defect Category	ICD-9 Codes	Code
Chromosomal	758.00-758.81	CHROM
Gastrointestinal	750.3-751.8	DIGEST
CNS	740.0-742.9	CNS
Cleft lip/palate	749	CLEFT
Urogenital	752.5-753.9	UROGEN
Cardio	746.87-747.9	HEART
Muscskel	754-756.9	MUSK
Integumental	757.39	INTEG
All birth defects		ANOMLY3

SAS Code	Birth defect written by participant	Anomly1	Anomly2	Total	ICD-9 Codes	Name	Birth Defect Category
48	Aarskog Syndrome	1		1	758.81	Other conditions due to chromosome anomalies	CHROM
103	trisomy 18	1		1	758.2	Edwards syndrome: trisomy 18	CHROM
134	Syndrome d'Edwards	1		1	758.2	Edwards syndrome: trisomy 18	CHROM
178	Down's syndrome	1		1	758	Down's syndrome	CHROM
121	cleft palate, and no roof in mouth	1	1	2	749	Cleft palate	CLEFTS
187	hair lip, cleft palate	1		1	749	Cleft palate	CLEFTS
113	Cleft palate	2	1	3	749	Cleft palate	CLEFTS
32	hydrocephalic		1	1	742.3	Congenital hydrocephalus	CNS
80	microcephalic	1		1	742.1	Microcephalus	CNS
81	Encephalocele/encephalitis		1	1	742	Encephalocele	CNS
144	spina bifida	3		3	741.9	Spina bifida	CNS
73	Hischburg's disease	1		1	751.3	Hischsprung's disease and other congenital function disorders of the colon	DIGEST
76	Bowel intersuspension/bowel blockage	2		2	751.2	Atresia and stenosis of large intestine, rectum and anal canal	DIGEST
34	pyloric stenosis	5		5	750.5	Congenital hypertrophic pyloric stenosis	DIGEST
162	no esophagous	1		1	750.3	Tracheoespophageal fistula, esophagus Atresia and stenosis: absent esophagou listed.	DIGEST
17	tongue tied	5	1	6	750.0	Tongue tie: Ankyloglossia	DIGEST
14	Almost deaf/ profoundly deaf		1	1	744	Unspecified anomaly of ear with impairment of hearing	EARPROB
209	corarctation of aorta		1	1	747.1	Corarctation of Aorta	HEART
119	malformed valve in heart	1		1	746.9	Unspecified anomaly of heart	HEART
131	heart condition (techtroloyseto)	1		1	746.9	Unspecified anomaly of heart	HEART

SAS Code	Birth defect written by participant	Anomly1	Anomly2	Total	ICD-9 Codes	Name	Birth Defect Category
183	hole in heart, blind	1		1	746.9	Unspecified anomaly of heart	HEART
184	Asymetric hypertrophic cardiomyopathy	1		1	746.9	Unspecified anomaly of heart	HEART
51	hole in lower septile of heart	3		3	746.9	Unspecified anomaly of heart	HEART
102	heart defect/problem	3		3	746.9	Unspecified anomaly of heart	HEART
116	Congested heart (left part didn't form)	1		1	746.9	Unspecified anomaly of heart	HEART
45	Atrial septal defect	1		1	745.5	Ostium secundum type atrial septal defect	HEART
39	left ear excess top flip over	1		1	757.39	Other skin anomalies: accessory skin tags	INTEG
16	skin tags	2		2	757.39	Other skin anomalies: accessory skin tags	INTEG
114	extra ear lobe / extra skin on ear	2		2	757.39	Other skin anomalies: accessory skin tags	INTEG
36	skin tags on ear	4		4	757.39	Other skin anomalies: accessory skin tags	INTEG
88	port wine stain on arm	2		2	757.32	Vascular hamartomas: Port-wine stain	INTEG
118	birthmark	9		9	757.32	Vascular hamartomas: birthmarks	INTEG
98	diaphragmatic hernia	1		1	756.6	Anomalies of diaphragm: congenital hernia	MUSKSKEL
193	hole in diaphragm	1		1	756.6	Anomalies of diaphragm	MUSKSKEL
15	Ollier's Disease	2		2	756.4	Chondrodystrophy: Ollier's disease	MUSKSKEL
84	extra bone on sternum	1		1	756.3	Other anomalies of ribs and sternum	MUSKSKEL
188	no soft spot - head already fused together		1	1	756	Anomalies of the skull	MUSKSKEL
1	sutures closed prematurely	1		1	756	Anomalies of the skull	MUSKSKEL
61	partially fused skull	1		1	756	Anomalies of the skull	MUSKSKEL
174	fusion of sutures bones in the skull	1		1	756	Anomalies of the skull	MUSKSKEL
106	missing thumb	1		1	755.21	Transverse deficiency of upper limb: congential absence of fingers (partial)	MUSKSKEL
33	syndactyly, diabetes	1		1	755.1	Syndactyly	MUSKSKEL
101	two toes joined	1		1	755.1	Syndactyly	MUSKSKEL
120	toes joined and fingers joined	1		1	755.1	Syndactyly	MUSKSKEL
41	extra thumb	1		1	755.01	Polydactyly	MUSKSKEL
25	six fingers on each hand	1		1	755.01	Polydactyly	MUSKSKEL
136	pectineus excavatum	1		1	754.81	Pectus excavatum: congenital funnel chest	MUSKSKEL
189	crooked foot talipes equinovalgut	1		1	754.7	Other deformities of the foot	MUSKSKEL
35	club foot /feet	5	1	6	754.69	Talipes equinovalgus	MUSKSKEL
57	very flat feet	1		1	754.61	Congenital pes plansus: flat foot	MUSKSKEL
3	foot turned inward	3	1	4	754.60	Other deformities of the foot: Talipe valgus	MUSKSKEL
191	feet pointing in, crooked hips		1	1	754.3	Congenital dislocation of hip	MUSKSKEL
31	feet toe-in - caused by hips	1		1	754.3	Congenital dislocation of hip	MUSKSKEL
68	loose hip	1		1	754.3	Congenital dislocation of hip	MUSKSKEL

SAS Code	Birth defect written by participant	Anomly1	Anomly2	Total	ICD-9 Codes	Name	Birth Defect Category
72	hip not fully developed	1		1	754.3	Congenital dislocation of hip	MUSKSKEL
108	clicking hips	2		2	754.3	Congenital dislocation of hip	MUSKSKEL
7	hips displaced/hip problem that required harness	3	1	4	754.3	Congenital dislocation of hip	MUSKSKEL
9	dislocated hip	3		3	754.3	Congenital dislocation of hip	MUSKSKEL
143	congential hip/congenital hip displacement	3		3	754.3	Congenital dislocation of hip	MUSKSKEL
129	kidney problem	1		1	753.9	Unspecified anomaly of urinary system	UROGEN
197	kidney	1		1	753.9	Unspecified anomaly of urinary system	UROGEN
64	blocked kidneys	1		1	753.2	Unspecified obstructive defect of renal pelvis and ureter.	UROGEN
91	kidney blockage	1		1	753.2	Unspecified obstructive defect of renal pelvis and ureter.	UROGEN
87	hypospadias	3		3	752.6	hypospadias	UROGEN
12	undescended testes	2		2	752.5	Undescended testes	UROGEN

Appendix D: Other Hazardous Jobs

Other hazardous jobs off the farm (responses from questions C0048, c0053, c0056, c0056 in Form C)

Pesticide Jobs

Code	*Description*
481	Exterminator
19	Farm Laborer
67	Farm Manager
164	Farm Work/Welding
498	Farmer
35	Farming
44	Florist
70	Gardeners Helper
02	Greenhouse Duty Foreman
07	Greenhouse Work
32	Horticulturist
212	Landscape Laborer
335	Landscape Work
171	Nursery Work
309	Vegetable Farm
465	Worked In Orchard
107	Greenhouse Work
584	Pesticide Trials

Hazardous Jobs

Code	*Description*
100	Metallurgist
109	Dental Assistant
354	Dentist
185	Operating room technician
433	Pharmacist
80	Pharmacy tech
132	Radiological tech
90	X-ray tech
437	Pharmacist
233	Pharmacy assistant
439	Camera operation/dark room
512	Cleaning lady
545	Fire fighter, carpenter
457	Fireman
308	Gas station attendant
128	Hairdresser
30	Hairdresser apprentice
204	House/office cleaner
66	Housekeeper
103	Janitor
46	Dump-site furnace operator
442	Chemical worker
350	Gluemaker
549	Shift chemist
84	Leather Tanner
230	Aluminum die cast machine operator
23	Blacksmith
291	Grader operator
517	Grinding manifolds
280	Iron worker
38	Machinist
184	Sheet metal work
379	Steelwork
398	Tool and die maker
86	Welder
284	Welder, mechanic
247	Welder, pipefitter
217	Winding coils
179	Wood working
397	Manufacturer of aluminum products
118	Restoration of antique furniture
251	Steel/metal fabricator
482	Painter
403	Painting and wallpaperer
509	Handle petroleum products

Appendix E: Checking for Other Potential Covariates

Confounders were identified by individually adding those risk factors with crude odds ratios > 1.2 or < 0.8 to the base (effect of exposure plus *a priori* covariates on the outcome) or crude models (effect of the exposure on the outcome). If the exposure odds ratio changed by 10% or more the covariate was retained in the final model.

1. Base Models with *a priori* variables

Outcome	*A priori variables*
Any Birth defect	Exposure Maternal age at conception Maternal fever during pregnancy Child's sex Parity
Musculoskeletal Defects	Exposure Maternal age at conception Maternal fever during pregnancy Child's sex Parity
Hearing Problems	Exposure Frequent ear infections

2. Crude models

Asthma
Allergies
Epilepsy
Frequent ear infections
Persistent cough or bronchitis

Appendix E continued..

A priori analysis of reported farm use of organophosphate pesticides in the pre-conception period and any birth defect in all offspring

Model	*Variable Description*	*Odds Ratio of exposure (ORPHpr)*	*95% CI*	*Change in OR*	*% Change*
1. CRUDE MODEL					
ORPHpr	Organophosphate exposure in the pre-conception period	**1.108**	0.60, 2.04		
ORPHpr, MAGEC2		1.144	0.62, 2.11	-0.036	-3.25
ORPHpr, CLDSEX_C		1.112	0.60, 2.05	-0.004	-0.36
ORPHpr, FEVER		1.135	0.62, 2.09	-0.027	-2.44
ORPHpr, PARITY_C		1.123	0.61, 2.07	-0.015	-1.35
2. BASE MODEL					
ORPHpr, MAGE2, CLDSEX_C, FEVER, PARITY_C	Exposure (ORPHpr), mother's age at conception, child's sex, maternal fever during pregnancy, and parity	**1.157**	0.63, 2.14		
3. ADDITIONAL COVARIATES (those covariates whose odds ratio with the outcome was >1.2 or <0.8 added individually to the Base Model)					
M_ED2	Mothers education	1.139	0.62, 2.11	0.018	1.56
P_ED2	Fathers education	1.122	0.60, 2.08	0.035	3.03
INCOME_C	Income	0.935	0.48, 1.82	0.222	19.19
MDPROB	medical problems in pregnancy	1.152	0.62, 2.13	0.005	0.43
HAGEC2	fathers age at conception	1.119	0.60, 2.07	0.038	3.28
CAFFINE	drank tea or coffee in 1st tri	1.189	0.64, 2.20	-0.032	-2.77
COFFEE	drank 3+ cups in 1st trimester	1.176	0.64, 2.18	-0.019	-1.64
DRINK	drank alcohol	1.155	0.62, 2.14	0.002	0.17
MENARCHE	age at menarche	1.157	0.63, 2.14	0	0.00
FARMYR_CAT	year moved on farm	1.156	0.63, 2.14	0.001	0.09
RECALL_CAT	number of years of recall	1.186	0.64, 2.22	-0.029	-2.51
M_ETHNIC	mothers ethnicity:	1.161	0.63, 2.15	-0.004	-0.35
SEASON	season of conception	1.234	0.66, 2.32	-0.077	-6.66
SMOKE	smoked in 1st trimester	1.159	0.63, 2.15	-0.002	-0.17
prCHEM	husbands □hem. activity pr conc	1.223	0.65, 2.29	-0.066	-5.70
HSMOKER	father smoked	1.154	0.62, 2.14	0.003	0.26
H_smoker	father was a heavy smoker	1.165	0.63, 2.16	-0.008	-0.69
BMI	Body Mass Index	1.198		-0.041	-3.54
WTGAIN2	weight gain during pregnancy	1.119		0.038	3.28

Variable	*Additional Covariates added to Base Model*	*OR*	*95% CI*
4. FINAL MODEL			
ORPHpr	income_c	**0.94**	**0.48, 1.82**

Appendix E continued..

Fungicide Exposure during pregnancy and the risk of allergies or hayfever in offspring

Model	*Variable Description*	*Beta Coeff*	*Low CI*	*Upper CI*	*Exposure OR*	*Low CI*	*Upper CI*	*Change in OR*	*% Change*
CRUDE MODEL									
FUNGprg2	Fungicide exposure during pregnancy verses no pesticide exposure during pregnancy	-0.0429	-0.3842	0.2985	**0.958**	0.68	1.35		
COVARIATE ANALYSIS: Change in exposure OR when adding covariates									
BRSTL	breast feeding	-0.0398			**0.961**	1.00	1.00	-0.003	-0.31
CAGE_C	child's age at time of questionnaire	0.4504			**1.569**	1.00	1.00	-0.611	-63.77
CLDSEX_C	Child's sex	-0.0333			**0.967**	1.00	1.00	-0.009	-0.96
CSECT	C-section delivery	-0.0246			**0.976**	1.00	1.00	-0.018	-1.85
FARMYR_C	year moved on farm	0.0157			**1.016**	1.00	1.00	-0.058	-6.04
FEVER	maternal fever during pregnancy	-0.0234			**0.977**	1.00	1.00	-0.019	-1.97
FDRUGS	fertility drugs taken prior to conception	-0.0471			**0.954**	1.00	1.00	0.004	0.42
HAGEC2	fathers age at conception	0.1287			**1.137**	1.00	1.00	-0.179	-18.72
HYPOT	maternal hypothyroidism	-0.0579			**0.944**	1.00	1.00	0.014	1.49
INCOME_C	Income	-0.0067			**0.993**	1.00	1.00	-0.035	-3.69
LABORP	labor and delivery problems	-0.0348			**0.966**	1.00	1.00	-0.008	-0.81
LOWBWT	low birth weight	-0.0436			**0.957**	1.00	1.00	0.001	0.07
MALLERG	maternal history of allergies	-0.037			**0.964**	1.00	1.00	-0.006	-0.59
M_ED2	mothers education	-0.0488			**0.952**	1.00	1.00	0.006	0.59
M_ETHNIC	mothers ethnicity:	-0.0416			**0.959**	1.00	1.00	-0.001	-0.13
MAGEC2	maternal age at conception	0.0747			**1.078**	1.00	1.00	-0.120	-12.48
MDPROB	medical problems in pregnancy	-0.0589			**0.943**	1.00	1.00	0.015	1.59
MJHAZ	mother had haz job off farm	-0.0824			**0.921**	1.00	1.00	0.037	3.87
PARITY_C	parity	0.0251			**1.025**	1.00	1.00	-0.067	-7.04
P_ED2	Fathers education	-0.1317			**0.877**	1.00	1.00	0.081	8.50
PRETERM	pre-term birth	-0.0424			**0.958**	1.00	1.00	0.000	-0.05
WTGAIN_C	wt gain during pregnancy	-0.0707			**0.932**	1.00	1.00	0.026	2.74
Final Model	**Additional Covariates**								
all offspring	hagec2, magec2, cage_c,	0.5229	0.1409	0.9048	**1.687**	1.15	2.47		
males only	hagec2, magec2, cage_c,	0.9274	0.3928	1.462	**2.528**	1.48	4.31		
females only	hagec2, magec2, cage_c,	0.2682	-0.3589	0.8953	**1.308**	0.70	2.45		

Appendix F: Imputed Values

Percent imputed values for pesticide exposures in the analysis of Birth Defects

PESTICIDE	Real & Imputed Values	Real Exposed only	Imputed Exposed	% imputed
Pre-conception				
Herbicides	917	778	139	15.16
Fungicides	403	336	67	16.63
Insecticides	899	648	251	27.92
Other Pesticides	272	127	145	53.31
Phenoxy	522	470	52	9.96
Triazines	381	336	45	11.81
Organophosphates	347	227	120	34.58
Thiocarbamates	201	162	39	19.40
Carbaryl	285	200	85	29.82
Cyanazine	71	57	14	19.72
2,4-D	296	273	23	7.77
Dicamba	158	148	10	6.33
Post-conception				
Herbicides	395	325	70	17.72
Fungicides	355	336	19	5.35
Insecticides	751	556	195	25.97
Other Pesticides	253	124	129	50.99
Phenoxy	376	346	30	7.98
Triazines	282	253	29	10.28
Organophosphates	285	193	92	32.28
Thiocarbamates	167	130	37	22.16
2,4-D	210	200	10	4.76

Appendix G: Sensitivity Analysis

GEE vs MLE: Any Pesticide Exposure and Birth Defects in Male Offspring

Model	GEE OR	CI	MLE OR	CI	% Change in CI width
Fungicides	1.53	0.73, 3.19	1.55	0.77, 3.14	0.50
Insecticides	0.97	0.55, 1.71	0.96	0.53, 1.73	-0.24
Herbicides	0.88	0.48, 1.59	0.88	0.49, 1.59	0.08
Phenoxy	0.75	0.34, 1.67	0.78	0.36, 1.67	0.10
Triazine	0.79	0.32, 1.95	0.83	0.35, 1.97	0.04
Thiocarbamates	1.45	0.57, 3.68	1.47	0.57, 3.80	-0.72
Organophosphates	1.35	0.66, 2.80	1.32	0.61, 2.86	-0.65
2,4-D	1.25	0.55, 2.84	1.25	0.56, 2.81	0.24
Dicamba	**2.34**	0.97, 5.67	2.42	1.06, 5.53	7.28
Cyanazine	**4.62**	1.35, 15.79	4.99	1.63, 15.27	4.73

Correlation Structure Types: Allergies and Hayfever

MODEL	OR EXCH	CI	OR AR(1)	CI	OR IND	CI
Fungicides						
All offspring	1.69	1.15, 2.47	1.70	1.16, 2.47	1.72	1.16, 2.56
Males only	2.02	1. 23, 3.30	2.08	1.27, 3.40	2.15	1.31, 3.53
Insecticides						
All offspring	1.48	1.07, 2.03	1.48	1.08, 2.03	1.41	1.02, 1.95
Males only	1.55	1.02, 2.36	1.55	1.02, 2.36	1.56	1.02, 2.37
Herbicides						
All offspring	1.56	1.15, 2.11	1.57	1.17, 2.13	1.48	1.08, 2.01
Males only	1.64	1.10, 2.46	1.62	1.08, 2.42	1.68	1.13, 2.49
Phenoxy						
All offspring	1.43	1.03, 1.99	1.44	1.03, 2.01	1.35	0.96, 1.92
Males only	1.73	1.12, 2.62	1.70	1.10, 2.62	1.76	1.14, 2.71
Organophosphates						
All offspring	1.55	1.02, 2.36	1.53	1.01, 2.32	1.45	0.95, 2.22
Males only	1.66	0.96, 2.86	1.65	0.95, 2.86	1.66	0.96, 2.86
2,4-D						
All offspring	1.66	1.11, 2.49	1.67	1.11, 2.51	1.50	0.98, 2.29
Males only	1.84	1.08, 3.14	1.83	1.07, 3.14	1.81	1.05, 3.13

Parity=1

Pregnancy Exposures and Allergies in All Offspring

Model	GEE OR (All Preg)	CI	MLE OR (first preg only)	CI
Fungicides	1.69	1.15, 2.47	2.39	1.32, 4.31
Insecticides	1.48	1.07, 2.03	1.76	1.09, 2.84
Herbicides	1.56	1.15, 2.11	1.56	0.99, 2.46
Phenoxy	1.43	1.03, 1.99	1.56	0.94, 2.60
Organophosphates	1.55	1.02, 2.36	1.53	0.80, 2.92
2,4-D	1.66	1.11, 2.49	1.98	1.05, 3.71

Appendix H: Questionnaires

Form A

Health and Welfare Canada | Santé et Bien-être social Canada

Ontario Farm Family Health Study

Form A

To be completed by the farm operator

Si vous préférez ce questionnaire en français, veuillez cocher ☐

he information provided above on your name, address, and telephone number correct?

) Yes 2 ○ No ▸ Please make the appropriate correction below

RST NAME:	MIDDLE:	LAST NAME:
AILING ADDRESS: Street and Number/P.O. Box No./R.R. No.		
llage/Town	Postal Code	Telephone Number: ( )

INSTRUCTIONS FOR COMPLETING THE QUESTIONNAIRES

Three different questionnaires have been developed for this study.

1. **GREEN (Form A) –To be completed by the farm operator (the person who is responsible for the DAY-TO-DAY decisions on this farm)**
2. **BLUE (Form B) –To be completed by the husband**
3. **BEIGE (Form C) –To be completed by the wife**

- Each farm selected for this study should have received these three forms. For those farms where more than one family lives on the farm, some families will have received only a Form A, and some Form B and C. We ask that you and your spouse complete the questionnaires that have your names on it.
- Form A collects information on the farm operation, including the kinds of agricultural products grown or raised, the use of chemicals on the farm, diseases of farm animals, and types of structures on the farm (eg. silos, manure tanks). Information on the husband's lifestyle, activities on the farm, and health is collected in Form B. The purpose of Form C is to obtain information on the lifestyle, experiences, and health of the wife, as well as information on any major health problems of their children.
- Please answer the questions as completely and accurately as possible. Some of the questions ask you to check off the appropriate answer, others ask you to supply information, such as names of agricultural chemicals (pesticides) used on the farm. You may want to refer to your farm and household records to refresh your memory.
- Please do not write in the shaded areas.
- When you have finished answering all of the questions, please return the questionnaires to us in the envelopes provided. In families where both the husband and wife have been sent questionnaires, we have enclosed two self-addressed postage-paid envelopes so that you may (if you so desire) return your questionnaires separately.
- We realize that your time is very important to you and that you may think that it will take too much time to answer these questions. We have estimated that it will take less than one hour to complete a questionnaire, as there will be questions or parts of questions which you can skip because they do not apply to your circumstances.

Please remember that it is only through your cooperation that we will be able to determine whether farm families have a higher or lower risk of certain health problems than the general public.

Confidential when completed.

FOR OFFICE USE ONLY				Date:
ver ID#:	Mode of completion: 1 ○ Mail 2 ○ Telephone	Time:	JIC:	

9 1: 1991-08-14 NHW/HPB-165-04265

Canada

DESCRIPTION OF QUESTIONS

The purposes of this questionnaire are to characterize the farm operation by the kinds of agricultural products grown or raised on the farm and to identify some of the potentially harmful exposures that can occur on a farm. These exposures could include farm chemicals, molds, grain and other dusts, animal viruses and diseases, toxic gases and vapors, corrosive materials, engine exhausts, and veterinary medications, as well as long exposures to sunlight, intense heat or cold, and strenuous physical exercise.

Questions 1 - 4 - provide us with the age and sex of the person who is responsible for the day-to-day decisions on the farm (the "farm operator"), as well as providing information on whether the farm operator lives on the farm property and how long that person has been managing the farm.

Questions 5 - 20 - identify the size of the farm operation, the types of agricultural products grown or raised, and provides detailed information on the use of chemicals (either man-made or organic) on the farm, and information on diseases of livestock.

Questions 21 - 23 - obtain information on what changes in types of agricultural products grown or raised have occurred since the farm operator began working on the farm. In order to determine what factors might be affecting a family's health, it is important to know what they were exposed to in the past as well as what they are currently exposed to.

Questions 24 - 28 ask about the use of both commercial and farm-generated fertilizer on the farm, irrigation practices, and types of structures on the farm.

Question 29 - helps us to characterize the kind of farm by the amount of sales generated from each farm product.

Question 30 - aids us in identifying a number of pesticides that have been used historically on the farm.

1. What is your birth date? Day | Month | Year

2. Sex [1] ◯ Male [2] ◯ Female

3. Is your home (principal residence) located on the farm property?
[1] ◯ Yes [2] ◯ No ⟶ How far away is it from the farm buildings? [1] ____ Miles or [2] ____ Kilometres

4. When did you take on the responsibilities for the day to day management of this farm operation? Year 1 9 ____ ____

5. The land area units that you would prefer to use in this questionnaire are: (choose one only and use this unit throughout the entire questionnaire) [1] ◯ Acres or [2] ◯ Hectares

6. What is the total area of all land you operate? (include all land operated, whether owned, rented or leased from others, but do not include land you rent or lease to others) ____

7. Do you sell any produce (fruit, vegetables, field crops, etc.) that you have grown organically?
[1] ◯ Yes [2] ◯ No ⟶ Go to question 8.

a) What kind of produce do you grow organically?
[1] ◯ Fruit [2] ◯ Vegetables [3] ◯ Field crops [4] ◯ Other (specify) _____ ____

b) Do you apply any natural or organic chemicals to these products?
[1] ◯ Yes [2] ◯ No

8. Do you grow any grains, hay, fodder crops, oilseeds, or other field crops on this farm?

[1] ◯ Yes ⟶ Please provide information about the various crops sown or harvested in 1991, even if the crops were sown or planted in 1990. For each crop, please report the total area sown, indicate whether the seed was treated, indicate whether an inoculant or growth stimulator was applied with the seed during planting, and whether agricultural chemicals (either man-made or natural) were sprayed or dusted on the land to control weeds, insects, or disease.

[2] ◯ No
Go to question 10.

	AREA	SEED TREATED? (if yes ✓)	INNOCULANT USED? (if yes ✓)	CHEMICALS USED? (if yes ✓)	COMMENTS
GRAINS 1) Spring Wheat		◯	◯	◯	
2) Winter Wheat		◯	◯	◯	
3) Oats		◯	◯	◯	
4) Barley		◯	◯	◯	
5) Mixed grains (specify) ____ ____		◯	◯	◯	
6) Corn		◯	◯	◯	
7) Rye		◯	◯	◯	
8) Buckwheat		◯	◯	◯	
9) Other grains (specify) ____ ____		◯	◯	◯	
HAY AND FODDER CROPS 10) Corn for silage		◯	◯	◯	
11) All tame hay		◯	◯	◯	
12) Other fodder crops cut for green feed, hay, or silage (specify) ____ ____		◯	◯	◯	
OILSEEDS 13) Canola (Rapeseed)		◯	◯	◯	
14) Flaxseed		◯	◯	◯	
15) Soybeans		◯	◯	◯	
16) Sunflowers		◯	◯	◯	
OTHER FIELD CROPS 17) Potatoes (grown for sale)		◯	◯	◯	
18) Dry field beans		◯	◯	◯	
19) Dry field peas		◯	◯	◯	
20) Other field crops (specify) ____ ____		◯	◯	◯	
____ ____		◯	◯	◯	

9. (Continuation)

CROP:	CHEMICAL NUMBER 1	CHEMICAL NUMBER 2	CHEMICAL NUMBER 3
Name of chemical			
Name of manufacturer			
Reason for use	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____
Total area sprayed or dusted			
Total quantity used (concentrated form). Choose one unit only.	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb
Method of application			
Number of applications per year			
Month(s) of application (check all that apply)	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
Number of years using this chemical			

CROP:	CHEMICAL NUMBER 1	CHEMICAL NUMBER 2	CHEMICAL NUMBER 3
Name of chemical			
Name of manufacturer			
Reason for use	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____
Total area sprayed or dusted			
Total quantity used (concentrated form). Choose one unit only.	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb
Method of application			
Number of applications per year			
Month(s) of application (check all that apply)	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
Number of years using this chemical			

CROP:	CHEMICAL NUMBER 1	CHEMICAL NUMBER 2	CHEMICAL NUMBER 3
Name of chemical			
Name of manufacturer			
Reason for use	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ other (specify) ____
Total area sprayed or dusted			
Total quantity used (concentrated form). Choose one unit only.	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb	1 ☐ L or 3 ☐ gal 2 ☐ kg or 4 ☐ lb
Method of application			
Number of applications per year			
Month(s) of application (check all that apply)	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
Number of years using this chemical			

11. Are chemicals used on this farm to control weeds, insects or disease on any crops or produce?

1 ◯ Yes 2 ◯ No ——→ Go to question 12.

a) Are all of these chemicals custom-applied?

1 ◯ Yes ——→ Go to question 12.

2 ◯ No

b) What is the distance between the nearest residence of people living on this farm and:

	Yards	Metres
A. Where the chemicals are normally stored	1 ☐☐☐	or 2 ☐☐☐
B. Where the chemicals are usually mixed	1 ☐☐☐	or 2 ☐☐☐
C. Where the tank(s) are usually rinsed	1 ☐☐☐	or 2 ☐☐☐

12. Are you growing any greenhouse products for sale?

1 ◯ Yes 2 ◯ No

13. Are you growing any mushrooms for sale?

1 ◯ Yes 2 ◯ No

14. Are there any poultry on this farm?

1 ◯ Yes 2 ◯ No ——→ Go to question 15.

a) Please supply the numbers of the following (as of today):

	Quantity
A. Hens and pullets for laying	
B. All other chickens	
C. Turkeys	
D. Other poultry (specify) ☐☐	

b) Do you use chemicals or powders to control insects or disease on your poultry?

1 ◯ Yes 2 ◯ No ——→ Go to question 15.

What is the name of the chemical(s) used?

	☐☐☐
	☐☐☐
	☐☐☐

Check the months of the year when these chemicals are usually applied.

◯ Jan. ◯ Feb. ◯ Mar. ◯ Apr. ◯ May ◯ June

◯ July ◯ Aug. ◯ Sept ◯ Oct. ◯ Nov. ◯ Dec.

15. Are there any cattle or calves on this farm?

1 ◯ Yes 2 ◯ No ——→ Go to question 16.

a) Please supply the numbers of the following:

	Quantity
A. Total Beef	
B. Total Dairy	

b) Do you use chemicals or powders to control insects or disease on your cattle?

1 ◯ Yes 2 ◯ No ——→ Go to question 16.

What is the name of the chemical(s) used?

	☐☐☐
	☐☐☐
	☐☐☐

Check the months of the year when these chemicals are usually applied.

◯ Jan. ◯ Feb. ◯ Mar. ◯ Apr. ◯ May ◯ June

◯ July ◯ Aug. ◯ Sept. ◯ Oct. ◯ Nov. ◯ Dec.

16. Are there any other livestock on this farm?

1 ◯ Yes 2 ◯ No ——→ Go to question 17.

a) Please supply the numbers of the following:

	Quantity
A. Pigs	
B. Sheep or lambs	
C. Horses or ponies	
D. Goats	
E. Fox	
F. Rabbits	
G. Mink	
H. Other (specify) ☐☐	

b) Do you use chemicals or powders to control insects or disease on your livestock?

1 ◯ Yes 2 ◯ No ——→ Go to question 17.

What is the name of the chemical(s) used?

	☐☐☐
	☐☐☐
	☐☐☐
	☐☐☐

Check the months of the year when these chemicals are usually applied.

◯ Jan. ◯ Feb. ◯ Mar. ◯ Apr. ◯ May ◯ June

◯ July ◯ Aug. ◯ Sept. ◯ Oct. ◯ Nov. ◯ Dec.

17. Have you ever had poultry, cattle, or other livestock on this farm?

1 ◯ Yes 2 ◯ No ——→ Go to question 18.

Have any of these animals been seen by a veterinarian for the following diseases?
Please check all that apply, and write the year(s) in which the animals had these diseases. If your animals have never had any of these diseases, please check "None of the preceding".

1 Leukemia	2 Lymphoma	3 Brucellosis Abortus	4 Listeriosis	5 Q-Fever	6 Leptospirosis	7 Chlamydia Acidicosis	8 Maedi-Visna	9 Lyme Disease	10 None of the Preceding
◯ Yes	◯ Yes	◯ Yes	◯ Yes	◯ Yes	◯ Yes	◯ Yes	◯ Yes	◯ Yes	◯
19	19	19	19	19	19	19	19	19	
19	19	19	19	19	19	19	19	19	
19	19	19	19	19	19	19	19	19	

10. a) Do you grow any tree fruits, cultivated berries, grapes, vegetables, sod, or nursery products for sale?

[1] ◯ Yes ⟶ Please report total area of the various crops grown for sale in 1991 in the area provided below:

[2] ◯ No ⟶ Go to question 11. (page 9)

TREE FRUITS	AREA
1) Apple	
2) Pear	
3) Plum and Prune	
4) Cherry (sweet)	
5) Cherry (sour)	
6) Peach	
7) Apricot	
8) Other fruit trees (e.g. filbert nuts, nectarines, etc.) Specify:	

BERRIES AND GRAPES	AREA
9) Strawberries	
10) Raspberries	
11) Grapes	
12) Blueberries (cultivated high and low bush, and low bush grown on managed land)	
13) Cranberries	
14) Other berries and grapes (e.g. Saskatoons, loganberries, currants, etc.) Specify:	

VEGETABLES (grown for sale)	AREA	VEGETABLES (grown for sale)	AREA
15) Sweet corn		28) Radishes	
16) Tomatoes		29) Dry onions	
17) Cucumbers and gherkins		30) Green or bunching onions, shallots	
18) Green peas		31) Celery	
19) Green or wax beans		32) Lettuce	
20) Cabbage		33) Spinach	
21) Chinese cabbage		34) Peppers	
22) Cauliflower		35) Squash and pumpkins (include zucchini)	
23) Broccoli		36) Rhubarb	
24) Brussel sprouts		37) Asparagus, producing	
25) Carrots		38) Asparagus, not producing	
26) Rutabagas (turnips)		39) Other vegatables (e.g. bok choy, melons) Specify:	
27) Beets			

		AREA
TOTAL area of **nursery products** (Include area of cut flowers, bulbs, shrubs, trees, vines, ornamentals, etc. grown out-of-doors.)	40)	
TOTAL area of **sod** grown for sale	41)	

18. Are chemicals (insecticides, rodenticides, etc.) used around the farm buildings to control insects, mice, rats, or other pests?

1 ◯ Yes 2 ◯ No ⟶ Go to question 19.

a) What is the name of the chemical(s) used?

b) When are these chemicals usually applied? (Check all that apply.)

◯ Jan. ◯ Feb. ◯ Mar. ◯ Apr. ◯ May ◯ June
◯ July ◯ Aug. ◯ Sept. ◯ Oct. ◯ Nov. ◯ Dec.

19. Are chemicals (herbicides) used around the farm yard or buildings to control weeds or brush?

1 ◯ Yes 2 ◯ No ⟶ Go to question 20.

a) What is the name of the chemical(s) used?

b) When are these chemicals usually applied? (Check all that apply.)

◯ Jan. ◯ Feb. ◯ Mar. ◯ Apr. ◯ May ◯ June
◯ July ◯ Aug. ◯ Sept. ◯ Oct. ◯ Nov. ◯ Dec.

20. Is grain stored on this farm?

1 ◯ Yes 2 ◯ No ⟶ Go to question 21.

a) Are fumigants used on the stored grain?

1 ◯ Yes 2 ◯ No ⟶ Go to question 21.

b) What is the name of the fumigant(s) used?

c) When are these chemicals usually applied? (Check all that apply.)

◯ Jan. ◯ Feb. ◯ Mar. ◯ Apr. ◯ May ◯ June
◯ July ◯ Aug. ◯ Sept. ◯ Oct. ◯ Nov. ◯ Dec.

21. When did you first start working full-time on this farm?

Year: 1 9 | |

22. Have there been any changes in the types of agricultural products grown or livestock raised since you started working on this farm?

1 ◯ Yes 2 ◯ No ⟶ Go to question 23.

Please list the agricultural products or livestock that you used to have on this farm (but don't have anymore) and the years that you had these animals or crops.

YEAR FROM	YEAR TO	AGRICULTURAL CROPS OR LIVESTOCK
19	19	
19	19	
19	19	

23. Are there any chemicals which you regularly used in previous years, but have since stopped using?

1 ◯ Yes 2 ◯ No ⟶ Go to question 24.

Please supply the following information for each chemical:

Name of Chemical	Years Used From	Years Used To	Crops Used On
	19	19	
	19	19	
	19	19	

24. How many metric tonnes of the following forms or types of commercial fertilizer were applied on this land in 1991? Enter a "0" if you did not apply any.

Forms or Types of Commercial Fertilizer	Metric Tonnes
A. Dry granular (bagged and bulk)	
B. Pressurized liquid or gas (including anhydrous ammonia)	
C. Non-pressurized liquid	
D. Suspensions (a fluid requiring agitation)	

25. How much land was fertilized with the following forms of **farm-generated** fertilizer in 1991? Enter a "0" if you did not apply any.

	Area
A. Dry manure	
B. Liquid manure	

26. In 1991, was any of the land you operate irrigated by any controlled means? 1◯ Yes 2◯ No

27. Are there any silos on this farm?

1◯ Yes 2◯ No ⟶ Go to question 28.

a) What kind of silos do you have? (Check all that apply.)

1◯ Conventional (top loading)

2◯ Oxygen limiting (air tight)

3◯ Other (please specify) _____

b) What is stored in the silos? (Check all that apply.)

1◯ Haylage

2◯ Corn Silage

3◯ Other (please specify) _____

28. Are there any free-stall barns on this farm?

1◯ Yes ⟶ Do these barns have slatted floors for manure handling and storage? 1◯ Yes 2◯ No

2◯ No

29. What percentage of your total sales of farm products would you say comes from the following:

	%
a. Corn	
b. Soybeans	
c. Grain	
d. Other field crops	
e. Milk production	
f. Beef	
g. Eggs	
h. Poultry	
i. Pigs	
j. Other livestock (Specify)	
k. Fruit	
l. Vegetables	
m. Other farm products (Specify)	
TOTAL	**100%**

30. If you have ever used any of the following chemicals on your farm, please write beside that chemical the years in which you used it.

	CHEMICALS	YEAR FROM	TO
1	Atrazine	19	19
2	Amiben	19	19
3	2, 4-D	19	19
4	CIPC	19	19
5	Bladex	19	19
6	Blagal	19	19
7	Casoron	19	19
8	Compitox	19	19
9	Dinoseb	19	19
10	Mecoprop	19	19
11	MCPA	19	19
12	Target	19	19
13	Dycleer 24	19	19
14	Tricep	19	19
15	Royal MH 60 SG	19	19
16	Embutox 625	19	19
17	Triflurex 40 EC	19	19
18	Propaturf	19	19
19	Fusilade	19	19
20	Sevin	19	19

	CHEMICALS	YEAR FROM	TO
21	Imidan	19	19
22	Benlate	19	19
23	Captan	19	19
24	Folpet / Phaltan	19	19
25	Bayleton	19	19
26	Lorox	19	19
27	Basagran	19	19
28	Banvel	19	19
29	Blazine	19	19
30	Bromox	19	19
31	Calmix Pellets	19	19
32	Cobutox	19	19
33	Desormone	19	19
34	Reglone	19	19
35	Marksman	19	19
36	Dyvel	19	19
37	Killex	19	19
38	Excel	19	19
39	Rival	19	19
40	MCPP	19	19

	CHEMICALS	YEAR FROM	TO
41	Furadan	19	19
42	Birlane	19	19
43	Thiodan	19	19
44	Malathion	19	19
45	Parathion	19	19
46	Prolate	19	19
47	Difolatan	19	19
48	Ferbam	19	19
49	Dithane	19	19
50	Morestan	19	19
51	Laddok	19	19
52	Par III	19	19
53	Orthene	19	19
54	Turf-rite 2+2	19	19
55	Treflan	19	19
56	Cygon	19	19
57	Ethion	19	19
58	Methoxychlor	19	19
59	Tropotox Plus	19	19
60	Lasso	19	19

31. Are there any other chemicals (solvents, emulsifiers, herbicides, insecticides, disinfectants, etc.) that are used (or have been used) on this farm but have not been asked about in this questionnaire?

¹○ Yes ²○ No ——→ Go to question 32.

Please provide the following information for the chemicals:

NAME OF CHEMICAL	REASON FOR USE	MONTHS USED (CHECK ALL THAT APPLY)	YEARS USED	
			FROM	TO
		○Jan. ○Feb. ○Mar. ○Apr. ○May ○June ○July ○Aug. ○Sept. ○Oct. ○Nov. ○Dec.	19	19
		○Jan. ○Feb. ○Mar. ○Apr. ○May ○June ○July ○Aug. ○Sept. ○Oct. ○Nov. ○Dec.	19	19
		○Jan. ○Feb. ○Mar. ○Apr. ○May ○June ○July ○Aug. ○Sept. ○Oct. ○Nov. ○Dec.	19	19
		○Jan. ○Feb. ○Mar. ○Apr. ○May ○June ○July ○Aug. ○Sept. ○Oct. ○Nov. ○Dec.	19	19
		○Jan. ○Feb. ○Mar. ○Apr. ○May ○June ○July ○Aug. ○Sept. ○Oct. ○Nov. ○Dec.	19	19

32. Date of completion of questionnaire:	Day	Month	Year
			1 9

Thank you for completing this questionnaire.

If there is a FORM B (husband's) or FORM C (wife's) included in the package sent to you, please complete the appropriate form, and have your spouse complete the other questionnaire.
Please return the questionnaires in the enclosed self-addressed envelopes as soon as possible.

COMMENTS

If you are interested in a summary of the results please check here ☐

Form B

Health and Welfare Canada | Santé et Bien-être social Canada

Ontario Farm Family Health Study

Form B

To be completed by the Husband

Si vous préférez ce questionnaire en français, veuillez cocher ☐

Is the information provided above on your name, address, and telephone number correct?

1 ○ Yes 2 ○ No ▸ Please make the appropriate correction below

FIRST NAME:	MIDDLE:	LAST NAME:
MAILING ADDRESS: Street and Number/P.O. Box No./R.R. No.		
Village/Town	Postal Code	Telephone Number: ( )

INSTRUCTIONS FOR COMPLETING THE QUESTIONNAIRES

Three different questionnaires have been developed for this study.

1. **GREEN (Form A) –To be completed by the farm operator (the person who is responsible for the DAY-TO-DAY decisions on this farm)**
2. **BLUE (Form B) –To be completed by the husband**
3. **BEIGE (Form C) –To be completed by the wife**

- Each farm selected for this study should have received these three forms. For those farms where more than one family lives on the farm, some families will have received only a Form A, and some Form B and C. We ask that you and your spouse complete the questionnaires that have your names on it.
- Form A collects information on the farm operation, including the kinds of agricultural products grown or raised, the use of chemicals on the farm, diseases of farm animals, and types of structures on the farm (eg. silos, manure tanks). Information on the husband's lifestyle, activities on the farm, and health is collected in Form B. The purpose of Form C is to obtain information on the lifestyle, experiences, and health of the wife, as well as information on any major health problems of their children.
- Please answer the questions as completely and accurately as possible. Some of the questions ask you to check off the appropriate answer, others ask you to supply information, such as names of agricultural chemicals (pesticides) used on the farm. You may want to refer to your farm and household records to refresh your memory.
- Please do not write in the shaded areas.
- When you have finished answering all of the questions, please return the questionnaires to us in the envelopes provided. In families where both the husband and wife have been sent questionnaires, we have enclosed two self-addressed postage-paid envelopes so that you may (if you so desire) return your questionnaires separately.
- We realize that your time is very important to you and that you may think that it will take too much time to answer these questions. We have estimated that it will take less than one hour to complete a questionnaire, as there will be questions or parts of questions which you can skip because they do not apply to your circumstances.

Please remember that it is only through your cooperation that we will be able to determine whether farm families have a higher or lower risk of certain health problems than the general public.

Confidential when completed.

FOR OFFICE USE ONLY				Date:
Interviewer ID#:	Mode of completion: 1 ○ Mail 2 ○ Telephone	Time:	JIC:	

8-5103-260.1: 1991-08-14 NHW/HPB-165-04265

Canada

DESCRIPTION OF QUESTIONS

The purposes of this questionnaire are to obtain information on the lifestyle and experiences of the husband that could affect his or his family's health and to obtain information on the husband's health status. Some of the potentially harmful exposures that can occur on a farm include farm chemicals, molds, grain and other dusts, animal viruses and diseases, toxic gases and vapors, corrosive materials, engine exhausts, and veterinary medications, as well as long exposures to sunlight, intense heat or cold, and strenuous physical exercise.

Medical research has discovered that often a disease such as lung cancer can be caused by a number of factors which act either alone or together. In order to determine whether one particular exposure or experience caused a certain disease, we must be able to rule out other potential factors which may have caused that disease. For example smoking has long been associated with lung cancer. If in this study we found that one particular group of farmers had a higher rate of lung cancer we must first find out if they are also heavy smokers before we could say that the lung cancer that they had was due to an exposure on the farm. For this reason we ask questions about a lot of things which have nothing to do with farming but which might potentially affect your health.

This questionnaire is divided into 3 sections. Part A obtains information on where you live, your family background, education, employment, activities on the farm, and use of chemicals and protective equipment while mixing or applying these chemicals. A number of public health studies have found that disease rates can vary by province or country of birth, source of drinking water, occupational exposures, ethnic background, religion, and level of education. We are also interested in how many farmers supplement their income by working off the farm and what kinds of jobs they are doing.

Part B provides us with information on your general health and specific health problems which you may have had. Using information on your height, weight and age, we can determine if you have any weight problems which might affect your health. We ask for your assessment of your health and factors which you think may contribute to your health. There is also a question on injuries which have occurred on the farm.

Part C asks about your lifestyle. There are a number of lifestyle factors which can either hurt or improve your health. These include smoking, alcohol consumption, drinking tea, coffee, or cola soft drinks, and eating fish or wildlife. A number of medical studies have shown that our health can also be affected by household income.

PART A: GENERAL INFORMATION

A1. On this farm operation, are you ...
(Please check all that apply):

1 ○ the owner

2 ○ the farm operator (responsible for the day-to-day decisions made on the farm)

3 ○ an employee or hired hand

4 ○ other; please specify:

A2. What is your birth date?

Day Month 19 Year

A3. What was the date of your marriage (legal or common-law) to your current wife?

Day Month 19 Year

A4. Have you been married (legally or common-law) more than once?

1 ○ Yes 2 ○ No ▸ GO TO A5.

Did you and your **former spouse(s)** ever have any problems having a healthy child?

1 ○ Yes ▸ What was this problem? Check all that apply.

1 ○ miscarriage or spontaneous abortion

2 ○ male infertility problems

3 ○ female infertility problems

4 ○ stillbirth

5 ○ birth defects

6 ○ child died before 1st birthday

7 ○ Other (Specify)

2 ○ No ▸ Number of children by former spouse(s)

3 ○ Never tried to have a baby

A5. Is your home (principal residence) located next to or on the farm property?

1 ○ Yes ▸ GO TO A6.

2 ○ No ▸ How far away is it from the farm property?

miles OR kilometres

A6. What is the land surrounding your house and lawns used for? Please check all that apply and include any land owned or rented by your neighbour if applicable.

1 ○ pasture

2 ○ woodlot

3 ○ hay

4 ○ field crops, please specify:

5 ○ other, please specify:

A7. What is the source of your drinking water?

1 ○ drilled well

2 ○ dug well

3 ○ spring

4 ○ municipal water system

5 ○ bottled water

6 ○ cistern

A8. Were you born in Canada?

1 ○ Yes ▸ Which province?

2 ○ No ▸ In what country were you born?

A9. In what country was your father born? 1

In what country was your mother born? 2

A10. What was your father's usual occupation? 1

What was your mother's usual occupation? 2

A11. To which ethnic or cultural group(s) did your ancestors belong? Mark or specify as many as applicable.

01 ○ French

02 ○ English

03 ○ German

04 ○ Scottish

05 ○ Irish

06 ○ Italian

07 ○ Ukrainian

08 ○ Dutch (Netherlands)

09 ○ Jewish

10 ○ Polish

11 ○ Black

12 ○ Chinese

13 ○ Other (Specify)

A12. To what religious denomination do you belong? Select one only.

01 ○ None
02 ○ Roman Catholic
03 ○ United
04 ○ Anglican
05 ○ Presbyterian
06 ○ Lutheran
07 ○ Baptist
08 ○ Jewish
09 ○ Mennonite
10 ○ Mormon
11 ○ Jehovah's Witnesses
12 ○ Pentecostal
13 ○ Other (Specify)

A13. What is the **highest** grade (or year) of schooling that you have completed?

1 ○ Any of Grades 1 to 8
2 ○ Any of Grades 9 to 11
3 ○ High School Graduate
4 ○ Started college or university but did not complete
5 ○ Community College Diploma (Please specify type of diploma)
6 ○ University degree (Please specify highest degree)

A14. Are you currently employed at a job site **off** this farm?

1 ○ Yes 2 ○ No ▸ GO TO A15.

Briefly describe the kind of work you do in your job. (For example, elementary school teacher, salesperson, bank clerk.)

What kind of product or service is produced or provided in the business where you work? Give full description, (e.g., leather tanning shop, retail shoe store, government office.)

During what year did you start work at this job?

19 ☐☐

How many hours per week do you normally work at this job?

☐☐

A15. Have you held any other jobs (lasting more than six months) at sites **off** this farm since the date of your marriage?

1 ○ Yes 2 ○ No ▸ GO TO A16.

JOB #1

Briefly describe the kind of work you did in your job.

What kind of product or service was produced or provided in the business where you worked?

During what years did you work at this job?

FROM 19 ☐☐ TO 19 ☐☐

JOB #2

Briefly describe the kind of work you did in your job.

What kind of product or service was produced or provided in the business where you worked?

During what years did you work at this job?

FROM 19 ☐☐ TO 19 ☐☐

JOB #3

Briefly describe the kind of work you did in your job.

What kind of product or service was produced or provided in the business where you worked?

During what years did you work at this job?

FROM 19 ☐☐ TO 19 ☐☐

A16. Approximately how many days off do you have per **month** (i.e., days when you are not working at a job or on the farm)?

☐☐ days (May – Nov.) ☐☐ days (Dec. – Apr.)

A17. While you were growing up, did you live mostly on a farm or ranch, or did you live somewhere else?

1 ○ a farm or ranch (Please specify the kind of products grown or raised on this farm)
2 ○ a municipality with a population of less than 5,000
3 ○ a municipality with a population of 5,000 or more

A18. Altogether, how many years have you lived on a farm?

☐☐ years

WE WOULD NOW LIKE TO GET SOME INFORMATION ON THE KINDS OF WORK **YOU** DO ON THE FARM AND HOW OFTEN YOU DO THIS WORK.

A19. Looking back over the past five years, how often have you done the following activities. Give your best estimate of the number of days during the year and which months of the year you do these activities. Please include custom work when answering these questions. Even if you worked only part of a day, count that as one day.

	Never	Occasionally	Regularly	# of Days during year	During months of
a) milking cows	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
b) plowing	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
c) harrowing or disking	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
d) cultivating	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
e) planting	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
f) applying fertilizer, manure	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
g) mixing or applying chemicals to crops for weed or brush control	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
h) mixing or applying chemicals to crops for insect or disease control	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
i) mixing or administering chemicals to livestock to control insects & disease	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
j) mixing or applying chemicals around the farm yard and buildings to control weeds and brush	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
k) mixing or applying chemicals around the farm buildings to control pests	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
l) harvesting crops, including driving machinery or trucks	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
m) working with farm livestock (other than milking dairy cows)	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
n) bookkeeping, maintaining records, paying bills, banking or preparing tax forms	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
o) working in the family garden	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
p) working in dusty areas, for example, with wood shavings, shovelling grain, corn, beans, etc.	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
q) heavy lifting, for example, pails, crates, handling bales of hay or straw, feed bags, etc.	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
r) filling, servicing or unloading a silo	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.

A20. Do you use chemicals to spray or dust flowers, shrubs, vegetables or fruit in your family garden? If you use more than 2 chemicals in your garden, supply information on the 2 chemicals you use most often.

1 ○ Yes 2 ○ No ▸ GO TO A21.

Please provide the following information for each chemical:

	CHEMICAL #1	CHEMICAL #2
Name		
Reason for use	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ Other (Specify):	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ Other (Specify):
How do you apply it	1 ○ spray 2 ○ dust 3 ○ Other (Specify):	1 ○ spray 2 ○ dust 3 ○ Other (Specify):
During what months	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
How many years have you been using this chemical?	years	years

A21. Do **you** use chemicals to spray or dust family pets for insects or disease?

1 ○ Yes 2 ○ No ▸ GO TO A22.

Please provide the following information for each chemical:

	CHEMICAL #1	CHEMICAL #2
Name		
Reason for use	1 ○ insects 2 ○ disease 3 ○ Other (Specify):	1 ○ insects 2 ○ disease 3 ○ Other (Specify):
How do you apply it	1 ○ spray 2 ○ dust 3 ○ Other (Specify):	1 ○ spray 2 ○ dust 3 ○ Other (Specify):
During what months	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
How many years have you been using this chemical?	years	years

A22. Do **you** use chemicals to control weeds in your yard or lawn?

1 ○ Yes 2 ○ No ▸ GO TO A23.

Please provide the following information for each chemical:

	CHEMICAL #1	CHEMICAL #2
Name		
How do you apply it	1 ○ spray 2 ○ dust 3 ○ Other (Specify):	1 ○ spray 2 ○ dust 3 ○ Other (Specify):
During what months	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
How many years have you been using this chemical?	years	years

A23. Do **you** mix, load or apply any pesticides (herbicides, insecticides, fungicides, fumigants, rodenticides, etc.) on this farm?

1 ○ Yes 2 ○ No ▸ GO TO A24.

a) Please check the frequency that you use each of the following types of protective equipment and indicate your best guess of the year that you started using it:

	Never	Occasionally	Regularly	Year
1) tractor with a cab for crop spraying	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
2) plastic, rubber or vinyl gloves	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
3) cloth or leather gloves	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
4) face shield or goggles	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
5) coveralls or overalls	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
6) plastic or chemically resistant apron	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
7) respirator or mask with pesticide filters	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐
8) Other (specify) ☐☐☐☐☐☐☐☐☐☐	1 ○	2 ○ ▸	3 ○ ▸	19 ☐☐

b) How soon after handling these chemicals would you change to **clean work clothes**?

1 ○ right away

2 ○ at the end of the work day

3 ○ at the end of the following day or later

c) Are the clothes that you have worn while handling and applying these chemicals washed separately from the regular household laundry?

1 ○ Yes

2 ○ No

A24. Do **you own (or jointly own)** this farm?

1 ○ Yes ▸ a) How much **net farm income** did you earn in 1990 **before taxes**, but after production expenses were subtracted?

1 ○ operated at a loss

2 ○ less than $10,000

3 ○ $10,000 - $30,000

4 ○ $30,001 - $50,000

5 ○ $50,001 - $70,000

6 ○ $70,001 - $100,000

7 ○ greather than $100,000

b) In rough figures, what is the total **debt** for your operation today, including all mortgages for farm or ranch property, and other loans for machinery, animals, seeds, chemicals, or other things?

$ ☐☐☐☐☐☐

2 ○ No ▸ What was your **gross income** in 1990 **before taxes** from farm employment?

1 ○ less than $10,000

2 ○ $10,000 - $30,000

3 ○ $30,001 - $50,000

4 ○ $50,001 - $70,000

5 ○ $70,001 - $100,000

6 ○ greather than $100,000

A25. How much income did **you and your wife** earn in 1990 from other sources **before taxes**? Please include income from investments, businesses other than the farm operation, and off-farm employment.

1 ○ less than $10,000

2 ○ $10,000 - $20,000

3 ○ $20,001 - $30,000

4 ○ $30,001 - $50,000

5 ○ greather than $50,000

A26. How many people (adults and children), including yourself, are supported by your family's total income?

☐☐ persons

YOUR COMMENTS:

PART B: YOUR HEALTH HISTORY

B1. How tall are you?

1 ☐☐ feet ☐☐ in. OR 2 ☐☐☐ cm.

B2. How much do you weigh?

1 ☐☐☐ lbs. OR 2 ☐☐☐ kg.

B3. Did you have any life-threatening health problems at birth or a birth defect?

1 ○ Yes 2 ○ No ▸ GO TO B4.

What was this health problem or birth defect?

☐☐☐ 1

B4. For each of the conditions or diseases listed below, please indicate whether a doctor has ever told you that you had that health problem. If you have been diagnosed at any time with any of these diseases, please provide the additional information requested. If you never had these diseases/conditions, please indicate this by checking *'Never had any of the above'*.

DISEASE/ CONDITION	EVER HAD?	YEAR OF DIAGNOSIS	NAME OF DRUG REGULARLY TAKEN
a) Over-active thyroid	1 ○ Yes ▸	19☐☐	☐☐☐
b) Under-active thyroid	1 ○ Yes ▸	19☐☐	☐☐☐
c) Diabetes	1 ○ Yes ▸	19☐☐	☐☐☐
d) High blood pressure	1 ○ Yes ▸	19☐☐	☐☐☐
e) Heart disease	1 ○ Yes ▸	19☐☐	☐☐☐
f) Epilepsy	1 ○ Yes ▸	19☐☐	☐☐☐
g) Asthma	1 ○ Yes ▸	19☐☐	☐☐☐
h) Arthritis/ Rheumatism	1 ○ Yes ▸	19☐☐	☐☐☐
i) Prostate disease	1 ○ Yes ▸	19☐☐	☐☐☐
j) Parkinson's disease	1 ○ Yes ▸	19☐☐	☐☐☐
k) Farmer's lung disease	1 ○ Yes ▸	19☐☐	☐☐☐
l) Silage filler's disease	1 ○ Yes ▸	19☐☐	☐☐☐
m) Allergies to hay, molds, grain dust	1 ○ Yes ▸	19☐☐	☐☐☐
n) Never had any of the above	2 ○ Never		

B5. Have you ever been diagnosed as having a tumor or cancer?

1 ○ Yes 2 ○ No ▸ GO TO B6.

a) During what year was this diagnosis made?

19☐☐

b) What kind of cancer or tumor was it?

☐☐☐

c) Did you take any medicines (chemotherapy) that the doctor prescribed for this tumor or cancer?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐☐ weeks ☐☐ months ☐☐ years

d) Did you receive any radiation treatment for this cancer?

1 ○ Yes 2 ○ No

B6. Have you ever been diagnosed as having fertility problems?

1 ○ Yes 2 ○ No ▸ GO TO B7.

a) What was the problem?

☐☐☐

b) During what year was this diagnosis made?

19☐☐

c) Did you take any medicines that the doctor prescribed for this problem?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐☐ weeks ☐☐ months ☐☐ years

B7. Have you ever seen a doctor for skin problems (for example dermatitis, eczema)?

1 ○ Yes 2 ○ No ▸ GO TO B8.

a) What kind of skin problem was it?

☐☐☐

b) During what year was this diagnosis made?

19☐☐

c) Did you take any medicines that the doctor prescribed for this illness?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐☐ weeks ☐☐ months ☐☐ years

B8. Have you ever had any abdominal surgery?

1 ○ Yes 2 ○ No ▸ GO TO B9.

a) Why did you have this surgery?

☐☐☐

b) When did you have this surgery?

19☐☐

B9. Do you suffer from any other health problems (for example, ulcers, gall bladder attacks, frequent headaches, urinary tract or bladder infections, etc)?

1 ○ Yes 2 ○ No ▸ GO TO B10.

What are these health problems?

1 ☐☐☐

2 ☐☐☐

3 ☐☐☐

B10. Compared to other men of your age, would you say that your health is:

1 ○ excellent
2 ○ good
3 ○ fair
4 ○ poor

B11. Is there anything about your life on the farm that you believe to be harmful to your health?

1 ○ Yes 2 ○ No ▸ GO TO B12.

a) What is it? 1

b) What effect(s) do you think it has? 2

B12. Is there anything about your life on the farm that you believe makes you a healthier person?

1 ○ Yes 2 ○ No ▸ GO TO B13.

a) What is it?

B13. As a whole, would you describe your life as ...

1 ○ Very stressful
2 ○ Fairly stressful
3 ○ Not very stressful
4 ○ Not at all stressful

B14. Which of the following factors contributes **most** to how stressed you feel? Check **one** only.

1 ○ money worries
2 ○ family problems
3 ○ your own health problems
4 ○ feel over-worked
5 ○ other - specify:
6 ○ I don't feel stressed

B15. During the past 12 months, did you have an accident or injury on the farm that was serious enough to require a visit to the doctor or emergency room of a hospital?

1 ○ Yes 2 ○ No ▸ GO TO C1.

a) Please describe what part of you was injured and the nature of the injury (e.g. broken arm, secondary burns to the face) 1

b) What equipment were you working with? 2

c) What were you doing when this injury occurred? 3

PART C: LIFESTYLE FACTORS

C1. Are you currently smoking 1 or more cigarettes or cigars per day?

1 ○ Yes ▸ a) How many cigarettes or cigars per day are you smoking?

b) How many years have you been smoking?

c) What type of cigarettes do you usually smoke?

1 ○ low tar
2 ○ other filtered cigarettes
3 ○ unfiltered cigarettes

d) What brand of cigarettes or cigars do you usually smoke?

GO TO C2.

2 ○ No ▸ a) Did you ever smoke 1 or more cigarettes or cigars per day (for at least one year)?

1 ○ Yes 2 ○ No ▸ GO TO C2.

a) How many cigarettes or cigars did you smoke per day?

b) How many years did you smoke?

c) During what year did you quit?

19

C2. Are you currently smoking a pipe?

1 ○ Yes ▸ a) How many pipes of tobacco do you smoke per day?

b) How many years have you been smoking a pipe?

2 ○ No ▸ Were you ever a regular pipe smoker (1 or more pipes per day for at least one year)?

1 ○ Yes 2 ○ No ▸ GO TO C3.

a) How many pipes did you smoke per day?

b) How many years did you smoke a pipe?

c) During what year did you quit?

19

C3. Was your mother a regular smoker during your childhood?

1 ○ Yes 2 ○ No

C4. Was your father a regular smoker during your childhood?

1 ○ Yes 2 ○ No

C5. During the past year, how many drinks of beer, wine or hard liquor (whiskey, gin, vodka, rum, brandy, etc.) have you had during an average **week**? Enter a "0" if you had less than 1 drink per week of that beverage.

cans or bottles of beer per week 1 ☐

glasses of wine per week 2 ☐

drinks of hard liquor per week 3 ☐

C6. How many drinks of beer, wine or hard liquor did you drink during an average **week** when you first got married to your present wife? Enter a "0" if you had less than 1 drink per week of that beverage.

cans or bottles of beer per week 1 ☐

glasses of wine per week 2 ☐

drinks of hard liquor per week 3 ☐

C7. Do you drink coffee?

1 ○ Yes 2 ○ No ▶ GO TO C8.

a) How many cups of coffee per day do you usually drink?

☐ cups

b) What kind of coffee do you usually drink?(Check **one** only)

1 ○ caffeinated

2 ○ decaffeinated

C8. Do you drink tea?

1 ○ Yes 2 ○ No ▶ GO TO C9.

a) How many cups of tea per day do you usually drink?

☐ cups

b) What kind of tea do you usually drink? (Check **one** only)

1 ○ regular

2 ○ decaffeinated

3 ○ herbal

4 ○ other - specify

☐ ☐

C9. How many servings of cola drinks (for example, Coke, Pepsi, etc.) do you consume:

per day? 1 ☐

OR

per week? 2 ☐

C10. Did you catch and eat any Ontario sport fish in 1991?

1 ○ Yes 2 ○ No ▶ GO TO C11.

Where were these fish caught? Check all that apply.

1 ○ St. Lawrence River

2 ○ Niagara River

3 ○ Detroit River, Lake St. Clair, or St. Clair River

4 ○ Lake Superior

5 ○ Lake Huron, Georgian Bay, or St. Mary's River

6 ○ Lake Ontario

7 ○ Lake Erie

8 ○ Inland lakes, rivers or streams of Ontario

C11. Have you eaten any wildfowl or game in the past 12 months?

1 ○ Yes 2 ○ No

C12. How often do you come into contact with the following materials? Please think of your hobbies, crafts, work around the house or farm, repair and maintenance work, and off-farm employment or volunteer work when answering this question.

	Never	Number of days per month
a) Fumes from gasoline, diesel, kerosene or fuel oils	1 ○	2 ☐
b) Fumes from solvents, glues, paints, turpentine, stains or varnishes	1 ○	2 ☐
c) Dust fom silica, granite, or rocks	1 ○	2 ☐
d) Glass fibre dust or asbestos	1 ○	2 ☐
e) Radioactive materials	1 ○	2 ☐
f) Dust or fumes from lead, cadmium, nickel, chromium or mercury	1 ○	2 ☐
g) Coal tar, pitch, asphalt or creosote	1 ○	2 ☐
h) Electrical transformers	1 ○	2 ☐
i) Welding or soldering fumes	1 ○	2 ☐
j) Lubricating oils, or hydraulic fluids	1 ○	2 ☐
k) Dust from woodworking	1 ○	2 ☐
l) Natural fibres, such as jute, cotton, wool, etc.	1 ○	2 ☐
m) Photographic chemicals	1 ○	2 ☐

C13. Date of completion of questionnaire:

☐☐ Day ☐☐ Month 19☐☐ Year

THANK YOU VERY MUCH
FOR PARTICIPATING IN THIS
IMPORTANT RESEARCH STUDY.

PLEASE RETURN YOUR QUESTIONNAIRE
IN THE ENVELOPE PROVIDED
AS SOON AS POSSIBLE.

Form C

Health and Welfare Canada | Santé et Bien-être social Canada

Ontario Farm Family Health Study

Form C

To be completed by the Wife

Si vous préférez ce questionnaire en français, veuillez cocher ☐

Is the information provided above on your name, address, and telephone number correct?

1 ○ Yes 2 ○ No ▸ Please make the appropriate correction below

FIRST NAME:	MIDDLE:	LAST NAME:
MAILING ADDRESS: Street and Number/P.O. Box No./R.R. No.		
Village/Town	Postal Code	Telephone Number: ( )

INSTRUCTIONS FOR COMPLETING THE QUESTIONNAIRES

Three different questionnaires have been developed for this study.

1. **GREEN (Form A) –To be completed by the farm operator (the person who is responsible for the DAY-TO-DAY decisions on this farm)**
2. **BLUE (Form B) –To be completed by the husband**
3. **BEIGE (Form C) –To be completed by the wife**

- Each farm selected for this study should have received these three forms. For those farms where more than one family lives on the farm, some families will have received only a Form A, and some Form B and C. We ask that you and your spouse complete the questionnaires that have your names on it.
- Form A collects information on the farm operation, including the kinds of agricultural products grown or raised, the use of chemicals on the farm, diseases of farm animals, and types of structures on the farm (eg. silos, manure tanks). Information on the husband's lifestyle, activities on the farm, and health is collected in Form B. The purpose of Form C is to obtain information on the lifestyle, experiences, and health of the wife, as well as information on any major health problems of their children.
- Please answer the questions as completely and accurately as possible. Some of the questions ask you to check off the appropriate answer, others ask you to supply information, such as names of agricultural chemicals (pesticides) used on the farm. You may want to refer to your farm and household records to refresh your memory.
- Please do not write in the shaded areas.
- When you have finished answering all of the questions, please return the questionnaires to us in the envelopes provided. In families where both the husband and wife have been sent questionnaires, we have enclosed two self-addressed postage-paid envelopes so that you may (if you so desire) return your questionnaires separately.
- We realize that your time is very important to you and that you may think that it will take too much time to answer these questions. We have estimated that it will take less than one hour to complete a questionnaire, as there will be questions or parts of questions which you can skip because they do not apply to your circumstances.

Please remember that it is only through your cooperation that we will be able to determine whether farm families have a higher or lower risk of certain health problems than the general public.

Confidential when completed.

FOR OFFICE USE ONLY				Date:
Interviewer ID#:	Mode of completion: 1 ○ Mail 2 ○ Telephone	Time:	JIC:	

8-5103-261.1: 1991-08-14 NHW/HPB-165-04265

Canada

DESCRIPTION OF QUESTIONS

The purposes of this questionnaire are to obtain information on the lifestyle and experiences of the wife that could affect her or her family's health and to obtain information on their health status. Some of the potentially harmful exposures that can occur on a farm include farm chemicals, molds, grain and other dusts, animal viruses and diseases, toxic gases and vapors, corrosive materials, engine exhausts, and veterinary medications, as well as long exposures to sunlight, intense heat or cold, and strenuous physical exercise.

Medical research has discovered that often a disease such as lung cancer can be caused by a number of factors which act either alone or together. In order to determine whether one particular exposure or experience caused a certain disease, we must be able to rule out other potential factors which may have caused that disease. For example smoking has long been associated with lung cancer. If in this study we found that one particular group of farmers had a higher rate of lung cancer we must first find out if they are also heavy smokers before we could say that the lung cancer that they had was due to an exposure on the farm. For this reason we ask questions about a lot of things which have nothing to do with farming but which might potentially affect your health.

This questionnaire is divided into 4 sections. Part A obtains information on where you live, your family background, education, employment, activities on the farm, and use of chemicals and protective equipment while mixing or applying these chemicals. A number of public health studies have found that disease rates can vary by province or country of birth, source of drinking water, occupational exposures, ethnic background, religion, and level of education. We are also interested in how many farmers supplement their income by working off the farm and what kinds of jobs they are doing.

Part B provides us with information on your general health and specific health problems which you may have had. Using information on your height, weight and age, we can determine if you have any weight problems which might affect your health. We ask for your assessment of your health and factors which you think may contribute to your health. There is also a question on injuries to you which have occurred on the farm.

Part C asks about your lifestyle. There are a number of lifestyle factors which can either hurt or improve your health. These include smoking, alcohol consumption, drinking tea, coffee, or cola soft drinks, and eating fish or wildlife.

Part D obtains information on your pregnancies and your children's health. We ask about factors which may have affected your pregnancy or your children's health such as exposures to infections or cigarette smoke, as well as specific health problems which your children may have had as a baby or later in life.

PART A: GENERAL INFORMATION

A1. On this farm operation, are you ...
(Please check all that apply):

1 ◯ the owner

2 ◯ the farm operator (responsible for the day-to-day decisions made on the farm)

3 ◯ an employee or hired hand

4 ◯ other; please specify:

A2. What is your birth date?

Day Month 19 Year

A3. What was the date of your marriage (legal or common-law) to your current husband?

Day Month 19 Year

A4. Have you been married (legally or common-law) more than once?

1 ◯ Yes 2 ◯ No ▸ GO TO A5.

Did you and your **former spouse(s)** ever have any problems having a healthy child?

1 ◯ Yes ▸ What was this problem? Check all that apply.

1 ◯ miscarriage or spontaneous abortion

2 ◯ male infertility problems

3 ◯ female infertility problems

4 ◯ stillbirth

5 ◯ birth defects

6 ◯ child died before 1st birthday

7 ◯ Other (Specify)

2 ◯ No ▸ Number of children by former spouse(s)

3 ◯ Never tried to have a baby

A5. Do you have any adopted or foster children?

1 ◯ Yes 2 ◯ No

how many?

A6. During what year did you move onto this farm operation?

19 Year

A7. Were you born in Canada?

1 ◯ Yes ▸ Which province?

2 ◯ No ▸ In what country were you born?

A8. In what country was your father born? 1

In what country was your mother born? 2

A9. What was your father's usual occupation? 1

What was your mother's usual occupation? 2

A10. To which ethnic or cultural group(s) did your ancestors belong? Mark or specify as many as applicable.

01 ◯ French
02 ◯ English
03 ◯ German
04 ◯ Scottish
05 ◯ Irish
06 ◯ Italian
07 ◯ Ukrainian
08 ◯ Dutch (Netherlands)
09 ◯ Jewish
10 ◯ Polish
11 ◯ Black
12 ◯ Chinese
13 ◯ Other (Specify)

A11. To what religious denomination do you belong?
Select one only.

01 ◯ None
02 ◯ Roman Catholic
03 ◯ United
04 ◯ Anglican
05 ◯ Presbyterian
06 ◯ Lutheran
07 ◯ Baptist
08 ◯ Jewish
09 ◯ Mennonite
10 ◯ Mormon
11 ◯ Jehovah's Witnesses
12 ◯ Pentecostal
13 ◯ Other (Specify)

A12. What is the **highest** grade (or year) of schooling that you have completed?

1 ○ Any of Grades 1 to 8

2 ○ Any of Grades 9 to 11

3 ○ High School Graduate

4 ○ Started college or university but did not complete

5 ○ Community College Diploma
(Please specify type of diploma)

6 ○ University degree (Please specify highest degree)

A13. Are you currently employed at a job site **off** this farm?

1 ○ Yes 2 ○ No ▸ GO TO A14.

Briefly describe the kind of work you do in your job.
(For example, elementary school teacher, salesperson, bank clerk.)

What kind of product or service is produced or provided in the business where you work?
Give full description, (e.g., leather tanning shop, retail shoe store, government office.)

During what year did you start work at this job?

19

How many hours per week do you normally work at this job?

A14. Have you held any other jobs (lasting more than six months) at sites **off** this farm since the date of your marriage?

1 ○ Yes 2 ○ No ▸ GO TO A15.

JOB #1

Briefly describe the kind of work you did in your job.

What kind of product or service was produced or provided in the business where you worked?

During what years did you work at this job?

FROM 19 TO 19

JOB #2

Briefly describe the kind of work you did in your job.

What kind of product or service was produced or provided in the business where you worked?

During what years did you work at this job?

FROM 19 TO 19

JOB #3

Briefly describe the kind of work you did in your job.

What kind of product or service was produced or provided in the business where you worked?

During what years did you work at this job?

FROM 19 TO 19

A15. Approximately how many days off do you have per **month** (i.e., days when you are not working at a job or on the farm)?

days (May – Nov.) days (Dec. – Apr.)

A16. While you were growing up, did you live mostly on a farm or ranch, or did you live somewhere else?

1 ○ a farm or ranch (Please specify the kind of products grown or raised on this farm)

2 ○ a municipality with a population of less than 5,000

3 ○ a municipality with a population of 5,000 or more

A17. Altogether, how many years have you lived on a farm?

years

WE WOULD NOW LIKE TO GET SOME INFORMATION ON THE KINDS OF WORK YOU DO ON THE FARM AND HOW OFTEN YOU DO THIS WORK.

A18. Looking back over the past five years, how often have you done the following activities. Give your best estimate of the number of days during the year and which months of the year you do these activities. Please include custom work when answering these questions. Even if you worked only part of a day, count that as one day.

	Never	Occasionally	Regularly	# of Days during year	During months of
a) milking cows	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
b) plowing	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
c) harrowing or disking	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
d) cultivating	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
e) planting	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
f) applying fertilizer, manure	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
g) mixing or applying chemicals to crops for weed or brush control	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
h) mixing or applying chemicals to crops for insect or disease control	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
i) mixing or administering chemicals to livestock to control insects & disease	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
j) mixing or applying chemicals around the farm yard and buildings to control weeds and brush	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
k) mixing or applying chemicals around the farm buildings to control pests	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
l) harvesting crops, including driving machinery or trucks	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
m) working with farm livestock (other than milking dairy cows)	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
n) bookkeeping, maintaining records, paying bills, banking or preparing tax forms	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
o) working in the family garden	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
p) working in dusty areas, for example, with wood shavings, shovelling grain, corn, beans, etc.	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
q) heavy lifting, for example, pails, crates, handling bales of hay or straw, feed bags, etc.	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
r) filling, servicing or unloading a silo	1 ○	2 ○ ▶	3 ○ ▶		○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.

A19. Do **you** use chemicals to spray or dust flowers, shrubs, vegetables or fruit in your family garden? If you use more than 2 chemicals in your garden, supply information on the 2 chemicals you use most often.

1 ○ Yes 2 ○ No ▸ GO TO A20.

Please provide the following information for each chemical:

	CHEMICAL #1	CHEMICAL #2
Name		
Reason for use	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ Other (Specify):	1 ○ insects 2 ○ weeds 3 ○ disease 4 ○ Other (Specify):
How do you apply it	1 ○ spray 2 ○ dust 3 ○ Other (Specify):	1 ○ spray 2 ○ dust 3 ○ Other (Specify):
During what months	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
How many years have you been using this chemical?	years	years

A20. Do **you** use chemicals to spray or dust family pets for insects or disease?

1 ○ Yes 2 ○ No ▸ GO TO A21.

Please provide the following information for each chemical:

	CHEMICAL #1	CHEMICAL #2
Name		
Reason for use	1 ○ insects 2 ○ disease 3 ○ Other (Specify):	1 ○ insects 2 ○ disease 3 ○ Other (Specify):
How do you apply it	1 ○ spray 2 ○ dust 3 ○ Other (Specify):	1 ○ spray 2 ○ dust 3 ○ Other (Specify):
During what months	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
How many years have you been using this chemical?	years	years

A21. Do **you** use chemicals to control weeds in your yard or lawn?

1 ○ Yes 2 ○ No ▸ GO TO A22.

Please provide the following information for each chemical:

	CHEMICAL #1	CHEMICAL #2
Name		
How do you apply it	1 ○ spray 2 ○ dust 3 ○ Other (Specify):	1 ○ spray 2 ○ dust 3 ○ Other (Specify):
During what months	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept. ○ Oct. ○ Nov. ○ Dec.
How many years have you been using this chemical?	years	years

A22. Do you mix, load or apply any pesticides (herbicides, insecticides, fungicides, fumigants, rodenticides, etc.) on this farm?

1 ○ Yes 2 ○ No ▸ GO TO A23.

a) Please check the frequency that you use each of the following types of protective equipment and indicate your best guess of the year that you started using it:

	Never	Occasionally	Regularly	Year
1) tractor with a cab for crop spraying	1○	2○ ▸	3○ ▸	19
2) plastic, rubber or vinyl gloves	1○	2○ ▸	3○ ▸	19
3) cloth or leather gloves	1○	2○ ▸	3○ ▸	19
4) face shield or goggles	1○	2○ ▸	3○ ▸	19
5) coveralls or overalls	1○	2○ ▸	3○ ▸	19
6) plastic or chemically resistant apron	1○	2○ ▸	3○ ▸	19
7) respirator or mask with pesticide filters	1○	2○ ▸	3○ ▸	19
8) Other (specify)	1○	2○ ▸	3○ ▸	19

b) How soon after handling these chemicals would you change to **clean work clothes**?

1 ○ right away

2 ○ at the end of the work day

3 ○ at the end of the following day or later

c) Are the clothes that you have worn while handling and applying these chemicals washed separately from the regular household laundry?

1 ○ Yes

2 ○ No

A23. How did you hear about this study?

1 ○ in a magazine or newspaper

2 ○ on radio or television

3 ○ from friends or relatives

4 ○ never heard about it until I received this questionnaire

A24. What convinced you to participate in this study? Please check all that apply.

1 ○ concern about my family's health

2 ○ I think this is an important area of research

3 ○ the government was supporting this research with my tax dollars

4 ○ other reasons; please explain these:

YOUR COMMENTS

PART B: YOUR HEALTH HISTORY

B1. How tall are you?

1 [ ] [ ] feet in. OR 2 [ ] cm.

B2. How much do you usually weigh (when you are not pregnant)?

1 [ ] lbs. OR 2 [ ] kg.

B3. Did you have any life-threatening health problems at birth or a birth defect?

1 ○ Yes 2 ○ No ▸ GO TO B4.

What was this health problem or birth defect?

[ ] 1

B4. For each of the conditions or diseases listed below, please indicate whether a doctor has ever told you that you had that health problem. If you have been diagnosed at any time with any of these diseases, please provide the additional information requested. If you never had these diseases/conditions, please indicate this by checking *'Never had any of the above'*.

DISEASE/ CONDITION	EVER HAD?	YEAR OF DIAGNOSIS	NAME OF DRUG REGULARLY TAKEN
a) Over-active thyroid	1○ Yes ▸	19	▸
b) Under-active thyroid	1○ Yes ▸	19	▸
c) Diabetes	1○ Yes ▸	19	▸
d) High blood pressure	1○ Yes ▸	19	▸
e) Heart disease	1○ Yes ▸	19	▸
f) Epilepsy	1○ Yes ▸	19	▸
g) Asthma	1○ Yes ▸	19	▸
h) Arthritis/ Rheumatism	1○ Yes ▸	19	▸
i) Pelvic inflammatory disease	1○ Yes ▸	19	▸
j) Salpingitis or infection of the Fallopian tubes	1○ Yes ▸	19	▸
k) Parkinson's disease	1○ Yes ▸	19	▸
l) Endometriosis	1○ Yes ▸	19	▸
m) Allergies to hay, molds, grain dust	1○ Yes ▸	19	▸
n) Never had any of the above	2○ Never		

B5. Have you ever been diagnosed as having a tumor or cancer?

1 ○ Yes 2 ○ No ▸ GO TO B6.

a) During what year was this diagnosis made?

19 ☐☐

b) What kind of cancer or tumor was it?

☐ ☐☐☐

c) Did you take any medicines (chemotherapy) that the doctor prescribed for this tumor or cancer?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐ weeks ☐ months ☐ years

d) Did you receive any radiation treatment for this cancer?

1 ○ Yes 2 ○ No

B6. Have you ever seen a doctor for skin problems (for example dermatitis, eczema)?

1 ○ Yes 2 ○ No ▸ GO TO B7.

a) What kind of skin problem was it?

☐ ☐☐☐

b) During what year was this diagnosis made?

19 ☐☐

c) Did you take any medicines that the doctor prescribed for this illness?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐ weeks ☐ months ☐ years

B7. Have you ever had any abdominal surgery (other than for Caesarian deliveries or appendicitis)?

1 ○ Yes 2 ○ No ▸ GO TO B8.

a) Why did you have this surgery?

☐ ☐☐☐

b) When did you have this surgery?

19 ☐☐

B8. Did you have problems with acne as a teenager or as an adult?

1 ○ Yes 2 ○ No ▸ GO TO B9.

a) How old were you when you got this condition?

☐

b) Did you take any medicine prescribed by a doctor for this condition?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐ weeks ☐ months ☐ years

c) Do you still have problems with acne?

1 ○ Yes 2 ○ No

B9. Have you ever been vaccinated for rubella? (Rubella is also called the German measles).

1 ○ Yes 2 ○ No ▸ GO TO B10.

During what year did you receive this shot?

19 ☐☐

B10. Have you had your appendix removed?

1 ○ Yes 2 ○ No ▸ GO TO B11.

Did it rupture or perforate?

1 ○ Yes 2 ○ No

B11. Was there ever a time when you and your partner tried for **six months or more** to have children but were **unsuccessful**?

1 ○ Yes 2 ○ No ▸ GO TO B12.

a) Did this occur immediately after using oral contraceptives (the Pill) for at least one year?

1 ○ Yes 2 ○ No

b) During what year(s) did you have this problem?

FROM 19 ☐☐ TO 19 ☐☐

c) How many months did you and your partner try?

☐ months

d) Did a doctor tell you what was causing this problem?

1 ○ Yes 2 ○ No

What was the problem?

☐ ☐☐☐

e) Did you take any medicines that the doctor prescribed for this condition?

1 ○ Yes 2 ○ No

How many weeks, months or years did you take this medicine?

☐ weeks ☐ months ☐ years

B12. How old were you when you first began having your menstrual periods?

B13. Have you ever seen a doctor for menstrual problems? (For example, irregular periods, spotting, painful periods, heavy bleeding, etc.)

1 ○ Yes 2 ○ No ▸ GO TO B14.

a) What were these problems?

b) During what year was this diagnosis made?

19

c) Did you take any medicines that the doctor prescribed for this problem?

1 ○ Yes 2 ○ No

How many weeks, months, or years did you take this medicine?

weeks months years

B14. Have you reached menopause yet?

1 ○ Yes ▸ How old were you when your periods stopped?

2 ○ No ▸ Would you say that the pain associated with your period is usually:

1 ○ mildly discomforting

2 ○ not painful

3 ○ painful

B15. Do you suffer from any other health problems (for example, ulcers, gall bladder attacks, frequent headaches, urinary tract or bladder infections, etc)?

1 ○ Yes 2 ○ No ▸ GO TO B16.

What are these health problems?

1

2

3

B16. Compared to other women of your age, would you say that your health is:

1 ○ excellent

2 ○ good

3 ○ fair

4 ○ poor

B17. Is there anything about your life on the farm that you believe to be harmful to your health?

1 ○ Yes 2 ○ No ▸ GO TO B18.

a) What is it?

1

b) What effect(s) do you think it has?

2

B18. Is there anything about your life on the farm that you believe makes you a healthier person?

1 ○ Yes 2 ○ No ▸ GO TO B19.

a) What is it?

B19. As a whole, would you describe your life as ...

1 ○ Very stressful

2 ○ Fairly stressful

3 ○ Not very stressful

4 ○ Not at all stressful

B20. Which of the following factors contributes **most** to how stressed you feel? Check **one** only.

1 ○ money worries

2 ○ family problems

3 ○ your own health problems

4 ○ feel over-worked

5 ○ other - specify:

6 ○ I don't feel stressed

B21. During the past 12 months, did you have an accident or injury on the farm that was serious enough to require a visit to the doctor or emergency room of a hospital?

1 ○ Yes 2 ○ No ▸ GO TO C1.

a) Please describe what part of you was injured and the nature of the injury (e.g. broken arm, secondary burns to the face)

1

b) What equipment were you working with?

2

c) What were you doing when this injury occurred?

3

YOUR COMMENTS

PART C: LIFESTYLE FACTORS

C1. Are you currently smoking 1 or more cigarettes or cigars per day?

1 ○ Yes ▸ a) How many cigarettes or cigars per day are you smoking?

b) How many years have you been smoking?

c) What type of cigarettes do you usually smoke?

1 ○ low tar

2 ○ other filtered cigarettes

3 ○ unfiltered cigarettes

d) What brand of cigarettes or cigars do you usually smoke?

GO TO C2.

2 ○ No ▸ a) Did you ever smoke 1 or more cigarettes or cigars per day (for at least one year)?

1 ○ Yes 2 ○ No ▸ GO TO C2.

a) How many cigarettes or cigars did you smoke per day?

b) How many years did you smoke?

c) During what year did you quit?

19

C2. Was your mother a regular smoker during your childhood?

1 ○ Yes 2 ○ No

C3. Was your father a regular smoker during your childhood?

1 ○ Yes 2 ○ No

C4. During the past year, how many drinks of beer, wine or hard liquor (whiskey, gin, vodka, rum, brandy, etc.) have you had during an average **week**? Enter a "0" if you had less than 1 drink per week of that beverage.

cans or bottles of beer per week 1

glasses of wine per week 2

drinks of hard liquor per week 3

C5. How many drinks of beer, wine or hard liquor did you drink during an average **week** when you first got married to your present husband? Enter a "0" if you had less than 1 drink per week of that beverage.

cans or bottles of beer per week 1

glasses of wine per week 2

drinks of hard liquor per week 3

C6. Do you drink coffee?

1 ○ Yes 2 ○ No ▸ GO TO C7.

a) How many cups of coffee per day do you usually drink?

cups

b) What kind of coffee do you usually drink?(Check **one** only)

1 ○ caffeinated

2 ○ decaffeinated

C7. Do you drink tea?

1 ○ Yes 2 ○ No ▸ GO TO C8.

a) How many cups of tea per day do you usually drink?

cups

b) What kind of tea do you usually drink?(Check **one** only)

1 ○ regular

2 ○ decaffeinated

3 ○ herbal

4 ○ other - specify

C8. How many servings of cola drinks (for example, Coke, Pepsi, etc.) do you consume:

per day? 1

OR

per week? 2

C9. Did you catch and eat any Ontario sport fish in 1991?

1 ○ Yes 2 ○ No ▸ GO TO C10.

Where were these fish caught? Check all that apply.

1 ○ St. Lawrence River

2 ○ Niagara River

3 ○ Detroit River, Lake St. Clair, or St. Clair River

4 ○ Lake Superior

5 ○ Lake Huron, Georgian Bay, or St. Mary's River

6 ○ Lake Ontario

7 ○ Lake Erie

8 ○ Inland lakes, rivers or streams of Ontario

C10. Have you eaten any wildfowl or game in the past 12 months?

1 ○ Yes 2 ○ No

C11. Do you drink milk?

1 ○ Yes 2 ○ No ▸ GO TO C12.

a) Approximately how many glasses of milk do you drink per day?

glasses

b) What kind of milk do you usually drink? (Check **one** only)

1 ○ 2 % or 1 %

2 ○ Homogenized

3 ○ Skim milk

4 ○ Raw milk from the farm

5 ○ Other - specify:

C12. Have you ever regularly used an electric blanket on your bed?

1 ○ Yes 2 ○ No ▸ GO TO C13.

Do you still use one?

1 ○ Yes ▸ How many years have you used it? ☐☐

2 ○ No ▸ During what years did you use it?

FROM 19☐☐ TO 19☐☐

C13. Have you ever regularly slept on a water bed?

1 ○ Yes 2 ○ No ▸ GO TO C14.

Are you still sleeping on a water bed?

1 ○ Yes ▸ How many years have you been sleeping on a water bed? ☐☐

2 ○ No ▸ During what years did you sleep on a water bed?

FROM 19☐☐ TO 19☐☐

C14. How often do you come into contact with the following materials? Please think of your hobbies, crafts, work around the house or farm, repair and maintenance work, and off-farm employment or volunteer work when answering this question.

	Never	Number of days per month
a) Fumes from gasoline, diesel, kerosene or fuel oils	1 ○	2 ☐☐
b) Fumes from solvents, glues, paints, turpentine, stains or varnishes	1 ○	2 ☐☐
c) Dust fom silica, granite, or rocks	1 ○	2 ☐☐
d) Glass fibre dust or asbestos	1 ○	2 ☐☐
e) Radioactive materials	1 ○	2 ☐☐
f) Dust or fumes from lead, cadmium, nickel, chromium or mercury	1 ○	2 ☐☐
g) Coal tar, pitch, asphalt or creosote	1 ○	2 ☐☐
h) Electrical transformers	1 ○	2 ☐☐
i) Welding or soldering fumes	1 ○	2 ☐☐
j) Lubricating oils, or hydraulic fluids	1 ○	2 ☐☐
k) Dust from woodworking	1 ○	2 ☐☐
l) Natural fibres, such as jute, cotton, wool, etc.	1 ○	2 ☐☐
m) Photographic chemicals	1 ○	2 ☐☐

C15. What is today's date?

☐☐ Day ☐☐ Month 19☐☐ Year

YOUR COMMENTS

PART D: REPRODUCTIVE HISTORY

THE FOLLOWING QUESTIONS ARE ABOUT YOUR PREGNANCIES AND YOUR CHILDREN'S HEALTH. IT MIGHT HELP YOU TO REMEMBER YOUR PREGNANCIES IF YOU WRITE DOWN ON A SEPARATE PIECE OF PAPER EACH OF YOUR PREGNANCIES IN ORDER OF WHEN THEY OCCURRED, WITH THE OUTCOME OF THAT PREGNANCY (FOR EXAMPLE, MISCARRIAGE, OR THE NAME OF THE CHILD).

D1. How many children did you want to have when you first got married? ☐

How many boys? 1 ☐ How many girls? 2 ☐

D2. Are you going to try to have a (or another) baby?

1 ○ Yes 2 ○ No

D3. Have you ever been pregnant?

1 ○ Yes ▸ How many times? (Include current pregnancy, live births, stillbirths, miscarriages, and abortions by a doctor). ☐

If you have ever been pregnant or are currently pregnant ▸ GO TO D4.

2 ○ No ▸ You have completed this questionnaire, and we would like to thank you very much for your cooperation. Please write any comments you have in the space provided.

Please return this questionnaire as soon as possible in the postage-paid envelope provided.

D4. How many of your pregnancies resulted in a live birth? ☐

D5. How many pregnancies resulted in a miscarriage? (The unintentional loss of the pregnancy when the pregnancy had lasted **less than 5 months**). ☐

D6. How many pregnancies were terminated by an abortion by a doctor? ☐

D7. How many pregnancies resulted in a stillbirth? (The baby was born dead when you were **5 months or more** pregnant). ☐

WE HAVE ALLOWED SPACE FOR YOU TO RECORD INFORMATION ON UP TO FIVE PREGNANCIES. IF YOU HAVE HAD MORE THAN FIVE PREGNANCIES, PLEASE ANSWER THE QUESTIONS FOR YOUR FIRST FIVE PREGNANCIES.

WE SUGGEST THAT YOU ANSWER ALL OF THE QUESTIONS REGARDING YOUR FIRST PREGNANCY AND THEN RETURN TO THIS PAGE TO ANSWER THE QUESTIONS ON SUBSEQUENT PREGNANCIES.

	FIRST PREGNANCY	SECOND PREGNANCY
D8. Did this pregnancy end with:	1 ○ a single live birth 2 ○ twins or other multiple births 3 ○ a miscarriage (also called a spontaneous abortion) 4 ○ stillbirth 5 ○ an induced abortion by a doctor 6 ○ an ectopic or tubal pregnancy 7 ○ a hydatiform mole 8 ○ other, please specify: ☐☐☐ 9 ○ don't know as currently pregnant	1 ○ a single live birth 2 ○ twins or other multiple births 3 ○ a miscarriage (also called a spontaneous abortion) 4 ○ stillbirth 5 ○ an induced abortion by a doctor 6 ○ an ectopic or tubal pregnancy 7 ○ a hydatiform mole 8 ○ other, please specify: ☐☐☐ 9 ○ don't know as currently pregnant
D9. How was this pregnancy first diagnosed?	1 ○ by a doctor 2 ○ by a home pregnancy test 3 ○ other, please specify: ☐☐	1 ○ by a doctor 2 ○ by a home pregnancy test 3 ○ other, please specify: ☐☐
D10. How many weeks pregnant were you (from the week of your last menstrual period) when you **found out** you were pregnant?	☐ weeks	☐ weeks
D11. Did you experience any medical problems during this pregnancy? For example did you have gestational diabetes, high blood pressure, toxemia or any other condition that your doctor was concerned about?	1 ○ Yes 2 ○ No Please describe these conditions: ☐☐☐ Were you hospitalized during this pregnancy (other than for delivery)? 1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No Please describe these conditions: ☐☐☐ Were you hospitalized during this pregnancy (other than for delivery)? 1 ○ Yes 2 ○ No
D12. Did you take any drugs or medications during this pregnancy that were prescribed by your doctor? For example, antibiotics, sleeping pills, tranquilizers, or medicine for morning sickness.	1 ○ Yes 2 ○ No What were the names of these medications? 1 ☐☐☐ 2 ☐☐☐	1 ○ Yes 2 ○ No What were the names of these medications? 1 ☐☐☐ 2 ☐☐☐

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
1 ○ a single live birth	1 ○ a single live birth	1 ○ a single live birth
2 ○ twins or other multiple births	2 ○ twins or other multiple births	2 ○ twins or other multiple births
3 ○ a miscarriage (also called a spontaneous abortion)	3 ○ a miscarriage (also called a spontaneous abortion)	3 ○ a miscarriage (also called a spontaneous abortion)
4 ○ stillbirth	4 ○ stillbirth	4 ○ stillbirth
5 ○ an induced abortion by a doctor	5 ○ an induced abortion by a doctor	5 ○ an induced abortion by a doctor
6 ○ an ectopic or tubal pregnancy	6 ○ an ectopic or tubal pregnancy	6 ○ an ectopic or tubal pregnancy
7 ○ a hydatiform mole	7 ○ a hydatiform mole	7 ○ a hydatiform mole
8 ○ other, please specify:	8 ○ other, please specify:	8 ○ other, please specify:
9 ○ don't know as currently pregnant	9 ○ don't know as currently pregnant	9 ○ don't know as currently pregnant
1 ○ by a doctor	1 ○ by a doctor	1 ○ by a doctor
2 ○ by a home pregnancy test	2 ○ by a home pregnancy test	2 ○ by a home pregnancy test
3 ○ other, please specify:	3 ○ other, please specify:	3 ○ other, please specify:
☐☐ weeks	☐☐ weeks	☐☐ weeks
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
Please describe these conditions:	Please describe these conditions:	Please describe these conditions:
Were you hospitalized during this pregnancy (other than for delivery)?	Were you hospitalized during this pregnancy (other than for delivery)?	Were you hospitalized during this pregnancy (other than for delivery)?
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
What were the names of these medications?	What were the names of these medications?	What were the names of these medications?
1 ☐☐☐	1 ☐☐☐	1 ☐☐☐
2 ☐☐☐	2 ☐☐☐	2 ☐☐☐

D13. For the following possible activities on a farm operation, please indicate how regularly you did these activities during each of your pregnancies. Give your best estimate of the number of days during the year and which months of the year you did these activities. Please include custom work when answering these questions.

FREQUENCIES
N = Never O = Occasionally R = Regularly

	FIRST PREGNANCY		SECOND PREGNANCY	
	FREQUENCIES	During the months of:	FREQUENCIES	During the months of:
a) milking cows	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
b) plowing	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
c) harrowing or disking	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
d) cultivating	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
e) planting	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
f) applying fertilizer, manure	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
g) mixing or applying chemicals to crops for weed or brush control	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
h) mixing or applying chemicals to crops for insect or disease control	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
i) mixing or administering chemicals to livestock to control insects & disease	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
j) mixing or applying chemicals around the farm yard and buildings to control weeds and brush	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
k) mixing or applying chemicals around the farm buildings to control pests	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
l) harvesting crops, including driving machinery or trucks	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
m) working with farm livestock (other than milking dairy cows)	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
n) bookkeeping, maintaining records, paying bills, banking or preparing tax forms	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
o) working in the family garden	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
p) working in dusty areas, for example, with wood shavings, shovelling grain, corn, beans, etc.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
q) heavy lifting, for example, pails, crates, handling bales of hay or straw, feed bags, etc.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
r) filling, servicing or unloading a silo	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▸ # of days ○ R ▸	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.

THIRD PREGNANCY		FOURTH PREGNANCY		FIFTH PREGNANCY	
FREQUENCIES	During the months of:	FREQUENCIES	During the months of:	FREQUENCIES	During the months of:
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
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○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.
○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.	○ N ○ O ▶ ○ R ▶ # of days	○ Jan. ○ Feb. ○ Mar. ○ Apr. ○ May ○ June ○ July ○ Aug. ○ Sept ○ Oct. ○ Nov. ○ Dec.

	FIRST PREGNANCY	SECOND PREGNANCY
D14. During the time period **one month before you got pregnant and three months into this pregnancy**, were you: (Please check " √ " if true)	01 ○ given a general anesthetic, that is, put to sleep for surgery or other problem 02 ○ given an x-ray, including dental x-rays 03 ○ exposed to someone who had the German measles (Rubella), chicken pox, red measles, or mumps 04 ○ given a shot for the flu, German measles or some other vaccination 05 ○ smoking 1 or more cigarettes per day 06 ○ drinking 3 or more alcoholic drinks on any one occasion 07 ○ consuming 3 or more cups of coffee per day 08 ○ consuming 3 or more cups of tea per day 09 ○ using cocaine or crack 10 ○ smoking hashish or marijuana 11 ○ none of the above	01 ○ given a general anesthetic, that is, put to sleep for surgery or other problem 02 ○ given an x-ray, including dental x-rays 03 ○ exposed to someone who had the German measles (Rubella), chicken pox, red measles, or mumps 04 ○ given a shot for the flu, German measles or some other vaccination 05 ○ smoking 1 or more cigarettes per day 06 ○ drinking 3 or more alcoholic drinks on any one occasion 07 ○ consuming 3 or more cups of coffee per day 08 ○ consuming 3 or more cups of tea per day 09 ○ using cocaine or crack 10 ○ smoking hashish or marijuana 11 ○ none of the above
D15. Were you or your husband using any form of birth control **when you became pregnant**?	1 ○ Yes ▸ What kind of birth control were you using? ☐☐ 2 ○ No a) what method of birth control were you or your husband using **before you tried to become pregnant**? ☐☐ b) approximately how many months or menstrual cycles (from the month or cycle when you stopped using birth control) did it take you to become pregnant? ☐ months or cycles	1 ○ Yes ▸ What kind of birth control were you using? ☐☐ 2 ○ No a) what method of birth control were you or your husband using **before you tried to become pregnant**? ☐☐ b) approximately how many months or menstrual cycles (from the month or cycle when you stopped using birth control) did it take you to become pregnant? ☐ months or cycles
D16. Were you or your husband taking any drugs or medications prescribed by a doctor to help you get pregnant?	1 ○ Yes 2 ○ No What were the names of these medications? ☐☐☐ ☐☐☐	1 ○ Yes 2 ○ No What were the names of these medications? ☐☐☐ ☐☐☐
D17. Did you have any pets in your house during this pregnancy?	1 ○ No 2 ○ Dog 3 ○ Cat 4 ○ Fish 5 ○ Bird 6 ○ Other, please specify: ☐☐	1 ○ No 2 ○ Dog 3 ○ Cat 4 ○ Fish 5 ○ Bird 6 ○ Other, please specify: ☐☐

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
01 ○ given a general anesthetic, that is, put to sleep for surgery or other problem	01 ○ given a general anesthetic, that is, put to sleep for surgery or other problem	01 ○ given a general anesthetic, that is, put to sleep for surgery or other problem
02 ○ given an x-ray, including dental x-rays	02 ○ given an x-ray, including dental x-rays	02 ○ given an x-ray, including dental x-rays
03 ○ exposed to someone who had the German measles (Rubella), chicken pox, red measles, or mumps	03 ○ exposed to someone who had the German measles (Rubella), chicken pox, red measles, or mumps	03 ○ exposed to someone who had the German measles (Rubella), chicken pox, red measles, or mumps
04 ○ given a shot for the flu, German measles or some other vaccination	04 ○ given a shot for the flu, German measles or some other vaccination	04 ○ given a shot for the flu, German measles or some other vaccination
05 ○ smoking 1 or more cigarettes per day	05 ○ smoking 1 or more cigarettes per day	05 ○ smoking 1 or more cigarettes per day
06 ○ drinking 3 or more alcoholic drinks on any one occasion	06 ○ drinking 3 or more alcoholic drinks on any one occasion	06 ○ drinking 3 or more alcoholic drinks on any one occasion
07 ○ consuming 3 or more cups of coffee per day	07 ○ consuming 3 or more cups of coffee per day	07 ○ consuming 3 or more cups of coffee per day
08 ○ consuming 3 or more cups of tea per day	08 ○ consuming 3 or more cups of tea per day	08 ○ consuming 3 or more cups of tea per day
09 ○ using cocaine or crack	09 ○ using cocaine or crack	09 ○ using cocaine or crack
10 ○ smoking hashish or marijuana	10 ○ smoking hashish or marijuana	10 ○ smoking hashish or marijuana
11 ○ none of the above	11 ○ none of the above	11 ○ none of the above
1 ○ Yes ▸ What kind of birth control were you using?	1 ○ Yes ▸ What kind of birth control were you using?	1 ○ Yes ▸ What kind of birth control were you using?
2 ○ No	2 ○ No	2 ○ No
a) what method of birth control were you or your husband using **before you tried to become pregnant?**	a) what method of birth control were you or your husband using **before you tried to become pregnant?**	a) what method of birth control were you or your husband using **before you tried to become pregnant?**
b) approximately how many months or menstrual cycles (from the month or cycle when you stopped using birth control) did it take you to become pregnant? ___ months or cycles	b) approximately how many months or menstrual cycles (from the month or cycle when you stopped using birth control) did it take you to become pregnant? ___ months or cycles	b) approximately how many months or menstrual cycles (from the month or cycle when you stopped using birth control) did it take you to become pregnant? ___ months or cycles
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
What were the names of these medications?	What were the names of these medications?	What were the names of these medications?
1 ○ No	1 ○ No	1 ○ No
2 ○ Dog	2 ○ Dog	2 ○ Dog
3 ○ Cat	3 ○ Cat	3 ○ Cat
4 ○ Fish	4 ○ Fish	4 ○ Fish
5 ○ Bird	5 ○ Bird	5 ○ Bird
6 ○ Other, please specify:	6 ○ Other, please specify:	6 ○ Other, please specify:

	FIRST PREGNANCY	SECOND PREGNANCY
D18. Did you have a fever of 100°F (38°C) or higher during this pregnancy?	1 ○ Yes 2 ○ No What month of the pregnancy did you have a fever? (e.g. 2nd, 5th month)	1 ○ Yes 2 ○ No What month of the pregnancy did you have a fever? (e.g. 2nd, 5th month)
D19. Did you experience nausea or vomiting during this pregnancy?	1 ○ Frequently 2 ○ Occasionally 3 ○ No	1 ○ Frequently 2 ○ Occasionally 3 ○ No
D20. Are you **currently pregnant** ...	for the first time? 1 ○ Yes ▸ a) How many weeks pregnant are you? ____ weeks b) What is your expected date of delivery? ____ Day ____ Month Go to * below. 2 ○ No ▸ Go to ** below.	for the second time? 1 ○ Yes ▸ a) How many weeks pregnant are you? ____ weeks b) What is your expected date of delivery? ____ Day ____ Month Go to * below. 2 ○ No ▸ Go to ** below.
YOUR COMMENTS	* If you are currently pregnant with your first child, then you have finished answering the questionnaire. Thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	* If you are currently pregnant with your second child, then you have finished answering the questionnaire. Thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.
	** If you are **not currently pregnant**, please move on to: • Section E if your first pregnancy ended in a **single live birth** (PAGE 20). • Section F if your first pregnancy ended in **twins or other multiple births** (PAGE 24). • Section G if your first pregnancy ended in a **miscarriage** (PAGE 30). • Section H if your first pregnancy ended in a **stillbirth** (PAGE 32). • Section I if your first pregnancy ended in an **induced abortion** (PAGE 34). • Section J if your first pregnancy ended in an **ectopic, tubal or other pregnancy outcome** (PAGE 34).	** If you are **not currently pregnant**, please move on to: • Section E if your second pregnancy ended in a **single live birth** (PAGE 20). • Section F if your second pregnancy ended in **twins or other multiple births** (PAGE 24). • Section G if your second pregnancy ended in a **miscarriage** (PAGE 30). • Section H if your second pregnancy ended in a **stillbirth** (PAGE 32). • Section I if your second pregnancy ended in an **induced abortion** (PAGE 34). • Section J if your second pregnancy ended in an **ectopic, tubal or other pregnancy outcome** (PAGE 34).

THIRD PREGNANCY

○ Yes 2 ○ No

What month of the pregnancy did you have a fever? (e.g. 2nd, 5th month)

○ Frequently
○ Occasionally
○ No

For the third time?

○ Yes ▸ a) How many weeks pregnant are you?

weeks

b) What is your expected date of delivery?

Day Month

Go to * below.

○ No ▸ Go to ** below.

* If you are currently pregnant with your third child, then you have finished answering the questionnaire.

Thank you for participating in this very important research project.

Please return the questionnaires in the envelope provided as soon as possible.

* If you are **not currently pregnant**, please move on to:

- Section E if your third pregnancy ended in a **single live birth** (PAGE 20).
- Section F if your third pregnancy ended in **twins or other multiple births** (PAGE 24).
- Section G if your third pregnancy ended in a **miscarriage** (PAGE 30).
- Section H if your third pregnancy ended in a **stillbirth** (PAGE 32).
- Section I if your third pregnancy ended in an **induced abortion** (PAGE 34).
- Section J if your third pregnancy ended in an **ectopic, tubal or other pregnancy outcome** (PAGE 34).

FOURTH PREGNANCY

1 ○ Yes 2 ○ No

What month of the pregnancy did you have a fever? (e.g. 2nd, 5th month)

1 ○ Frequently
2 ○ Occasionally
3 ○ No

For the fourth time?

1 ○ Yes ▸ a) How many weeks pregnant are you?

weeks

b) What is your expected date of delivery?

Day Month

Go to * below.

2 ○ No ▸ Go to ** below.

* If you are currently pregnant with your fourth child, then you have finished answering the questionnaire.

Thank you for participating in this very important research project.

Please return the questionnaires in the envelope provided as soon as possible.

** If you are **not currently pregnant**, please move on to:

- Section E if your fourth pregnancy ended in a **single live birth** (PAGE 20).
- Section F if your fourth pregnancy ended in **twins or other multiple births** (PAGE 24).
- Section G if your fourth pregnancy ended in a **miscarriage** (PAGE 30).
- Section H if your fourth pregnancy ended in a **stillbirth** (PAGE 32).
- Section I if your fourth pregnancy ended in an **induced abortion** (PAGE 34).
- Section J if your fourth pregnancy ended in an **ectopic, tubal or other pregnancy outcome** (PAGE 34).

FIFTH PREGNANCY

1 ○ Yes 2 ○ No

What month of the pregnancy did you have a fever? (e.g. 2nd, 5th month)

1 ○ Frequently
2 ○ Occasionally
3 ○ No

For the fifth time?

1 ○ Yes ▸ a) How many weeks pregnant are you?

weeks

b) What is your expected date of delivery?

Day Month

Go to * below.

2 ○ No ▸ Go to ** below.

* If you are currently pregnant with your fifth child, then you have finished answering the questionnaire.

Thank you for participating in this very important research project.

Please return the questionnaires in the envelope provided as soon as possible.

** If you are **not currently pregnant**, please move on to:

- Section E if your fifth pregnancy ended in a **single live birth** (PAGE 20).
- Section F if your fifth pregnancy ended in **twins or other multiple births** (PAGE 24).
- Section G if your fifth pregnancy ended in a **miscarriage** (PAGE 30).
- Section H if your fifth pregnancy ended in a **stillbirth** (PAGE 32).
- Section I if your fifth pregnancy ended in an **induced abortion** (PAGE 34).
- Section J if your fifth pregnancy ended in an **ectopic, tubal or other pregnancy outcome** (PAGE 34).

SECTION E: TO BE COMPLETED IF YOUR . . . PREGNANCY RESULTED IN A **SINGLE LIVE BIRTH.**

	FIRST PREGNANCY	SECOND PREGNANCY
E1. When was the baby born?	Day ☐☐ Month ☐☐ 19 ☐☐ Year	Day ☐☐ Month ☐☐ 19 ☐☐ Year
E2. What is this child's first name?	☐	☐
E3. During this pregnancy, how much weight did you gain?	1 ☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.
E4. Was the baby born . . .	1 ○ on time 2 ○ earlier than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐	1 ○ on time 2 ○ earlier than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐
E5. Was the baby a . . .	1 ○ boy 2 ○ girl	1 ○ boy 2 ○ girl
E6. How much did this baby weigh at birth?	1 ☐ lbs. ☐ oz. OR 2 ☐ grams	1 ☐ lbs. ☐ oz. OR 2 ☐ grams
E7. Did this baby have any birth defects or abnormalities that were diagnosed at birth or since birth?	1 ○ Yes → Please describe these birth defects: ☐ ☐ 2 ○ No	1 ○ Yes → Please describe these birth defects: ☐ ☐ 2 ○ No
E8. Did you experience any problems during labor and delivery?	1 ○ Yes → What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐ 2 ○ No	1 ○ Yes → What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐ 2 ○ No
E9. Did you breast feed (nurse) this child?	1 ○ Yes → For how many months did you breast feed? ☐ months 2 ○ No	1 ○ Yes → For how many months did you breast feed? ☐ months 2 ○ No

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
Day ☐☐ Month ☐☐ 19☐☐ Year	Day ☐☐ Month ☐☐ 19☐☐ Year	Day ☐☐ Month ☐☐ 19☐☐ Year
☐	☐	☐
☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.
○ on time ○ earlier than expected By how many days? 1 ☐ OR how many weeks? 2 ☐ ○ later than expected By how many days? 1 ☐ OR how many weeks? 2 ☐	1 ○ on time 2 ○ earlier than expected By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected By how many days? 1 ☐ OR how many weeks? 2 ☐	1 ○ on time 2 ○ earlier than expected By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected By how many days? 1 ☐ OR how many weeks? 2 ☐
○ boy 2 ○ girl	1 ○ boy 2 ○ girl	1 ○ boy 2 ○ girl
☐ lbs. ☐ oz. OR 2 ☐ grams	1 ☐ lbs. ☐ oz. OR 2 ☐ grams	1 ☐ lbs. ☐ oz. OR 2 ☐ grams
○ Yes 2 ○ No Please describe these birth defects: ☐ ☐☐☐ ☐ ☐☐☐	1 ○ Yes 2 ○ No Please describe these birth defects: ☐ ☐☐☐ ☐ ☐☐☐	1 ○ Yes 2 ○ No Please describe these birth defects: ☐ ☐☐☐ ☐ ☐☐☐
○ Yes 2 ○ No What were these problems? ○ Caesarian section ○ Induced labor ○ Premature rupture of water membranes ○ Breech delivery ○ Labor lasting longer than 24 hours ○ Other, please specify: ☐ ☐☐☐	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐ ☐☐☐	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐ ☐☐☐
○ Yes 2 ○ No For how many months did you breast feed? ☐ months	1 ○ Yes 2 ○ No For how many months did you breast feed? ☐ months	1 ○ Yes 2 ○ No For how many months did you breast feed? ☐ months

	FIRST PREGNANCY	SECOND PREGNANCY
E10. Please look through this list of health problems. If a doctor has ever said that this child had any of these conditions, indicate which ones with a check mark. Check all that apply. If this child has never had any of the following or any other serious mental or physical health problem, please indicate this by checking "none of the above".	01 ○ persistent ear infections 02 ○ hearing problems 03 ○ diabetes 04 ○ asthma 05 ○ migraine headaches 06 ○ hay fever or other allergies 07 ○ epilepsy or seizures 08 ○ neurological disorders (other than epilepsy) 09 ○ chronic bronchitis or persistent cough 10 ○ cancer, please specify: ____ ___ 11 ○ other mental or physical health problem, please specify: ____ ___ 12 ○ none of the above	01 ○ persistent ear infections 02 ○ hearing problems 03 ○ diabetes 04 ○ asthma 05 ○ migraine headaches 06 ○ hay fever or other allergies 07 ○ epilepsy or seizures 08 ○ neurological disorders (other than epilepsy) 09 ○ chronic bronchitis or persistent cough 10 ○ cancer, please specify: ____ ___ 11 ○ other mental or physical health problem, please specify: ____ ___ 12 ○ none of the above
E11. Has this child ever been taken to a doctor or the emergency room of a hospital for an accident or injury which occurred on the farm?	1 ○ Yes 2 ○ No Please describe the injury (eg., broken arm) ____ ___ How did this injury occur? ____ ___ When did this injury occur? Day ___ Month ___ 19 Year ___	1 ○ Yes 2 ○ No Please describe the injury (eg., broken arm) ____ ___ How did this injury occur? ____ ___ When did this injury occur? Day ___ Month ___ 19 Year ___
E12. Is this child still alive?	1 ○ Yes 2 ○ No When did this child die? Day ___ Month ___ 19 Year ___ What was the cause of death? ____ ___	1 ○ Yes 2 ○ No When did this child die? Day ___ Month ___ 19 Year ___ What was the cause of death? ____ ___
COMMENTS	• If you have had more than one pregnancy, please move back to the questions about your **second** pregnancy (Page 12). • If you have only been pregnant once, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than two pregnancies, please move back to the questions about your **third** pregnancy (Page 12). • If you have only been pregnant twice, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
01 ○ persistent ear infections	01 ○ persistent ear infections	01 ○ persistent ear infections
02 ○ hearing problems	02 ○ hearing problems	02 ○ hearing problems
03 ○ diabetes	03 ○ diabetes	03 ○ diabetes
04 ○ asthma	04 ○ asthma	04 ○ asthma
05 ○ migraine headaches	05 ○ migraine headaches	05 ○ migraine headaches
06 ○ hay fever or other allergies	06 ○ hay fever or other allergies	06 ○ hay fever or other allergies
07 ○ epilepsy or seizures	07 ○ epilepsy or seizures	07 ○ epilepsy or seizures
08 ○ neurological disorders (other than epilepsy)	08 ○ neurological disorders (other than epilepsy)	08 ○ neurological disorders (other than epilepsy)
09 ○ chronic bronchitis or persistent cough	09 ○ chronic bronchitis or persistent cough	09 ○ chronic bronchitis or persistent cough
10 ○ cancer, please specify:	10 ○ cancer, please specify:	10 ○ cancer, please specify:
11 ○ other mental or physical health problem, please specify:	11 ○ other mental or physical health problem, please specify:	11 ○ other mental or physical health problem, please specify:
12 ○ none of the above	12 ○ none of the above	12 ○ none of the above
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
Please describe the injury (eg., broken arm)	Please describe the injury (eg., broken arm)	Please describe the injury (eg., broken arm)
How did this injury occur?	How did this injury occur?	How did this injury occur?
When did this injury occur? Day Month 19 Year	When did this injury occur? Day Month 19 Year	When did this injury occur? Day Month 19 Year
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
When did this child die? Day Month 19 Year	When did this child die? Day Month 19 Year	When did this child die? Day Month 19 Year
What was the cause of death?	What was the cause of death?	What was the cause of death?
• If you have had more than three pregnancies, please move back to the questions about your **fourth** pregnancy (Page 12). • If you have only been pregnant three times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than four pregnancies, please move back to the questions about your **fifth** pregnancy (Page 12). • If you have only been pregnant four times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than five pregnancies, please specify it in the comments area on the last page. • If you have only been pregnant five times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

SECTION F: TO BE COMPLETED IF YOUR . . . PREGNANCY RESULTED IN **TWINS OR OTHER MULTIPLE BIRTHS.**

	FIRST PREGNANCY	SECOND PREGNANCY
F1. How many babies did you deliver?	☐☐ babies	☐☐ babies
F2. When were the babies born?	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
F3. During this pregnancy, how much weight did you gain?	1 ☐☐☐ lbs. OR 2 ☐☐☐ kg.	1 ☐☐☐ lbs. OR 2 ☐☐☐ kg.
F4. Were the babies born . . .	1 ○ on time 2 ○ earlier than expected → By how many days? 1 ☐☐ OR how many weeks? 2 ☐☐ 3 ○ later than expected → By how many days? 1 ☐☐ OR how many weeks? 2 ☐☐	1 ○ on time 2 ○ earlier than expected → By how many days? 1 ☐☐ OR how many weeks? 2 ☐☐ 3 ○ later than expected → By how many days? 1 ☐☐ OR how many weeks? 2 ☐☐
F5. Did you experience any problems during labor and delivery?	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐☐☐	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐☐☐
F6. Did you breast feed (nurse) these children?	1 ○ Yes 2 ○ No For how many months did you breast feed? ☐☐ months	1 ○ Yes 2 ○ No For how many months did you breast feed? ☐☐ months
F7. What did you name the babies? List them in order of their birth. In subsequent questions identify each baby using this number.	Baby # First Name 1 ☐☐☐ 2 ☐☐☐ 3 ☐☐☐	Baby # First Name 1 ☐☐☐ 2 ☐☐☐ 3 ☐☐☐
F8. For each of the babies, please indicate whether they were stillborn, and their sex.	Baby # Stillborn? Sex 1 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 2 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 3 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female	Baby # Stillborn? Sex 1 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 2 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 3 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
☐ babies	☐ babies	☐ babies
Day ☐☐ Month ☐☐ 19☐☐ Year	Day ☐☐ Month ☐☐ 19☐☐ Year	Day ☐☐ Month ☐☐ 19☐☐ Year
1 ☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.
1 ○ on time 2 ○ earlier than expected By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected By how many days? 1 ☐ OR how many weeks? 2 ☐	1 ○ on time 2 ○ earlier than expected By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected By how many days? 1 ☐ OR how many weeks? 2 ☐	1 ○ on time 2 ○ earlier than expected By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected By how many days? 1 ☐ OR how many weeks? 2 ☐
1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐
1 ○ Yes 2 ○ No For how many months did you breast feed? ☐ months	1 ○ Yes 2 ○ No For how many months did you breast feed? ☐ months	1 ○ Yes 2 ○ No For how many months did you breast feed? ☐ months
Baby # First Name 1 ☐ 2 ☐ 3 ☐	Baby # First Name 1 ☐ 2 ☐ 3 ☐	Baby # First Name 1 ☐ 2 ☐ 3 ☐
Baby # Stillborn? Sex 1 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 2 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 3 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female	Baby # Stillborn? Sex 1 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 2 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 3 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female	Baby # Stillborn? Sex 1 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 2 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female 3 1 ○ Yes 2 ○ No 1 ○ Male 2 ○ Female

	FIRST PREGNANCY	SECOND PREGNANCY
F9. What was the birth weight of each baby?	Baby # Birthweight 1 1 [ ][ ] lbs. [ ][ ] oz. OR 2 [ ][ ][ ][ ] grams 2 1 [ ][ ] lbs. [ ][ ] oz. OR 2 [ ][ ][ ][ ] grams 3 1 [ ][ ] lbs. [ ][ ] oz. OR 2 [ ][ ][ ][ ] grams	Baby # Birthweight 1 1 [ ][ ] lbs. [ ][ ] oz. OR 2 [ ][ ][ ][ ] grams 2 1 [ ][ ] lbs. [ ][ ] oz. OR 2 [ ][ ][ ][ ] grams 3 1 [ ][ ] lbs. [ ][ ] oz. OR 2 [ ][ ][ ][ ] grams
F10. Did any of these babies have any birth defects that were diagnosed at birth or since birth?	1 ○ Yes 2 ○ No For each baby (#1, 2 or 3) please describe these birth defects: 1 [ ] [ ][ ][ ] 2 [ ] [ ][ ][ ] 3 [ ] [ ][ ][ ]	1 ○ Yes 2 ○ No For each baby (#1, 2 or 3) please describe these birth defects: 1 [ ] [ ][ ][ ] 2 [ ] [ ][ ][ ] 3 [ ] [ ][ ][ ]
F11. Please look through this list of health problems. If a doctor has ever said that these children had any of these conditions, indicate which ones with a check mark and circle the child number (#) which had this condition. Check all that apply. If these children have never had any of the following or any other serious mental or physical health problem, please indicate this by checking "none of the above".	Child # 01 ○ persistent ear infections 1 2 3 02 ○ hearing problems 1 2 3 03 ○ diabetes 1 2 3 04 ○ asthma 1 2 3 05 ○ migraine headaches 1 2 3 06 ○ hay fever or other allergies 1 2 3 07 ○ epilepsy or seizures 1 2 3 08 ○ neurological disorders (other than epilepsy) 1 2 3 09 ○ chronic bronchitis or persistent cough 1 2 3 10 ○ cancer, please specify: 1 2 3 [ ] [ ][ ][ ] 11 ○ other mental or physical health problem, please specify: 1 2 3 [ ] [ ][ ][ ] 12 ○ none of the above 1 2 3	Child # 01 ○ persistent ear infections 1 2 3 02 ○ hearing problems 1 2 3 03 ○ diabetes 1 2 3 04 ○ asthma 1 2 3 05 ○ migraine headaches 1 2 3 06 ○ hay fever or other allergies 1 2 3 07 ○ epilepsy or seizures 1 2 3 08 ○ neurological disorders (other than epilepsy) 1 2 3 09 ○ chronic bronchitis or persistent cough 1 2 3 10 ○ cancer, please specify: 1 2 3 [ ] [ ][ ][ ] 11 ○ other mental or physical health problem, please specify: 1 2 3 [ ] [ ][ ][ ] 12 ○ none of the above 1 2 3

THIRD PREGNANCY

Baby # Birthweight

1 [1] lbs. [ ] oz. OR [2] grams

2 [1] lbs. [ ] oz. OR [2] grams

3 [1] lbs. [ ] oz. OR [2] grams

[1] ○ Yes [2] ○ No

For each baby (#1, 2 or 3) please describe these birth defects:

1 [ ]

2 [ ]

3 [ ]

	Child #
01 ○ persistent ear infections	1 2 3
02 ○ hearing problems	1 2 3
03 ○ diabetes	1 2 3
04 ○ asthma	1 2 3
05 ○ migraine headaches	1 2 3
06 ○ hay fever or other allergies	1 2 3
07 ○ epilepsy or seizures	1 2 3
08 ○ neurological disorders (other than epilepsy)	1 2 3
09 ○ chronic bronchitis or persistent cough	1 2 3
10 ○ cancer, please specify: [ ]	1 2 3
11 ○ other mental or physical health problem, please specify: [ ]	1 2 3
12 ○ none of the above	1 2 3

FOURTH PREGNANCY

Baby # Birthweight

1 [1] lbs. [ ] oz. OR [2] grams

2 [1] lbs. [ ] oz. OR [2] grams

3 [1] lbs. [ ] oz. OR [2] grams

[1] ○ Yes [2] ○ No

For each baby (#1, 2 or 3) please describe these birth defects:

1 [ ]

2 [ ]

3 [ ]

	Child #
01 ○ persistent ear infections	1 2 3
02 ○ hearing problems	1 2 3
03 ○ diabetes	1 2 3
04 ○ asthma	1 2 3
05 ○ migraine headaches	1 2 3
06 ○ hay fever or other allergies	1 2 3
07 ○ epilepsy or seizures	1 2 3
08 ○ neurological disorders (other than epilepsy)	1 2 3
09 ○ chronic bronchitis or persistent cough	1 2 3
10 ○ cancer, please specify: [ ]	1 2 3
11 ○ other mental or physical health problem, please specify: [ ]	1 2 3
12 ○ none of the above	1 2 3

FIFTH PREGNANCY

Baby # Birthweight

1 [1] lbs. [ ] oz. OR [2] grams

2 [1] lbs. [ ] oz. OR [2] grams

3 [1] lbs. [ ] oz. OR [2] grams

[1] ○ Yes [2] ○ No

For each baby (#1, 2 or 3) please describe these birth defects:

1 [ ]

2 [ ]

3 [ ]

	Child #
01 ○ persistent ear infections	1 2 3
02 ○ hearing problems	1 2 3
03 ○ diabetes	1 2 3
04 ○ asthma	1 2 3
05 ○ migraine headaches	1 2 3
06 ○ hay fever or other allergies	1 2 3
07 ○ epilepsy or seizures	1 2 3
08 ○ neurological disorders (other than epilepsy)	1 2 3
09 ○ chronic bronchitis or persistent cough	1 2 3
10 ○ cancer, please specify: [ ]	1 2 3
11 ○ other mental or physical health problem, please specify: [ ]	1 2 3
12 ○ none of the above	1 2 3

	FIRST PREGNANCY	SECOND PREGNANCY
F12. Have any of these children ever been taken to a doctor or the emergency room of a hospital for an accident or injury which occurred on the farm?	1 ○ Yes 2 ○ No **Who was injured (first name)?** Please describe the injury (eg., broken arm) How did this injury occur? When did this injury occur? Day Month 19 Year **Who was injured (first name)?** Please describe the injury (eg., broken arm) How did this injury occur? When did this injury occur? Day Month 19 Year	1 ○ Yes 2 ○ No **Who was injured (first name)?** Please describe the injury (eg., broken arm) How did this injury occur? When did this injury occur? Day Month 19 Year **Who was injured (first name)?** Please describe the injury (eg., broken arm) How did this injury occur? When did this injury occur? Day Month 19 Year
F13. Are all of these children still alive?	1 ○ Yes 2 ○ No How many of these children have died? **First Name** Date of death Day Month 19 Year What was the cause of death? **First Name** Date of death Day Month 19 Year What was the cause of death?	1 ○ Yes 2 ○ No How many of these children have died? **First Name** Date of death Day Month 19 Year What was the cause of death? **First Name** Date of death Day Month 19 Year What was the cause of death?
YOUR COMMENTS	• If you have had more than one pregnancy, please move back to the questions about your **second** pregnancy (Page 12). • If you have only been pregnant once, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than two pregnancies, please move back to the questions about your **third** pregnancy (Page 12). • If you have only been pregnant twice, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

THIRD PREGNANCY

1 ○ Yes 2 ○ No

Who was injured (first name)?

Please describe the injury (eg., broken arm)

How did this injury occur?

When did this injury occur?
Day Month 19 Year

Who was injured (first name)?

Please describe the injury (eg., broken arm)

How did this injury occur?

When did this injury occur?
Day Month 19 Year

○ Yes 2 ○ No

How many of these children have died?

First Name

Date of death
Day Month 19 Year

What was the cause of death?

First Name

Date of death
Day Month 19 Year

What was the cause of death?

If you have had more than three pregnancies, please move back to the questions about your **fourth** pregnancy (Page 12).

If you have only been pregnant three times, we would like to thank you for participating in this very important research project.

Please return the questionnaires in the envelope provided as soon as possible.

FOURTH PREGNANCY

1 ○ Yes 2 ○ No

Who was injured (first name)?

Please describe the injury (eg., broken arm)

How did this injury occur?

When did this injury occur?
Day Month 19 Year

Who was injured (first name)?

Please describe the injury (eg., broken arm)

How did this injury occur?

When did this injury occur?
Day Month 19 Year

1 ○ Yes 2 ○ No

How many of these children have died?

First Name

Date of death
Day Month 19 Year

What was the cause of death?

First Name

Date of death
Day Month 19 Year

What was the cause of death?

- If you have had more than four pregnancies, please move back to the questions about your **fifth** pregnancy (Page 12).
- If you have only been pregnant four times, we would like to thank you for participating in this very important research project.

Please return the questionnaires in the envelope provided as soon as possible.

FIFTH PREGNANCY

1 ○ Yes 2 ○ No

Who was injured (first name)?

Please describe the injury (eg., broken arm)

How did this injury occur?

When did this injury occur?
Day Month 19 Year

Who was injured (first name)?

Please describe the injury (eg., broken arm)

How did this injury occur?

When did this injury occur?
Day Month 19 Year

1 ○ Yes 2 ○ No

How many of these children have died?

First Name

Date of death
Day Month 19 Year

What was the cause of death?

First Name

Date of death
Day Month 19 Year

What was the cause of death?

- If you have had more than five pregnancies, please specify it in the comments area on the last page.
- If you have only been pregnant three times, we would like to thank you for participating in this very important research project.

Please return the questionnaires in the envelope provided as soon as possible.

SECTION G: TO BE COMPLETED IF YOUR . . . PREGNANCY RESULTED IN A **MISCARRIAGE.**

	FIRST PREGNANCY	SECOND PREGNANCY
G1. How many weeks pregnant were you when you miscarried?	☐☐ weeks	☐☐ weeks
G2. Had you seen a doctor about this pregnancy before you miscarried?	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
G3. Did you go to a hospital or doctor during or after your miscarriage for medical attention?	1 ○ Yes 2 ○ No Which of the following did your doctor say may have caused the miscarriage: 1 ○ anomalies of the uterus 2 ○ infections of the uterine lining 3 ○ cervical incompetence 4 ○ hormonal dysfunction or imbalance 5 ○ chromosomal abnormalities 6 ○ other causes, please specify what they were: ☐☐☐ 7 ○ the doctor did not know why you miscarried	1 ○ Yes 2 ○ No Which of the following did your doctor say may have caused the miscarriage: 1 ○ anomalies of the uterus 2 ○ infections of the uterine lining 3 ○ cervical incompetence 4 ○ hormonal dysfunction or imbalance 5 ○ chromosomal abnormalities 6 ○ other causes, please specify what they were: ☐☐☐ 7 ○ the doctor did not know why you miscarried
G4. What was the date of your miscarriage?	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
G5. During this pregnancy, how much weight did you gain?	1 ☐☐ lbs. OR 2 ☐☐ kg.	1 ☐☐ lbs. OR 2 ☐☐ kg.
YOUR COMMENTS	• If you have had more than one pregnancy, please move back to the questions about your **second** pregnancy (Page 12). • If you have only been pregnant once, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than two pregnancies, please move back to the questions about your **third** pregnancy (Page 12). • If you have only been pregnant twice, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
☐ weeks	☐ weeks	☐ weeks
○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
○ Yes 2 ○ No ↓ hich of the following did your doctor ıy may have caused the miscarriage: ○ anomalies of the uterus ○ infections of the uterine lining ○ cervical incompetence ○ hormonal dysfunction or imbalance ○ chromosomal abnormalities ○ other causes, please specify what they were: ☐☐☐ ○ the doctor did not know why you miscarried	1 ○ Yes 2 ○ No ↓ Which of the following did your doctor say may have caused the miscarriage: 1 ○ anomalies of the uterus 2 ○ infections of the uterine lining 3 ○ cervical incompetence 4 ○ hormonal dysfunction or imbalance 5 ○ chromosomal abnormalities 6 ○ other causes, please specify what they were: ☐☐☐ 7 ○ the doctor did not know why you miscarried	1 ○ Yes 2 ○ No ↓ Which of the following did your doctor say may have caused the miscarriage: 1 ○ anomalies of the uterus 2 ○ infections of the uterine lining 3 ○ cervical incompetence 4 ○ hormonal dysfunction or imbalance 5 ○ chromosomal abnormalities 6 ○ other causes, please specify what they were: ☐☐☐ 7 ○ the doctor did not know why you miscarried
☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.
• If you have had more than three pregnancies, please move back to the questions about your **fourth** pregnancy (Page 12). • If you have only been pregnant three times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than four pregnancies, please move back to the questions about your **fifth** pregnancy (Page 12). • If you have only been pregnant four times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than five pregnancies, please specify it in the comments area on the last page. • If you have only been pregnant four times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

SECTION H: TO BE COMPLETED IF YOUR . . . PREGNANCY RESULTED IN A **STILLBIRTH.**

	FIRST PREGNANCY	SECOND PREGNANCY
H1. When was the baby born?	Day ☐☐ Month ☐☐ 19 ☐☐ Year	Day ☐☐ Month ☐☐ 19 ☐☐ Year
H2. During this pregnancy, how much weight did you gain?	1 ☐ lbs. OR 2 ☐ kg.	1 ☐ lbs. OR 2 ☐ kg.
H3. Was the baby born . . .	1 ○ on time 2 ○ earlier than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐	1 ○ on time 2 ○ earlier than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐ 3 ○ later than expected → By how many days? 1 ☐ OR how many weeks? 2 ☐
H4. Was the baby a . . .	1 ○ boy 2 ○ girl	1 ○ boy 2 ○ girl
H5. How much did this baby weigh at birth?	1 ☐ lbs. ☐ oz. OR 2 ☐ grams	1 ☐ lbs. ☐ oz. OR 2 ☐ grams
H6. Did this baby have any birth defects or abnormalities that were diagnosed at birth?	1 ○ Yes 2 ○ No Please describe these birth defects: ☐☐☐ ☐☐☐	1 ○ Yes 2 ○ No Please describe these birth defects: ☐☐☐ ☐☐☐
H7. Did you experience any problems during labor and delivery?	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐☐☐	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify: ☐☐☐
H8. Did your doctor tell you what may have caused this baby to be stillborn?	1 ○ Yes 2 ○ No What did your doctor say was the cause? ☐☐☐	1 ○ Yes 2 ○ No What did your doctor say was the cause? ☐☐☐
YOUR COMMENTS	• If you have had more than one pregnancy, please move back to the questions about your **second** pregnancy (Page 12). • If you have only been pregnant once, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than two pregnancies, please move back to the questions about your **third** pregnancy (Page 12). • If you have only been pregnant twice, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
Day Month 19 Year	Day Month 19 Year	Day Month 19 Year
1 lbs. OR 2 kg.	1 lbs. OR 2 kg.	1 lbs. OR 2 kg.
1 ○ on time 2 ○ earlier than expected By how many days? 1 OR how many weeks? 2 3 ○ later than expected By how many days? 1 OR how many weeks? 2	1 ○ on time 2 ○ earlier than expected By how many days? 1 OR how many weeks? 2 3 ○ later than expected By how many days? 1 OR how many weeks? 2	1 ○ on time 2 ○ earlier than expected By how many days? 1 OR how many weeks? 2 3 ○ later than expected By how many days? 1 OR how many weeks? 2
1 ○ boy 2 ○ girl	1 ○ boy 2 ○ girl	1 ○ boy 2 ○ girl
1 lbs. oz. OR 2 grams	1 lbs. oz. OR 2 grams	1 lbs. oz. OR 2 grams
1 ○ Yes 2 ○ No Please describe these birth defects:	1 ○ Yes 2 ○ No Please describe these birth defects:	1 ○ Yes 2 ○ No Please describe these birth defects:
1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify:	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify:	1 ○ Yes 2 ○ No What were these problems? 1 ○ Caesarian section 2 ○ Induced labor 3 ○ Premature rupture of water membranes 4 ○ Breech delivery 5 ○ Labor lasting longer than 24 hours 6 ○ Other, please specify:
1 ○ Yes 2 ○ No What did your doctor say was the cause?	1 ○ Yes 2 ○ No What did your doctor say was the cause?	1 ○ Yes 2 ○ No What did your doctor say was the cause?
• If you have had more than three pregnancies, please move back to the questions about your **fourth** pregnancy (Page 12). • If you have only been pregnant three times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than four pregnancies, please move back to the questions about your **fifth** pregnancy (Page 12). • If you have only been pregnant four times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than five pregnancies, please specify it in the comments area on the last page. • If you have only been pregnant five times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

SECTION I: TO BE COMPLETED IF YOUR . . . PREGNANCY RESULTED IN AN **INDUCED ABORTION.**

	FIRST PREGNANCY	SECOND PREGNANCY
I1. How many weeks pregnant were you when you had the abortion?	☐☐ weeks	☐☐ weeks
I2. What was the date of your abortion?	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
I3. Was this pregnancy aborted because the baby had either birth defects, chromosomal damage or some genetic problems?	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
YOUR COMMENTS	• If you have had more than one pregnancy, please move back to the questions about your **second** pregnancy (Page 12). • If you have only been pregnant once, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than two pregnancies, please move back to the questions about your **third** pregnancy (Page 12). • If you have only been pregnant twice, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

SECTION J: TO BE COMPLETED IF YOUR . . . PREGNANCY RESULTED IN AN **ECTOPIC, TUBAL OR OTHER PREGNANCY OUTCOME.**

	FIRST PREGNANCY	SECOND PREGNANCY
J1. What was the outcome of this pregnancy? For example, tubal pregnancy, hydatidiform mole, etc.	☐ ☐☐☐	☐ ☐☐☐
J2. How many weeks pregnant were you when this pregnancy ended?	☐☐ weeks	☐☐ weeks
J3. What was the date when this pregnancy ended?	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
YOUR COMMENTS	• If you have had more than one pregnancy, please move back to the questions about your **second** pregnancy (Page 12). • If you have only been pregnant once, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than two pregnancies, please move back to the questions about your **third** pregnancy (Page 12). • If you have only been pregnant twice, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
☐☐ weeks	☐☐ weeks	☐☐ weeks
☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No	1 ○ Yes 2 ○ No
• If you have had more than three pregnancies, please move back to the questions about your **fourth** pregnancy (Page 12). • If you have only been pregnant three times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than four pregnancies, please move back to the questions about your **fifth** pregnancy (Page 12). • If you have only been pregnant four times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than five pregnancies, please specify it in the comments area on the last page. • If you have only been pregnant five times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.

THIRD PREGNANCY	FOURTH PREGNANCY	FIFTH PREGNANCY
☐ ☐☐☐	☐ ☐☐☐	☐ ☐☐☐
☐☐ weeks	☐☐ weeks	☐☐ weeks
☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year	☐☐ Day ☐☐ Month 19☐☐ Year
• If you have had more than three pregnancies, please move back to the questions about your **fourth** pregnancy (Page 12). • If you have only been pregnant three times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than four pregnancies, please move back to the questions about your **fifth** pregnancy (Page 12). • If you have only been pregnant four times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.	• If you have had more than five pregnancies, please specify it in the comments area on the last page. • If you have only been pregnant five times, we would like to thank you for participating in this very important research project. Please return the questionnaires in the envelope provided as soon as possible.