Neuropsychological functioning and pesticide exposure in children aged 6-11

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Abstract

Pesticide exposure has been linked with numerous health concerns in both adults and children, including problems with cognition and behaviour. Research in this area is complicated by different pesticide exposure profiles across different countries, and results may not generalise to a New Zealand context. The current study aimed to investigate the effects of pesticide exposure in New Zealand children. It extended previous research by studying more cognitive domains, thus providing a more thorough understanding of effects on cognitive functioning. Four hundred and forty three children from the Wellington and Hawkes Bay regions were assessed using subtests from the NEPSY-II, WISC-IV and TEA-Ch. Pesticide exposure was measured using questionnaire and dust sample data which served as proxies for both pre- and post-natal exposure.

Prenatal exposure was found to be significantly associated with lower memory scores, while postnatal exposure was associated with lower scores in working memory, facial memory and executive functioning. No effects were found for attention, motor speed, processing speed, verbal memory, and social perception. These results suggest the presence of effects of pesticide exposure on some aspects of child neuropsychological development in New Zealand. While the results are based on initial analyses, and are thus preliminary, the thesis will contribute to a larger project looking at pesticides and public health, and provide important information for regulators around public safety in the future.

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Finally, I want to thank Caroline Louden for giving me the courage to take the first step.

Wer ein Warum hat, kann Wie ertragen

(He who has a "why" can bear any "how")

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Chapter 1: Overview

The current doctoral thesis stemmed from a large collaborative research study assessing the effects of pesticide exposure on cognitive development in children aged six to eleven years involving the School of Psychology and the Centre for Public Health (CPHR), both at Massey University. The current doctoral research study was nested within this larger study that was funded by the Health Research Council (HRC). It is hoped that the current thesis will contribute to the overall knowledge-base on the health effects of pesticide exposure in relation to children's neuropsychological functioning. The larger study is composed of three separate phases (Figure 1) which are further explained below.

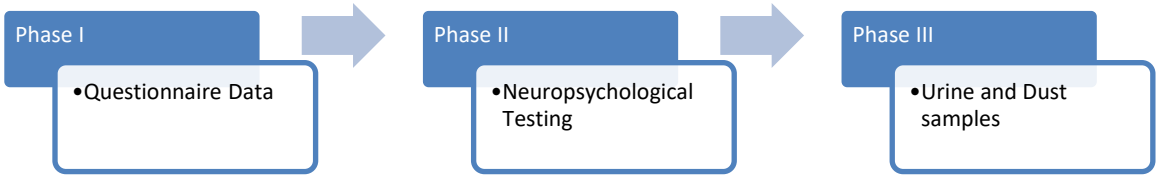

Figure 1. Outline of the larger HRC funded study.

Phase I

In Phase I of the larger study, questionnaire data was collected from about 900 children from three populations based on their likely exposure to pesticides (urban, rural and agricultural). The urban group was primarily recruited from the Wellington Region, and initially both the rural and farming populations were recruited from the Hawkes Bay region (an area which was selected due to it's large concentration of farms and orchards). However, difficulties in recruitment necessitated extension to other rural/farming areas within New Zealand including the Nelson Bays and

Horowhenua regions, which have comparable levels of farms and orchards to the Hawkes Bay Region. All participants were recruited through schools[1]

Involvement in Phase 1 consisted of parental completion of a 24-page questionnaire (Appendix A). The questionnaire data collected information on lifestyle factors, home pesticide use, parental occupation, and proximity to high pesticide use areas. Demographics such as parental income were also collected through this questionnaire. Alongside this questionnaire, two behavioural measures were also used; the Behaviour Assessment for Children 2nd Edition (BASC) and the Behaviour Rating Inventory of Executive Functioning (BRIEF). The BASC uses both parent and teacher rating scales to assess the behaviour and emotions of children (PsychCorp, 2016). Both the parent and teacher forms were used. The BRIEF assesses difficulties in executive functioning through a parent report form (PAR.iConnect, 2016). Data from these questionnaires were not used in the current thesis but will be included when the larger study is written up.

Phase II

Phase II of the larger study involved the neuropsychological assessment of participating children to gather data on their current cognitive functioning. This is the phase that the current author was primarily involved with. In total, the larger study aimed to gather data on 450 children evenly spread across the three groups: urban, rural and farming. Assessments were conducted by five different assessors, discussed below, who were qualified[2] in the use of the neuropsychological measures.

Participants for this second phase were selected from those involved in Phase I, and assessments were conducted at their schools or homes. It was originally planned to randomly select participants for Phase II, however—due to both time and recruitment constraints—this was not possible. Within the first year of the study it became clear that recruitment numbers from each school were very low. Due to time and funding constraints it was also not possible to continue to try and

[1] Recruitment is further discussed in Chatper 7

[2] All assessors had a minimum of five years of university education and had completed two postgraduate psychology papers that covered neuropsychological assessment: 175.722 Principles of Clinical Neuropsychology; 175782 Clinical Asssessment.

boost recruitment numbers. This necessitated the use of all participants who had consented to participate from both the Hawkes Bay and Nelson Bays regions. To ensure that the sample was representative (and control for response bias) a refusal questionnaire was administered to participants who had withdrawn from the study or indicated that they did not want to take part. This questionnaire was designed to be a quick screen of common behavioural problems in children and was based on the BASC and BRIEF forms (a copy of this questionnaire can be found in Appendix B). Data from the refusal questionnaire was not used in the current thesis. The methodology and measures used in Phase II of the wider study will be further discussed in the Chapter 7 of this thesis.

Phase III

The final phase of the study involved the collection of urine and dust samples from a selection of participants from Phase II. In conjunction with questionnaire data in the wider study, urine and dust samples were used to assess the levels of pesticide exposure in the study population and collected for a random selection of participants who had undergone neuropsychological testing. Both urine and dust samples were analysed by the University of Queensland National Research Centre for Environmental Toxicology. The urine analysis involved measuring up to seven organophosphate metabolites, two carbamate metabolites and five pyrethroid metabolites which cover the most commonly used pesticides in New Zealand. Data from this phase will be used by the larger study to classify pesticide exposure. The dust sample results, involving the measurement of chlorpyrifos, deltamethrin, cyfluthrin, permethrin and cypermethrin, were used as a measurement of current pesticide exposure.

The overall study was overseen by the principal investigators, Professor Jeroen Douwes from the CPHR and Professor Janet Leathem from the School of Psychology. Within the larger study there was also an overall study coordinator and four assessors who were involved with the collection of the neuropsychological data. The CPHR additionally utilised several research assistants to assist with the distribution of questionnaires, follow up phone calls, and data entry. The study coordinator undertook recruitment for the first phase and management of the collection of all the urine and dust samples from the third phase. This role also involved organising the logistics around research trips, following

up missed questionnaires and missing data, organising recruitment activities and entering data. Four assessors (all doctoral students enrolled in the Doctorate of Clinical Psychology at Massey University in Wellington) were involved with all aspects of the second phase of the study. Two were [3&4] using parts of the data for their own doctoral research. Responsibilities of the assessors were primarily the assessment of neuropsychological functioning in children but also extended to assistance with recruitment, liaising with schools to organise data collection, collection of teacher questionnaires, and national standards data. The current author was also involved with providing assistance in analysing and interpreting the data. A further breakdown of the tasks involved in the overall project and the current author's involvement is provided in Chapter seven, which discusses the method used in the current thesis.

Organisation of the Thesis

This thesis is divided into nine chapters. Chapter two discusses pesticide use across the world with a focus on reviewing differences across countries. The third chapter broadly reviews the cognitive development of children, with a focus on children aged six to eleven years. Chapter four reviews studies on the effects of pesticide exposure on cognitive development in children and discusses the gaps as they currently exist within the literature. Chapter five discusses why exposure to pesticides is particularly harmful in children. The sixth chapter outlines the aims and hypotheses of this thesis, while the seventh chapter outlines the methodology and measures used. Chapter eight presents the results of the current study and the ninth and final chapter discuss these findings and their contributions to the literature. As this thesis was conducted in conjunction with the author's training in psychology, a supplemental chapter discussing challenges and reflections is also included in Appendix C.

[3] Kate Ross McAlpine's research focused on investigating the applicability of international norms in a New Zealand context, and the relationship between school achievement and scores on the neuropsychological testing.
[4] Kathryn McLennan's research examined the performance of various measures and measurement issues with a focus on executive functioning (such as the relationship between subjective and objective assessment tools) when applied within a NZ context.

Chapter 2: Pesticide usage – then and now

Pesticides are a broad range of substances used to control unwanted pests and insects, and are used widely in the agricultural industry. This chapter will review the use of pesticides worldwide, looking at historic and current use alongside factors influencing differences in usage across countries.

Historic Pesticide use

Historically, pesticide use has moved from sparing use of naturally occurring substances and methods in the early days of farming (Costa, 2008) to being a crucial component in modern agriculture today. A guide to pesticides written by the British Medical Association (1992), states that as far back as 1000 BC the ancient Greek poet Homer wrote about sulphur fumigants. In 470 BC the ancient Greek philosopher Democritus wrote about controlling blight through the use of olive extract and in 200 BC documents detail the use of sulphur fumes to destroy plant blight. The ancient Romans also reportedly used the plant Hellebore as a pesticide, while the ancient Chinese used ants to control insects on their crops before moving to more chemical methods over time such as arsenic, sulphur, and lime (British Medical Association, 1992; Zhang, Jiang, & Ou, 2011). However pesticide use did not become widespread on a larger scale until the 1700s, a time characterised by the advent of capitalist type farming, a move away from traditional subsistence farming and the agricultural revolution (Overton, 1996). Pesticide use during this time was experimental, and although chemical methods such as arsenic and sulphur were employed, they were still naturally occurring substances (British Medical Association, 1992). The chemicals historically used (such as arsenic) are highly toxic to both humans and animals (Metcalf & Horowitz, 2000a) making their use dangerous. It was not until the 1900s that the advent of safer synthetic pesticides became available and popular (Levine, 2007), a move influenced by the rapid scientific advances caused by the First and Second World Wars. Four main types of pesticides arose as a result of these advances and will be discussed in turn; organochlorines, organophosphates, carbamates, and pyrethroids. A fifth major type of pesticides, neonicotinoids, arose within the last thirty years and will also be discussed.

Organochlorines

The insecticidal properties of the well-known organochloric pesticide[5] dichlorodiphenyltrichloroethane (DDT), were discovered by a Swiss chemist, Paul Mueller, in 1939 and later commercialised in 1944 (Costa, 2008). The popularity of DDT was sparked by its effectiveness in combating malaria and other insect borne illnesses during World War Two (Metcalf & Horowitz, 2000a). After the end of the war DDT quickly became the most frequently used insecticide around the world in both agriculture and widespread insect eradication programmes, such as those to eliminate fire ants and gypsy moths in the United States (British Medical Association, 1992). While the use of DDT and other organochlorines was widespread, there was little research conducted into their harmful properties in both people and the environment. As organochlorines are long lived pesticides resistant to degradation, human contamination through water and soil is common (Kaminski, Faubert Kaplan, & Holsapple, 2008). They are also detrimental to ecosystems through bio-accumulation in aquatic and bird life, making them very harmful to the environment (British Medical Association, 1992). Rachel Carson's book the 'Silent Spring' published in 1962 increased public awareness and concern around the harmful effects of widespread DDT spraying which led to the beginning of restrictions on DDT usage. The popularity of DDT began to wane in the 1970s and by 1991 bans on its use were in place in most developed countries (Joint FAO/UNEP Programme, 1991).

In New Zealand the use of DDT was banned in 1989 and since then studies have found acceptably low levels of DDT residue in the population (Buckland, Bates, Garrett, Ellis, & van Maaren, 2001) and environment (Ministry for the Environment, 1999) when compared with other countries. In 2001 a convention was held in Stockholm, Sweden, to address and limit the global environmental impact of persistent organic pollutants and currently there are 152 total signatories, including New Zealand (Stockholm Convention, 2008). This convention included the use of DDT which was severely restricted to use in extreme cases of disease control such as malaria (Stockholm

[5] Organochloric pesticides work through opening the sodium ion channels in neurons which leads to spasms and death in the organism (Costa, 2008)

Convention, 2009) effectively ending the use of DDT in the developed world. However, DDT, along with other organochlorines, continues to be used in some developing countries.

Organophosphates

The decreased popularity of DDT in the 1970s opened a gap for new pesticides to come onto the market, which was filled by organophosphates[6], carbamates[7] and pyrethroids[8]. Organophosphates were created by the German scientist Gerhard Schrader, who accidentally created Tabun whilst working to create effective organophosphate-based pesticides as an organophosphate nerve agent in 1936 (Ruthenberg, 2007). Under the Nazi regime he continued his work and discovered three other types of organophosphate nerve agents Sarin (1938), Soman (1944), and Cyclosarin (1949) (Ruthenberg, 2007). These chemical nerve agents work in a similar fashion to regular organophosphate pesticides, by targeting acetylcholinesterase. After World War 2, Schrader's discoveries were used to begin the creation of organophosphate pesticides leading to the creation of the first safe [9] organophosphate, malathion, in 1950 (Chambers, Meek, & Chambers, 2010). Initially organophosphates, in particular chlorpyrifos, were popular for both agricultural and home use. However due to concerns around children's exposure through diet and contact with contaminated surfaces, over recent years regulations generally restrict use to agricultural settings only (Testai, Buratti, & Di Consiglio, 2010).

Unlike organochlorines, current organophosphates present reduced danger to ecosystems and their use over organochlorines has had positive environmental impacts (Metcalf & Horowitz, 2000b). It is estimated that today organophosphates make up an estimated half of all insecticides used (Costa, 2008). However their use is decreasing worldwide due to health concerns, a trend mirrored in New Zealand with tighter controls and restrictions on organophosphate use being legislated for in June

[6] Organophosphates work through irreversibly preventing the deactivation of the neurotransmitter acetylcholine, which is integral to nervous system functioning and leads to eventual paralysis and death in the organism (Costa, 2008; Lotti, 2010).
[7] Similarly to organophosphates, carbamates work through preventing the deactivation of the neurotransmitter acetylcholine (Costa, 2008), however not irreversibly.
[8] Pyrethroids work through preventing the repolarisation of ion gated voltage channels, leading to paralysis in an organism (Costa, 2008).
[9] For a review of organophosphate pesticides classed by their hazardous risk see Lotti (2010)

2015 (Environmental Proection Authority, 2014; Environmental Protection Authority, 2013). Worldwide the use of organophosphates is steadily being replaced with nicotinoid pesticides, however this remains controversial.

Carbamates

Carbamates are another group of pesticides which rose in popularity after the decline of DDT use across the world. Although first discovered in the 1920s, their insecticidal properties were not discovered until 1954 when Kolbezen, Fukuto, and Metcalf (1954) developed the first N-methylcarbamates. These have a broad spectrum and are now the most commonly used carbamates across the world (Metcalf & Horowitz, 2000b). Their toxicity ranges from low to extremely harmful in humans. Unlike organophosphates, however, their effects are reversible (Costa, 2008). Currently carbamates are used in combating soil insects and a variant is used in combating mosquitos in human habitations as a replacement for DDT (Metcalf & Horowitz, 2000b). Similar to organophosphates, carbamate use is steadily being replaced by nicotinoids.

Pyrethroids

The last group of pesticides to arise as a result of the decline in popularity of DDT were pyrethroids. While insecticides derived from the chrysanthemum flowers have been used in some capacity since ancient times, their rapid degradation in sunlight necessitated the creation of more stable synthetic versions known as the ‘first generation’ of pyrethroids (Costa, 2008). Their active ingredients were still easily degraded by sunlight, leading to extensive modification and the creation of a more stable ‘second generation’ of pyrethroids which are currently in use (Kaneko, 2010). First generation pyrethroids are frequently used in household insect sprays, cattle sprays, and in grain silos where their fast acting paralysis of insects is valued (Metcalf & Horowitz, 2000b). They are also often used in companion animal parasite control products (Soderlund, 2013). Second generation pyrethroids are stable enough for both home and agricultural use (Kaneko, 2010). They are also vital in the fight against malaria in African countries (Ranson et al., 2011). Pyrethroids are generally considered the safest category of pesticides, with few reported deaths from pyrethroid exposure (Ray & Fry, 2006).

Further mammals have less sensitive ion channels, higher body temperatures and faster metabolisms contributing to their selective toxicity (Ray & Fry, 2006; Soderlund, 2013). Consequently, they have largely replaced organophosphates in home use. Similar to organophosphates, pyrethroids have low environmental toxicity and rapid degradation, particularly in sunlight (Costa, 2008), leading to a lower environmental burden. Currently pyrethroids are estimated to make up around 20% of the world market for pesticides (Soderlund, 2013), ranking second only to organophosphorus insecticides.

Neonicotinoids

Neonicotinoids[10] are the newest form of pesticides, developed in the 1980s by researchers at Shell (Kollmeyer et al., 1999). They were first discovered by modifying natural products such as pyrethrins (Tomizawa & Casida, 2005). Their properties allow them to be absorbed by plants, making them useful in many areas including agriculture, horticulture, and in speciality treatments to combat root feeding and boring insects (Simon-Delso et al., 2015). Their use has increased rapidly since their inception, and while use varies between crops, usage for some crops such as corn is estimated to be as high as 90% in the United states (Chen, Tao, McLean, & Lu, 2014; Douglas & Tooker, 2015; Hladik, Kolpin, & Kuivila, 2014). In 2005 their use was estimated at around 15% of the market (Tomizawa & Casida, 2005). Use is estimated to continue to increase (Douglas & Tooker, 2015), and it is anticipated that neonicotinoids will continue to supplant existing pesticides. Neonicotinoids are argued to be more selective than other pesticides. While they act as nicotine receptor agonists in insects, their effects are different and less harmful in mammals and birds (Tomizawa & Casida, 2005). However their metabolites have been argued to be harmful in mammals, (Tomizawa, 2004), and can lead to toxicity (Goulson, 2013) Further to this they are persistent in the environment (Anderson, Dubetz, & Palace, 2015; Hladik et al., 2014; Simon-Delso et al., 2015). This is also the case in New Zealand, where neonicotinoid residue has been detected in the environment (Chen et al., 2014). Unfortunately the very properties that make them effective as pesticides, namely their ability to be absorbed by plants, are what contribute to their increased environmental persistence (Bonmatin et al.,

[10] Neonicotinoids work through overstimulating and blocking the nicotinic acetylcholine receptors. This process leads to paralysis and death (Tomizawa & Casida, 2005; Yamamoto, 1999).

2015). This has led to considerable controversy surrounding neonicotinoids, as their use is argued to be tied with the recent global decrease in bees (Goulson, 2013), which has prompted calls for further research into consequences of their use. Few studies have looked into their potential effects on health in humans, although a systematic review suggests negative impacts on development and health in children due to chronic exposure (Cimino, Boyles, Thayer, & Perry, 2017). Neonicotinoids are resistant to removal by washing (Chen et al., 2014), making it important to continue to investigate the potential health outcomes due to their use.

Current World Pesticide Use

Insecticides, fungicides, and herbicides are the most common types of pesticides used (Grube, Donaldson, Timothy Kiely, & Wu, 2011) and pesticide usage of any type varies from country to country depending on agricultural practices and regulations. An estimate of world market data puts the amount to around 2.5 billion kg of pesticides used globally in 2007, with roughly 85% of pesticides used in the agricultural sector (Grube, Donaldson, Kiely, & Wu, 2011). While exact global statistics are unavailable, (Bravo et al., 2009), individual country level statistics provide a picture of current world wide usage.

The Food and Agriculture Organisation of the United Nations (2015)[11] reports that in 2007 usage for the United States was over 280,000 tonnes and 69,000 tonnes in Canada in 2011. In Oceania, Australia used around 35,000 tonnes in 2006 while New Zealand usage for 2007 was 4,800 tonnes (Food and Agrigulture Organisation of the United Nations Statistics Division, 2015). The usage for the European Union was estimated to be over 292,000 tonnes in 2005, and of this 23,000 tonnes were used in the United Kingdom (Eurostat, 2015). In Latin America, Brazil used over 350,000 tonnes of pesticides in 2013 (Food and Agrigulture Organisation of the United Nations Statistics Division, 2015) overtaking the United States as one of the largest consumers of pesticides globally. On the Asian continent, use in China was estimated at 146,000 tonnes in 2005 (Zhang et al., 2011), while Japan was estimated to use 52,000 tonnes in 2013 and India an estimated 40,000 tonnes

[11] Data available for each year varies from country to country and the most recent dates available are used.

in 2010 (Food and Agrigulture Organisation of the United Nations Statistics Division, 2015). Reliable data on pesticide use in the some parts of the developing world such as in the African continent are not generally readily available, however proxy data such as import or sales statistics can also be a means of estimating use (Bravo et al., 2009). In 1999 Sub-Saharan Africa imported pesticides valued at around US$500 million (United Nations Environment Programme, 2002), making up around 4.5% of all pesticides imported globally (US$11 billion) that year. In Central America around 33 million kg of active pesticides were imported in 2007 (Bravo et al., 2009), making up around 1.3% of all pesticides imported globally (2.5 billion kg) that year. In comparison to the larger users such the USA and Brazil, New Zealand uses comparatively low levels of pesticides, especially insecticides, given its large focus on agriculture. This makes it likely that exposure in New Zealand will be lower overall compared to other developed countries.

Regulations are one of the strongest influences on how pesticides are used in the modern world. Globally regulations differ on pesticide use and maximum residue limits (MRLs) in food with no one global rule applying. However, in general most developed countries have extensive regulations surrounding the safe use of pesticides. For example in the United States three separate acts govern the use of pesticides (United States Environmental Protection Agency, 2016). New Zealand has similar legislation in the 'Hazardous Substances and New Organisms Act'(Environmental Protection Authority, 2015) which requires registration and safety testing of any pesticide before it can be imported or used. Furthermore New Zealand is part of the Stockholm Convention on persistent organic pollutants (Stockholm Convention, 2009), meaning that environmentally harmful pesticides such as DDT cannot be used.

In contrast many developing countries lack effective regulations and tracking of what and how pesticides are used (Bravo et al., 2009). Further to this, pesticide use will have a different profile in the developed world. There are also serious concerns around misuse of pesticides in the developing world (De Silva, Samarawickrema, & Wickremasinghe, 2006) and it is estimated that around 99% of all pesticide related deaths occur in the developing world (World Health Organisation, 1990). In Brazil, one of the world's largest pesticide consumers, a recent Reuters investigation outlined

inefficiencies in enforcement of laws and safety testing of pesticides (Prada, 2015), leading to health concerns due to contaminated drinking water and food. Similar concerns are also present in India (Sharma, 2013) where the current legislation is governed by the dated Insecticides Act 1968 and the Insecticide Rules 1971 (Department of Agriculture Government of Maharatsha, 2015). Concerns around air, water, and soil pollution by pesticides alongside an increase in pesticide related deaths and widespread overuse are becoming increasingly common in China (Ding & Bao, 2014; Zhang et al., 2011).

The United Nations highlights similar problems in the African Continent where misuse of pesticides is disproportionately high (Food and Agrigulture Organisation of the United Nations, 2016). There is also often a lack of safety regulations around pregnant women working in developing countries such as in Ecuador (Handal, Lozoff, Breilh, & Harlow, 2007), compared with the developed world. In many developing countries such as Egypt agriculture is reliant on child and adolescent seasonal workers (Abdel Rasoul et al., 2008a). This means that children and pregnant women are likely to be more exposed than their counterparts in the developed world. Further to this, developing countries often continue to use many outdated and more toxic pesticides with lengthy half-lives[12] (Ecobichon, 2001) no longer used in the developed world. This difference in regulations and use means that individuals are likely to be exposed to different types of pesticides, exposed in different ways, and exposed to different doses making it difficult to directly compare the effects of pesticides across countries. It also makes it difficult to apply the findings of studies on the harmful effects of pesticides globally as each country has a different exposure profile.

In summary, this chapter has provided an overview of the history of pesticide use across the world. Pesticides began to be used on a large scale after the industrial revolution and four main types of pesticides were developed: organochlorines, organophosphates, carbamates, and pyrethroids. The last twenty years has seen organochlorines (such as DDT) largely banned across the world and organophosphates and pyrethroids steadily supplanted by neonicotinoids. While accurate global

[12] Half-life refers to time required for any specified property (e.g., the concentration of a substance in the body) to decrease by half and thus provides an indication of how quickly something decays.

pesticide usage data are not available, country level data suggest that usage is different from country to country. In New Zealand, pesticide usage is regulated through the Hazardous Substances and New Organisms Act (Environmental Protection Authority, 2015). New Zealand has a large agricultural sector utilising organophosphate, pyrethroid, and nicotinoid pesticides. While a large volume of pesticides are used, industries generally aim towards sustainable and environmentally friendly pesticide use (Manktelow, Stevens, Walker, & Gurnsey, 2005). This is in contrast with use in some of the more studied countries, such as Brazil. These differing levels of usage create unique pesticide exposure profiles for each country, making it difficult to directly compare the extent of exposure directly from country to country. This creates the need for individual country by country studies to fully understand the potential impact of pesticides across the world. The next chapter will discuss the factors influencing exposure in children and how they have unique risks not seen in the adult population.

Chapter 3: Pesticide Exposure

As a consequences of widespread pesticide use, people are exposed in various ways to various doses. In terms of dosage, acute exposure refers to an event where a large volume of a substance has been ingested, inhaled or absorbed through the skin and is, accordingly, relatively infrequent whereas chronic low-level exposure refers to repeated low-level doses of a substance over a longer period of time. In regard to pesticides, children, are most likely to be affected by chronic low-level exposure (Roberts & Karr, 2012) due to a number of different factors that are reviewed below.

Exposure Generally

Early studies investigating the level of exposure in children indicate that low level exposure to pesticides is common (Eskanazi, Bradman, & CastorinaR, 1999) with more recent work suggesting that this remains the case worldwide. Research suggests around 60 – 85% of children have detectable urine metabolites (Barr et al., 2010; Heudorf & Angerer, 2001; Schettgen, Heudorf, Drexler, & Angerer, 2002).

Exposure rates for pregnant women also fall in this range (Berkowitz et al., 2003; Berman et al., 2011; Forde et al., 2015; Huen et al., 2012) and, as pesticides have been shown to cross the placental barrier (Rauh et al., 2012), foetal exposure is also likely. Even the lowest range estimates of exposure still leave a large proportion of the global population of children exposed to low levels of pesticides making any effects from this potentially widespread. As even small effects can contribute substantially to population burden (Bellinger, 2012), the effects of low level exposure have the potential to cause widespread burdens.

Exposure Pathways

A number of different pathways for childhood exposure exist: diet, household use, proximity to pesticide use areas, and the 'take home' pathway. Of these factors, research suggests that diet is one of the most influential pathways (Boucher et al., 2013; Heudorf & Angerer, 2001; Schettgen et al., 2002; Seurin et al., 2012). This is true for organophosphates (Holme et al., 2016; Valcke et al., 2006), pyrethroids (Heudorf & Angerer, 2001; Saillenfait, Ndiaye, & Sabaté, 2015; Schettgen et al., 2002),

and organochlorines (Seurin et al., 2012) but no research investigating the effects of carbamates or neonicotinoids was found. However, given their frequent use in combating soil insects and mosquitoes as opposed to large scale use in agriculture, children may be exposed to them through different pathways.

Within diet it is likely that fruits and vegetables are the major source of pesticide exposure. As both urban and rural children have been found to eat similar quantities of fruits and vegetables (Holme et al., 2016), they are also likely to be a contributing source of exposure regardless of location. This is supported by findings that organic diets completely eliminate detectable traces of pesticides in children (Lu, Barr, Pearson, Bartell, & Bravo, 2006). One attempt to reduce pesticide exposure through fruit and vegetable consumption is the use of minimum residue limits (MRL), which most developed countries currently employ. However, even when fruits and vegetables fall within the MRL, detectable levels of pesticides are often still present (Quijano, Yusà, Font, & Pardo, 2016). Further when limits are in place, fruits and vegetables have been found to frequently exceed these limits in some cases (Yu, Liu, Liu, Wang, & Wang, 2016). Finally, as pesticides have been found in breastmilk (Weldon et al., 2011), diet is also a likely source of exposure for children who are breastfed, making diet a widespread pathway for exposure across the ages.

Home use of pesticides (insect sprays, pet care such as flea or worming treatments and use of insecticides and herbicides in gardening) is another potential exposure pathway of exposure for children. Surveys suggest that home usage of pesticides is around 60 to 80% in a variety of countries including the United States, China, and Israel (Berkowitz et al., 2003; Berman et al., 2011; Wu et al., 2011). Seasonal trends exist with usage increasing in the spring and summer months where children may play in the affected rooms on the day of application (Wu et al., 2011). Usage has also been found to be unaffected by socio-economic factors (Berkowitz et al., 2003), suggesting that the trend is likely stable regardless of income or type of residence. The main type of insecticides used at home, pyrethroids, degrade more slowly without exposure to sunlight (Metcalf & Horowitz, 2000) and therefore persist for longer periods of time becoming trapped in house dust or carpets. As pesticides

can be absorbed through both dermal contact and inhalation (Saillenfait, Ndiaye, & Sabaté, 2015), the slower degradation increases the window for chronic low levels of exposure through home use.

A further pathway to exposure is proximity to farmland and other high pesticide use areas such as orchards. Children living / attending kindergarten near pesticide treated farmland have higher levels of exposure compared to other children living in the same general area (Lu, Fenske, Simcox, & Kalman, 2000). Residences closer to high pesticide use areas such as farmlands or orchards have been found to have detectable levels of pesticides in house dust, clothing and surface wipe samples in up to 90% of samples (Bradman et al., 2007). During spraying, levels of pesticides increase further (Kawahara, Horikoshi, Yamaguchi, Kumagai, & Yanagisawa, 2005). As pesticides are easily inhaled, this may place children at greater exposure risk given they spend longer periods of time either at home or at childcare centres near the pesticide use areas than adults in the same family (Roberts & Karr, 2012). As urban children are less likely to live near pesticide use areas, the proximity pathway is likely to be more significant in rural children compared to their urban counterparts.

Another pathway for chronic low levels of exposure in children is known as the 'take home' pathway. Family members or other residents in the household working with pesticides may bring home residues on their work clothing, tools, skin or hair thus bringing pesticide traces into the home (Chensheng Lu, Fenske, Simcox, & Kalman, 2000). These residues may shed onto the carpet where they are easily inhaled or transferred to other clothing if separate washing machines are not used (Fenske, Lu, Barr, & Needham, 2002). In the same way as the proximity pathway, this is a pathway primarily affecting rural children where high pesticide use occupations are more common. This makes rural children at higher risk of exposure when compared with their urban counter parts.

Factors Influencing Pesticide Susceptibility

There are a number of factors which increase the effects of chronic long-term pesticide exposure in children compared to adults. Even when living in the same environment as adults, their age, their play activities and their dose-to-weight ratio make them disproportionately vulnerable.

The age of the child interacts with exposure. This is via changes in their neuropsychological development and metabolism, also known as toxicodynamic and toxicokinetic factors. Toxicodynamic factors refer to the age related developmental processes which create windows of extra sensitivity to toxic insults (Pope, 2010). Children's brains are still developing; a process reliant on a complex interplay where multiple brain areas are growing simultaneously and requiring the correct inputs from neurotransmitters (Weiss, 2000a). As pesticides can have effects on neurotransmitters such as acetylcholine, any exposure can affect normal neuropsychological development. Furthermore, as neuropsychological development in children is argued to have critical periods or 'growth spurts' (Westermann, Thomas, & Karmiloff-Smith, 2010; Heyer & Meredith, 2017), they may be especially sensitive to the effects of pesticide exposure during these periods. In this way, toxicodynamic factors increase the risk to children through their extra vulnerability at critical periods of their development.

Toxicokinetic factors refer to differences in absorption, elimination and biotransformation of pesticides (Pope, 2010). Animal studies have shown that rat pups are more susceptible to acute exposure to pesticides than low level chronic exposure where they appear to have better ability to recover (Chakraborti, Farrar, & Pope, 1993; Pope & Liu, 1997). This finding is similar in human children (Shafer, Meyer, & Crofton, 2005) where very young children seem less susceptible to the effects of low level exposure. One explanation for this is that very young children and animals lack the enzymes to process pesticides such as acetylcholinesterase and pseudocholinesterase, in particular common types of pesticides including both carbamates and organophosphates (Pope, 2010). Thus while the metabolites resulting from the processing of pesticides are harmful (Chambers, Meek, & Chambers, 2010), affecting the inability of very young children to process them, this may actually be protective from the harmful effects of some pesticides. As children grow they gain the enzymes required for processing pesticides and this is typically around age five, a period when the brain also becomes less plastic (Pope, 2010) and may become affected differently due to this. In this way, as children age the effects of pesticides may be different. While this may lessen the impact of pre-natal exposure, children exposed post-natally are likely at greater risk.

The way children play and interact with their environment also puts them at different levels of risk than adults. For instance, children's play behaviour is associated with different exposure levels and pathways than in adults. Children spend more time playing on or near areas which may contain pesticides, such as on carpeted floors or outside near sprayed fields. Age moderates this effect as children's behaviour changes across the developmental period. For instance, younger children are more likely to spend time playing on the floor (Paulson & Barnett, 2010) and are more likely to mouth objects in their environment which may cause them to ingest dust where pesticides have settled to other contaminated objects. (Weiss, Amler, & Amler, 2004). While older children do not mouth objects, or spend as much time playing on the floor, they still spend more time than adults in areas such as school fields and sports grounds. As both school and athletic fields frequently use pesticides (Gilden, Friedmann, Sattler, Squibb, & Mcphaul, 2012), older children are still generally likely to spend greater amounts of time near potential exposure sources than adults.

A further factor which makes children more vulnerable to pesticides than adults is their higher dose-to-weight ratio. Children are much lighter than adults and any ingested substances are likely to be relatively greater than in adults. The same is true for pesticides where any dose a child is exposed to is likely to be much greater for their weight in adults. The dose-to-weight ratio also plays a role in diet where children consume higher doses of fruits and vegetables, including juices, compared to their weight than adults (Weiss et al., 2004). The same is true for home use, where children’s inhalation of aerosolised pesticides or contaminated house dust or dermal absorption is likely to yield a greater effect of exposure for them with the same dose. In this way the dose-to-weight ratio has the consequence of placing children at greater risk by making the effects of any exposure relatively larger than in adults.

In sum, the factors discussed previously work together to place children at greater risk of environmental pesticides by increasing the likelihood of exposure through their behaviour across the developmental period, and making the effects of exposure comparably greater than in adults. This is further compounded by the sensitive nature of neuropsychological development in children which can be upset by exposure through both toxicodynamic and toxicokinetic factors. This means that while

low level pesticide exposure is common worldwide in both children and adults, it is likely to place children at greater risk than their adult counterparts.

Chapter 4 – Normal Cognitive Development

The potential effects of pesticide exposure on neuropsychological development in childhood are best considered in the context of normal development. This chapter will review theories of child development with an emphasis on cognitive development.

Theories of Development

One of the earliest and most widely adopted theories of child development was developed in the 1920s by Swiss clinical psychologist Jean Piaget who proposed four distinct stages in child development; sensorimotor (0 – 2 years), preoperational (2 – 7 years), concrete-operational (7 – 12 years) and the formal operational (12 years onwards)[13]. The child is seen as a scientist who through experimenting with their environment, and as the central driver of their own development passes through these stages (Piaget, 1952). Piaget's theory has been criticised however for not adequately taking into account factors such as environmental influences and developmental delays (Chen & Hancock, 2011).

This limitation is addressed in sociocultural theory which is heavily influenced by the work of the Russian psychologist Lev Vygotsky (Daniels, 2010). In this view a child's cognitive development is viewed as the result of their interaction with their environment (Chen & Hancock, 2011). Vygotsky's work also proposed the 'zone of proximal development' which described the range between a child accomplishing a task alone and with assistance (Daniels, 2010). However, this theory where the environment is seen as the primary driver of development, has also been criticised for being too narrowly focused.

Drawing on the work of Piaget and Vygotsky, Luria (1980) developed a five stage model of human development. His proposed stages map onto Piaget's stages (Goldstein, Naglieri, Princiotta, & Otero, 2014) and onto the typical growth spurts observed in the brain occurring from birth to two years, two to four years, five to eight years and twelve to eighteen years (Majovski & Breiger, 2009).

[13] For a review see (Miller, 2010)

In Luria's theory the first stage begins at conception and features the development of the brain stem structures. It is the first critical period of development with any insult to the brain likely to have serious flow on consequences. The second stage, in the second year of life, brings about the activation of the primary sensory areas of vision, hearing and touch and the primary motor areas. In the third stage during the preschool years children develop the secondary association areas of the brain, which allows for the use of symbolic materials and model physical movements. Stage four starts around seven to eight years of age and involves the activation of tertiary parietal and occipital lobes which allows for more efficient sensory input. The child is also more able to use complex mental abilities as a result of this development. Finally, the fifth stage begins around age eight and involves the further development of the frontal lobes, allowing for more advanced cognitions such as abstract thinking. Similarly to the work proposed by Vygotsky the stages are influenced and somewhat driven by the environment. The stages also build on one another, with brain areas and skills developed in the previous stages being used to aid in the development of skills utilised in the next stage.

During the progression through these stages the human brain also undergoes four major processes; the birth of neurons, the migration of neurons, differentiation and maturation of neurons and the pruning of neurons (Kolb & Fantie, 2009). All four processes, in particular myelination, mediate the development of more complex behaviours and cognitions such as complex motor movements and memory (Kolb & Fantie, 2009; Majovski & Breiger, 2009; Miller, 1994) and are necessary for normal cognitive development.

In this way child development is seen as a complex interplay of brain areas, the child's environment and their abilities which allows the child to develop through stages as they age. This creates a progressively specialised learning system which is constantly evolving to meet the demands imposed on it by the context (Westermann, Thomas, & Karmiloff-Smith, 2010). As each stage utilises skills from the previous stage, any disruptions or difficulties have the potential of flow on effects onto further child development. During development any insults to the brain, both physical and chemical can upset the normal developmental trajectory making children especially vulnerable to the effects of exposure to a variety of substances including pesticides.

Cognitive Development

As discussed above, human cognition does not develop in a vacuum, with a complex interplay existing between multiple simultaneous processes. In line with this it is more useful to view cognitive development and abilities in terms of multiple interacting domains of functioning as proposed by Lezak, Howieson, Bigler, and Tranel (2012). This domain centred view is also in line with current developments in general psychopathology research (Cuthbert & Insel, 2013) and measures of intelligence such as the Wechsler Intelligence Scale for Children (Wechsler, 2003a), which use multiple indices and domains to make up an overall score of functioning and intelligence. In line with this, this review will consider the development of different domains of functioning, as opposed to a single overall construct.

Motor Functioning

Motor functioning, the ability to engage in purposeful movements, was originally thought to be controlled by a central motor output device in the brain, damage to which results in motor deficits (Rumiati, Papeo, & Corradi-Dell'Acqua, 2010). However studies on apraxia have suggested that motor functioning is undertaken by many different areas of the brain (Gross & Grossman, 2008) and involves other cognitive skills such as executive functioning (Lezak et al., 2012). Children are born with basic motor reflexes mediated through the brainstem with motor control gradually migrating to the wider nervous system with age (Bergen & Woodin, 2011; Majovski & Breiger, 2009). As children's physical development mature they are better able to practice and refine their motor skills, leading to large improvements around the ages of three to five years (Fletcher, 2011). Coordination continues to improve from the age of five onwards (Bauer, Lukowski, & Pathman, 2011) and begins to plateau around the twelfth year of life (Gasser, Rousson, Caflisch, & Jenni, 2010). While children continue to refine their motor skills after this time (Bauer et al., 2011) their development is comparatively slower and less extensive, meaning the critical periods for motor development are from birth to age twelve.

Processing Speed

Processing speed refers to the speed at which an individual is able to carry out simple or automatic cognitive tasks and their general reaction times (Kail, 1991). The current overarching theory behind processing speed sees it as one central mechanism or single construct which mediates performance on other tasks (Kail, 1988). The idea of processing speed as a single construct is supported through the developmental trajectory of processing speed (Kail & Park, 1992) and overall the literature also supports the idea that processing speed is a distinct construct (McAuley & White, 2011).

Processing speed was originally argued to develop in an exponential fashion (Kail, 1988, 1991). However more recent studies suggest that a quadratic model of development which runs parallel to physical development is more accurate (Kail & Ferrer, 2007) with rapid initial development during childhood reaching a peak in early adulthood (Kail, 1988, 2000; Kail & Park, 1992). Physically the development and deterioration of white matter (Ferrer et al., 2013) and myelination (Travis, 1998) in the brain run parallel to the development of processing speed. This makes brain maturation an important facet of processing speed development and any disruptions to this are likely to disrupt it.

In relation to the other cognitive domains, processing speed works as a mediator of performance in executive functioning (Ferrer et al., 2013; Kail, 2007) and mediates the effects that working memory has on children's fluid reasoning (Fry & Hale, 1996; Nettelbeck & Burns, 2010). It is also heavily linked with overall IQ (Coyle, Pillow, Snyder, & Kochunov, 2011; Sheppard & Vernon, 2008). Furthermore the development of other cognitive domains is reliant on processing speed (Ferrer et al., 2013). Any deficits to processing speed are likely to have a large flow on effect onto overall functioning and it plays an influential role in the development of most of the cognitive domains. This makes it a crucial component to overall cognitive functioning.

Attention

Attention is a key component of human functioning and has a large impact on both successful development and the successful managing of everyday life. Attention is argued to rely on specific anatomical areas, which work as a network, and each area is involved with a different function of attention (Posner & Petersen, 1990). Three main networks are postulated to integrate behavioural and neuropsychological approaches to explaining attention: alerting, orienting, and executive control, with each network contributing distinct neurological components (Petersen & Posner, 2012; Posner & Petersen, 1990).

Alerting refers to the ability to become and remain aware of a stimulus, while orienting directs this awareness to the stimulus—this is the simplest attentional process (Posner & Petersen, 1990). The executive control system is similar to the concept of the central executive proposed by Baddeley and Hitch (1974), and manages attention when there are multiple different stimuli. In this system, alerting first informs a person that there is a stimulus, which is then oriented to through the use of the executive control. It is also generally recognised that there are four distinct subtypes of attention: selective, divided, sustained, and focused attention.

Selective attention refers to the ability to voluntarily attend to and search for stimuli amongst other distractors (Enns & Girgus, 1985). Focused attention is the ability to maintain attention on a fixed stimulus (Treisman & Gelade, 1980). The main difference to selective attention is that it is mostly directed at a single stimuli and does not contain a searching component (Ruff & Rothbart, 1996). Divided attention refers to the ability to pay attention to different stimuli (Spelke, Hirst, & Neisser, 1976), while sustained attention reflects the ability to maintain attention over time (Cohen, 1993). All four types of attention draw on the three networks proposed by Posner and Peterson (1990) to different degrees. Further to this there are also two physical types of attention, using both the auditory and visual pathways and visual and auditory attention, making attention a diverse and multidimensional construct.

Generally all types of visual attention develop with age, with more rapid increases until age eight and a plateauing effect around age ten (Rebok et al., 1997; Rueda et al., 2004; Trick & Enns, 1998). This trend is also mirrored in the less studied domain of auditory attention (Gomes, Molholm, Christodoulou, Ritter, & Cowan, 2000). One exception to this trend is the development of orientation skills, which are mostly complete by age six (Rueda et al., 2004; Ruff & Rothbart, 1996). Within the brain attention is reliant on frontal, parietal, and posterior regions (Petersen & Posner, 2012) and studies of children with attentional difficulties suggest that the anterior cingulate gyrus and the fronto-striatal regions are also involved with processing attention (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006). Brain maturation and development of these regions mirrors the development of attentional skills (Konrad et al., 2005).

It is also suggested that there are two main brain networks involved with attention, the dorsal attention network and the ventral attention network, which utilise the frontal eye fields, temporoparietal junction, and the ventral frontal cortex to assist in attention processing (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002). Both systems develop asymmetrically, with dorsal networks showing greater use in childhood with a shift to greater ventral use in adults (Farrant & Uddin, 2015). As the dorsal systems are more heavily involved with the orienting process (Corbetta & Shulman, 2002), this along with fMRI studies (Konrad et al., 2005), supports the idea that with age, attention development shifts away from simple processes to more advanced processes. As children get older, attention becomes more influenced by their ability to control their attention and inhibit the intrusion of distractors (Plude, Enns, & Brodeur, 1994), indicating that the executive functioning component, inhibition, may be influential on attentional capacities. This is further supported by findings which suggest that as task complexity rises, attention alone is not sufficient to achieve good results and complex task performance rises with age (Lavie, 2005). Additionally, task load influences children's attentional abilities. Task load has been found to have a larger detrimental effect in younger children (Betts, Mckay, Maruff, & Anderson, 2006; Lavie, 2010), indicating that children's processing speed plays a role in their attentional capacities. Children have also been found to perform better when given more choice about where and what to pay attention to (Dicarlo, Baumgartner, Ota,

& Geary, 2016), indicating that motivation plays a role in attentional capabilities. This suggests that attention does not develop in a vacuum with many other cognitive processes playing a role in its development and general attentional abilities.

Language

Language forms a fundamental part of human existence and deficits in this area can have far reaching consequences. There are two main theories of language acquisition: structural theories and usage based theories. Structural theories were pioneered by Noam Chomsky (1980) and emphasise an innate structural ability for a child to develop language, referred to as a 'language acquisition' device. Usage based theories focus on the acquisition of language through cultural learning and cognitive capacities (Tomasello, 2003) although a biological component to language acquisition is acknowledged. While there is no consensus on which theory best explains language acquisition, both theories attempt to make sense of how children reconstruct the linguistic utterances around them into language (Tomasello, 2010). Taken together both theories emphasise an interplay between inborn abilities and the child's environment, a process similar to general cognitive development as proposed by Luria.

In a similar way to other cognitive domains, language does not develop in isolation and is reliant on the concurrent development of motor skills, memory, and perceptual abilities (Kolb & Fantie, 2009). In the first few year of life children develop their language skills from babbling, to more complex speech around age three (Fletcher, 2011b; Kolb & Fantie, 2009; Tomasello, 2011). From five years onwards, children's conversational abilities see a large improvement. This trend continues until early adulthood with improvements in their abilities to grasp nuances and double meanings, alongside general vocabulary improvements (Bauer et al., 2011) suggesting that language develops steadily and skills are refined with age.

Memory

Memory refers to the ability to retain information and is one of the most important aspects of cognitive functioning as even minor impairments can lead to large disorienting effects (Lezak et al.,

2012). Within memory there are two main subtypes: short term memory and long-term memory. While working memory is at times included under the umbrella of memory, it is a key component of executive functioning and will be discussed under that section. Short term memory refers to information which is temporarily stored before being transferred into long term memory storage by the working memory systems (Cowan, 2014). It is very limited in storage, typically storing around seven items (Miller, 1956). Memories stored in the short term memory are either processed and transferred into long term memory or decay after around 30 seconds to a few minutes (Lezak et al., 2012). The development of short term memory is dependent on the same brain areas as working memory and is limited by working memory development (Cowan, 2014). Short term memory abilities increase steadily until around eighteen years of age (Schneider, Knopf, & Sodian, 2009) making childhood a critical period for short term memory development.

Within long term memory there are two main subsystems: declarative or explicit and non-declarative or implicit memory, and both processes operate in parallel (Schneider, 2010). While there are many more systems of long term memory it is argued that this two stage system is most useful in understanding memory competence (Lezak et al., 2012) and the extra systems will not be covered in this review. Declarative memory involves conscious or active recollection of past events (Lukowski & Bauer, 2014) and is where most difficulties are experienced (Lezak et al., 2012). It is also what is generally meant when memory is referred to in everyday situations (Squire, 2004). In contrast, implicit memory is an unintentional form of retention and recollection (Schacter, 1992) which governs many unconscious learning processes such as classical conditioning, motor skill learning, and the acquisition of habits (Lukowski & Bauer, 2014).

Information stored in long term memory is organised on the basis of meanings and associations between items (Lezak et al., 2012) and its storage capabilities are virtually limitless. Physically, non-declarative memory relies on different brain structures depending on the type of learning being used, for example classical conditioning relies on the cerebellum (Lukowski & Bauer, 2014). Many of the structures used in non-declarative memory are either present at birth or develop very early in life (Lukowski & Bauer, 2014; Schneider, 2010). Declarative memory is reliant on the

development of the hippocampus and the medial temporal lobes (Burgess, Maguire, & O'Keefe, 2002; Lukowski & Bauer, 2014; Piekema, Kessels, Mars, Petersson, & Fernández, 2006; Squire, 2004).

Generally the rudimentary stages of declarative memory have developed by age three and after this children begin to make use of memory strategies (Bergen & Woodin, 2011), increasing in school age years (Schneider, 2010). After age six children's declarative memory abilities increase steadily until they peak in early adulthood, with a spike after they begin to develop the ability to form categories which allows for their knowledge and memory capacities to increase (Bauer et al., 2011; Schneider, 2010). As already discussed memory abilities are mediated by processing speed and working memory skills. Further, as implicit memory is closely connected to the acquisition of motor skills, memory is also linked with motor development. This makes memory a crucial system for further development in children. Childhood is also a critical period of memory development, especially after age six when development spikes, making insults to the brain during this time especially damaging.

Executive Functioning and Working Memory

The executive functioning domain is characterised by abilities in engaging in purposeful, self-directed behaviours and planning (Lezak et al., 2012) and has been linked with many developmental outcomes in later life (Mischel et al., 2011; Moffitt et al., 2011). Executive functions work to moderate other cognitive processes and regulate both actions and cognitions (Miyake et al., 2000) making them critical to overall cognitive functioning. The development of executive functioning begins after the first year of life and can be effectively measured from age three onwards (Willoughby, Blair, Wirth, & Greenberg, 2010). Executive functioning consists of three separate subdomains, each of which performs different functions and develops differently. However children generally reach adult levels of competence on most executive functioning tasks around age twelve (Zelazo & Mueller, 2010) with some variation within the different subtypes of executive functioning.

A three domain structure proposed by Miyake et al. (2000) consisting of Shifting, Updating and Inhibition has been found to be the best fit for describing executive functioning (Garon, Bryson, & Smith, 2008). Shifting refers to the ability to switch attention between multiple tasks and mental sets while updating is the ability to update and monitor different working memory representations. Finally, inhibition concerns the ability to deliberately inhibit responses and stimuli when necessary. Empirically, the diverse three factor structure has been extensively replicated in older children and adults (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Best & Miller, 2010; Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003) however it is suggested that in very young children executive functioning is best explained using a unitary factor (Wiebe, Espy, & Charak, 2008; Willoughby et al., 2010). This may indicate that as children's age and brain maturation increases children's executive functioning abilities become more pronounced and move away from their unitary base into a more complex three factor model.

Shifting

Children's shifting abilities generally develop with age in a linear way, with a plateau around age twelve, however development is reliant on working memory and inhibition skills (Garon et al., 2008). At around three to four years of age children can generally shift between two rule sets (Hughes, 1998). After this age period rapid improvements occur around the ages of five to six (Luciana & Nelson, 1998) with slower but still consistent improvements from the ages of seven to twelve (Huizinga, Dolan, & van der Molen, 2006). Shifting abilities reach adult levels around age fifteen (Best & Miller, 2010).

Inhibition

Inhibition is a difficult concept to measure and different tasks show different levels of mastery at various ages, indicating that it is comprised of many different cognitive demands (Best & Miller, 2010). There is a rapid development of inhibitory abilities in early childhood up to age four (Carlson & Moses, 2005; Garon et al., 2008; Hughes, 1998). From age five to eight steady improvements continue to occur (Romine & Reynolds, 2005) and after this steady but slower

improvement continues until age twelve (Cragg & Nation, 2008; Romine & Reynolds, 2005) when children reach adult levels of ability.

Working Memory

Working memory is the process where information maintained in temporary storage is manipulated for other cognitive processes (Lezak et al., 2012). The original model of working memory proposed by Baddeley and Hitch (1974) contained one main component, the central executive, and two slave systems, the phonological loop and the visuo-spatial sketch pad. The central executive is a limited capacity master system which selects and operates the processes within working memory (Baddeley, 1983). It controls the other two slave systems and is the most important component of working memory (Baddeley, 1996). Baddeley later reformed this model to include a third component, the episodic buffer. The episodic buffer is a limited capacity temporary storage system controlled by the central executive which integrates information from a variety of sources and forms the link between working and long term memory (Baddeley, 2000). The model has again been recently revised to more clearly define the way the central executive uses the three slave systems. In this new model the episodic buffer forms the gateway for the central executive to access the phonological loop and the visuo-spatial sketchpad and binds the incoming information into usable chunks and episodes (Baddeley, Allen, & Hitch, 2011).

Structurally working memory relies upon the development and function of the medial temporal lobes, prefrontal cortex and the hippocampus (Ezzyat & Olson, 2008;Olson, Moore, Stark, & Chatterjee, 2006; Olson, 2006). The development of working memory is also heavily mediated by processing speed (Pickering, 2001), indicating that white matter maturation may also indirectly play a role in its development. In line with the development of these areas working memory development begins in preschool years (Garon et al., 2008) and steadily improves and levels off around the age of fourteen (Gathercole, Pickering, Ambridge, & Wearing, 2004). It develops gradually from preschool onwards, and the later adolescent period of development mainly sees a refinement in skills (Best & Miller, 2010).

Social Perception

Social perception, also known as social competence, is the ability to take another's perspective and apply past learning to social situations (Semrud-Clikeman, 2007). Effective social perception relies heavily on social interpersonal and communication skills (Bergen & Woodin, 2011; Fletcher, 2011) and Theory of Mind. Within social perception two main subcomponents exist: Theory of Mind and emotional competence. Theory of Mind is the ability to see that others also have desires, emotions, and thoughts and that their actions are consistent with these (Wellman et al., 2001) and forms a crucial subcomponent of social perception (Wellman, Cross, & Watson, 2001; Wellman, 2010). Emotional competence skills, are also strongly tied to social perception skills and their development is linked (Semrud-Clikeman, 2007; Trentacosta & Fine, 2010). Both concepts strongly influence the development of social perception and difficulties in their development can hamper a person's social perceptive abilities, making it important to consider the development of both components alongside social perceptual abilities.

In infancy children begin to understand that their caregiver's responses to objects and stimuli is meaningful (Semrud-Clikeman, 2007). In the preschool years children begin to have the ability to manage their emotions independently from their caregivers (Fletcher, 2011). This progresses to the development of basic social skills at the start of school age, which is refined to effective social perceptual abilities into adulthood (Semrud-Clikeman, 2007) making the school years an important time for the development and refinement of social perceptual skills. Within social perception, Theory of Mind development begins at birth. Infants are able to follow gaze beyond barriers around 12 – 24 months (Wellman, 2010) and it undergoes a spike around the age of three with more advanced perspective taking skills (Bergen & Woodin, 2011). From age seven children are able to understand that people are still capable of thinking, even when they are not obviously appearing to do so, and false belief understand is established in most children. From this age, further development builds on previous learning until adulthood with a more nuanced understanding of subtleties in social inference, for instance, or reading emotion cues (Wellman, 2010). This therefore is a very critical age period for the development of Theory of Mind and social perception. Emotional competence in

children develops with age, with milestones around preschool and primary school age, and is linked with overall brain maturation (Bauer et al., 2011; Bergen & Woodin, 2011; Fletcher, 2011). After this point, similarly to the development of overall social perception, skills are refined until adulthood.

The development of social perception is also mediated by language abilities (Milligan, Astington, & Dack, 2007), executive functioning (Hala, Hug, & Henderson, 2003) and to a lesser extent attention abilities (Fine, Semrud-Clikeman, Butcher, & Walkowiak, 2008; Semrud-Clikeman, Walkowiak, Wilkinson, & Minne, 2010). Any upsets to the development of these other domains is likely to have a strong influence on the development of social perceptual abilities, making it a very sensitive domain to the effects of brain insults.

In summary cognitive development is characterised by a complex interplay between multiple areas of the brain working in tandem. In line with this, no area of cognitive functioning develops in a vacuum, with multiple domains building on the development of each other. Further to this, certain cognitive domains such as processing speed work to moderate overall development. This makes damage to any one area significant as it can have flow on effects to other areas of functioning. The overall development of cognitive functioning undergoes periods of rapid development from birth to early adolescence. After this stage development is less characterised by rapid increases, but instead builds and refines the previous skills and gains. This makes the period of early cognitive development critical, and any disruptions or toxic insults during this time are likely to have more serious consequences than in older children. The next chapter will review the existing literature on cognitive development and pesticide exposure and discuss the available evidence for the effects of exposure on the cognitive domains.

Chapter 5: Pesticide Exposure and Neuropsychological Development in Children

As discussed in Chapter three, children are at greater risk of the effects of pesticide exposure compared to adults (Goldman & Koduru, 2000). They are also more likely to be exposed to chronic low levels of pesticides through their play activities and inability to understand the risks associated with exposure (Roberts & Karr, 2012). Current research on the effects of pesticide exposure on children has suggested that chronic exposure can have effects on physical, behavioural and neurocognitive development (Jurewicz & Hanke, 2008; Liu & Schelar, 2012; London et al., 2012; Muñoz-Quezada et al., 2013; Sokoloff et al., 2016), however, overall consensus is mixed (Bouchard et al., 2011; Colosio, Tiramani, Brambilla, Colombi, & Moretto, 2009). This has resulted in arguments around whether the current regulation of pesticide use is ineffective in protecting children (Grandjean & Landrigan, 2006; Harari et al., 2010; Koger, Schettler, & Weiss, 2005). Research on pesticide exposure has focused mainly on the effects of acute exposure with clear health deficits identified. However as chronic low level exposure is more common in children (Roberts & Karr, 2012) research may be failing to adequately address an important facet of pesticide exposure. This chapter will begin with an examination of the seminal exploratory studies of pesticide exposure. It will then review the literature on physical brain development and then review the existing literature on the effects of chronic low-level pesticide exposure on the neuropsychological development of children. The existing literature on the effects of exposure on global Intelligence Quotient (IQ) will then be reviewed. Then, in keeping with the idea that cognitive functioning is not effectively captured by one overarching construct such as IQ, the effects of exposure on individual areas of cognitive and behavioural functioning will also be reviewed. Finally, the limitations of the current literature will be discussed.

Exploratory studies have shown a relationship between neuropsychological development and chronic low level pesticide exposure. A seminal exploratory study conducted by Guillette, Meza, Aquilar, Soto, and Garcia (1998) examined the effects of post-natal pesticide exposure on 4 – 5 year old Mexican children living in the Yaqui Valley. The valley is divided into two distinct population groups, one living in the foothills where animal agriculture dominates industry and the other in the

valley itself where horticulture is the primary industry. The children share similar genetic backgrounds, diets and social patterns with the primary distinction being their exposure and proximity to pesticides. Gillette et al developed a Rapid Assessment Tool for Preschool Children (RATPC), which measured motor coordination (catching a ball or raisins in a cup), visual-spatial perceptual abilities (drawing a person) and memory (digit repetition for verbal short-term memory and recalling what the reward for participating was after 30 minutes for prospective memory). Overall children from the high exposure group in the valley performed lower than their low exposure peers, especially in the person drawing and motor coordination tasks. A study conducted by Kuruganti (2005) replicated these results, looking at the effects of exposure in a sample of 1648 Indian children aged 4 – 5 years and 9 – 13 years. Children were grouped into low and high exposure groups, based on their proximity to high pesticide areas such as cotton plantations and administered a RATPC based on the one developed by Guillette et al. (1998). Children who were highly exposed to pesticides performed significantly lower than their peers in all domains, with motor coordination being the most affected area. Neither study used well-validated measures, which are sensitive to slight changes in cognitive functioning and did not include a thorough investigation of all the cognitive domains of functioning. Further while both studies aimed to investigate post-natal exposure given the high concentrations of pesticides found in the water and food supplies pre-natal exposure was also likely. This, combined with their exploratory nature limits the extent to which their results can be generalised. Nevertheless, their findings provide a useful starting point into the potential effects of pesticide exposure in children.

Animal studies also suggest that chronic low level exposure has an effect on neurodevelopment (Moser, 2007). However as exposure can have an effect even when no overt toxicity is present (Pope, Chakraborti, Chapman, & Farrar, 1992; Sanchez-Santed, et al., 2004) and its effects can be subtle, there is difficulty finding consensus to the true effects of low level exposure. Some researchers argue that no effects exist due to chronic low level exposure (Costa, 2006; Eaton et al., 2008). Whereas other researchers argue that further research looking at chronic low level exposure is still needed in both animals and humans (Eskenazi et al., 1999; Moser, 2007; Pope, 2010; Roberts

& Karr, 2012; Saillenfait et al., 2015). Given the mixed consensus around the effects of pesticide exposure and its harmful consequences this area needs further investigation.

Brain Development

Both animal and human studies using brain imaging support findings that prenatal pesticide exposure in children is associated with deficits in multiple areas of functioning. Mullins et al., (2015), studied the effects of prenatal organophosphate exposure on brain development in guinea pigs. Prenatal exposure was linked with spatial learning and working memory deficits on the Morris Water Maze and animals had decreased brain weight and volume. Deficits and structural changes were especially prevalent in the frontal regions of the brain and in the white matter of the amygdala and striatum. These areas are consistent with spatial learning and working memory difficulties. As processing speed is reliant on white matter integrity (Ferrer et al., 2013), this may potentially also have been affected.

In humans, Rauh et al. (2012) found effects on the brain development of children after prenatal exposure to chlorpyrifos, an organophosphate pesticide. The study used magnetic resonance imaging to investigate the effects of long term chronic chlorpyrifos exposure in a non clinical sample of 40 children aged 5.9 to 11.2 years. The participating children had comparatively low prenatal exposure as measured through maternal report and umbilical cord blood samples, however were in the upper tertiles for post-natal exposure levels. They found abnormalities in the brain regions which govern attention (posterior temporal regions and the precuneus); social cognition (mesial superior frontal gyrus, cuneus and precuneus); emotion and inhibitory control (gyrus rectus); and executive functioning (left superior frontal gyrus). These findings map onto previous research which has found effects on attention and inhibitory control. Similar to results from Bouchard et al., (2011), effects were reported at low concentrations of pesticides (Rauh et al., 2012). This suggests that even low levels of prenatal exposure may have an effect on brain development in children.

Intelligence Quotient (IQ)

Chronic low level pesticide exposure in the prenatal period and, to a degree, in the postnatal period has been found to be negatively associated with IQ in children. Bouchard et al. (2011) looked at both pre- and postnatal chronic organophosphate pesticide exposure. As part of a bigger study by the Centre for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), 329 children aged seven years on a variety of measures. Maternal urine samples were collected during pregnancy to measure pre-natal exposure and child urine samples were collected at regular intervals until age five as a measurement of post-natal exposure. Prenatal but not postnatal pesticide concentrations were negatively associated with scores on the WISC-IV, on all domains including Full Scale IQ. An effect for dose was found with children in the higher exposure groups scoring seven points below their low exposure counterparts (Bouchard, et al., 2011). As the Full-Scale IQ has a mean of 100 points (Wechsler, 2003a), a decrease of seven points is a large decrease in ability. Further, on a population level, this may affect neuropsychological profiles across the board with a decrease in the numbers of children falling both in the normal and superior ranges, while increasing the proportion of children who fall below the average range (Landrigan & Garg, 2002).

An earlier study conducted by Eskenazi et al. (2008) had reported similar results. They investigated the relationship of the PON1 genotype and pesticide exposure. The PON1 gene is associated with a vulnerability to exposure, and likely contributes to deficits in cognitive development. Overall, WISC-IV scores were lowest in children who had been exposed to pesticides prenatally and carried the PON1 gene, supporting the idea of both a vulnerability to exposure, and an effect of prenatal exposure on IQ in later life. Results from Viel et al., (2015) further support this relationship. They tested 287 children aged six who had been prenatally exposed to pyrethroids, on two indices of the WISC-IV; working memory and verbal comprehension. Results showed a relationship between children's levels of pesticide exposure, however contrary to the findings of Bouchard et al. (2011), no relationship was found with maternal levels. While Full-Scale IQ was not measured, the working memory and verbal comprehension indices are an important component of IQ (Wechsler, 2003b), making deficits in this area likely to have an impact on overall cognitive

functioning. A further study conducted by Rowe et al. (2016) provides further evidence for the link between prenatal pesticide exposure and IQ. As part of the CHAMACOS study501 children who were prenatally exposed to pesticides were tested. Two groups of children from the CHAMACOS study were involved with one group with known lower levels of post-natal exposure being used as a control group. Results suggested that residential proximity to agricultural use of both organophosphates and carbamates during pregnancy is associated with lower Full-Scale IQ scores as children develop. This effect persisted when poverty was controlled for, suggesting that irrespective of living situation children's cognitive abilities may be affected. Children who lived closer to pesticide using areas also had greater deficits, providing evidence of an effect for proximity, as children living closer had up to four points difference on the scales. A more recent study conducted by Gunier et al. (2017) also part of the wider CHAMACOS study found decreases of around 2.6 points on children's full-scale IQ scores on the WISC as a result of pesticide exposure. While a decrease of less than three points is close to normal variation in testing profiles it still points to some effect as a result of pesticide exposure and is a significant factor on an overall population level. Overall the studies suggest that prenatal pesticide exposure has an effect on IQ scores during a child's neuropsychological development.

While there appears to be a relationship between prenatal pesticide exposure and IQ, the picture is less clear for postnatal exposure. Bouchard et al. (2011) reported a clear effect of prenatal but not postnatal pesticide exposure on IQ. Conversely, the study reviewed above by González-Alzaga et al. (2015) reports the opposite result. An effect was found for prenatal exposure, but this increased with postnatal exposure. This is in line with a proposed cumulative effect of postnatal exposure (Butler-Dawson, Galvin, Thorne, & Rohlman, 2016; Rohlman, Lasarev, Anger, & Mccauley, 2007). A final study conducted by Abdel Rasoul et al. (2008) looked at cognitive functioning scores on child and adolescent farm workers in Egypt. Using subtests from the WISC, an effect of exposure was found, with children exposed for longer having greater deficits. While occupational exposure is likely to be larger than residential exposure, no cases of acute exposure were present in this study. This conflicting body of evidence suggests that there are possible effects of

postnatal exposure; however, the overall picture is unclear. As IQ is highly correlated with school achievement and later life outcomes (Lezak et al., 2012), a clearer understanding of the relationship between pesticide exposure and IQ is needed.

Attention

Attention is the domain of functioning most studied in relation to pesticide exposure. Looking at the effects of prenatal exposure on 323 children aged three and a half and five years in California, Marks et al. (2010) found an effect of both pre- and postnatal exposure on attention. Children's scores on the NEPSY visual attention subtest, parental reports from the CBCL and scores on the Conner's Kiddie Continuous Performance Test were associated with exposure levels at age five. However, no effect was found at age three and a half, a result possibly explained by the cumulative nature of chronic low-level exposure and differences in development at this age. Results also indicated that prenatal exposure was a predictor for ADHD, with one of the main features of ADHD being difficulties with attention (American Psychiatric Association, 2013). The link between ADHD symptoms and prenatal chronic pesticide exposure was also reported by Polańska, Jurewicz, and Hanke (2013) and, to some degree, by Fortenberry et al. (2014), further suggesting a link between prenatal exposure and attentional problems in children.

A similar clear effect of attention also exists for postnatal exposure. Both the exploratory studies conducted by Guillette et al., (1998) and Kuruganti (2005) suggest an effect of postnatal exposure on attention which is further supported in the literature. Looking at farm workers aged ten to eighteen years in Brazil using the Behavioural Assessment and Research System (BARS[14]), Eckerman et al. (2007) found similar results. Two groups, farm children (n=38) and urban children (n=28) were compared and an effect for exposure was found with farm children performing lower than their urban peers on all tests. The strongest effects were for attention and motor speed tests. A similar study used the BARS in Egypt with farm workers aged twelve to twenty one years (Rohlman et al., 2016).

[14] The BARS measures the following domains of functioning: attention, processing speed, memory, working memory (Northwest Education Training and Assessment, 2017)

Participants who were more highly exposed showed higher levels of deficits on all areas, suggesting a similar effect of dose as in the findings from Eckerman et al. (2007).

While occupational exposure is likely to lead to higher levels of exposure, an effect is also found for non-occupational exposure. Sánchez Lizardi, O'Rourke, and Morris (2008) found that environmental postnatal exposure had an effect on the attention, sequencing and mental flexibility abilities of 48 Hispanic children living in California. While only short-term exposure was investigated, results still provided evidence for the relationship between attention and exposure. A further study by Butler-Dawson, Galvin, Thorne, and Rohlman, (2016) looked at the effects of chronic postnatal exposure on 206 children aged five to twelve years living in an orchard community in the USA. An effect of exposure on BARS scores was found for attention and motor function, further supporting the link between attention and low levels of pesticide exposure.

Research investigating the link between ADHD and postnatal pesticide exposure also supports an effect for exposure. Bouchard, Bellinger, Wright, and Weisskopf (2010) investigated the potential relationship of post-natal pesticide exposure and the presence of ADHD symptoms. Using data from a structured behavioural interview with the child's parents the researchers found that greater amounts of pesticide metabolites in the child's urine were linked with increased risks of the presence of ADHD symptoms in eight to fifteen-year olds. Similar findings were reported by Wagner-Schuman et al. (2015). Looking at 687 children aged eight to fifteen years from the national health and nutrition examination survey in the USA they found a link between postnatal pesticide exposure and ADHD symptoms. While both boys and girls were affected, boys were found to be affected twice as much, a finding consistent with the normal gender differences in ADHD (American Psychiatric Association, 2013). Finally a review by Polańska et al. (2013) had similar findings, where a strong link between pesticide exposure and ADHD was found across studies reviewed. As attention deficits are a major component of ADHD (American Psychiatric Association, 2013), these studies further support the link between postnatal exposure and attention. Overall the literature suggests a clear link between both pre- and postnatal chronic low-level exposure to pesticides and attention.

Motor Skills

Motor skill is the other area of functioning most frequently researched in relation to chronic low-level pesticide exposure. Within the literature, a somewhat mixed opinion as to the effects of exposure also exists, with some studies reporting no effects. Looking at prenatal exposure to pesticides in Poland, Greenland and the Ukraine, Høyer et al. (2015) assessed the development of 1103 children aged 7 – 8 years through parental reported coordination problems and developmental milestones. No effects were found in this study for exposure. Work looking at the effects of prenatal pesticide exposure and cognitive development at age four by Puertas et al. (2010) also corroborates this finding. Using the McCarthy Scales of Children's Abilities to assess motor and cognitive abilities in 104 children in Spain, they reported a significant decrease in working memory skills, but not motor skills, suggesting that no effect may exist. However other studies suggest an effect of exposure on motor skills.

In Mexico, Torres-Sánchez et al. (2009) reported that while effects of prenatal exposure on motor skills were present up to 12 months, after this period pesticide exposure effects were no longer present. Findings from Llop, et al. (2013) looking at infant development are similar. Using the Bayley Scales of Infant Development, they found negative effects on psychomotor development as a result of prenatal but not postnatal exposure. This may indicate that age may have some impact on the effects of exposure, with older children being potentially less affected. However further studies, reviewed below, report effects in older children, making this relationship unclear.

Sex differences may also be present in the effects of prenatal pesticide exposure on motor skills. Andersen, Debes, Wohlfahrt-Veje, Murata and Grandjean (2015) used sub-tests from the WISC-R and the Stanford Binet IV to assess cognitive functioning as a result of prenatal pesticide exposure in 203 children aged 6 – 11 years. A sex effect on motor speed was found, with girls having lower scores on their motor speed. This is in contrast to research conducted by Boucher et al. (2013) who assessed the effects of prenatal exposure to pesticides on the development of children aged 18 months in the French West Indies. Results indicated that fine motor control was significantly associated with pesticide exposure, however only in boys. While both studies used children of

different ages and different tests, the contradictory results suggest that effects may be sex selective, however the relationship is still unclear.

Finally, a difference in effects on broad and fine motor skills has also been observed. Despres et al. (2005) reported an effect of prenatal organochlorine exposure on 110 preschool Inuit children in Canada. Both gross and fine motor skills were assessed, and no effects were present on gross motor skills. Fine motor skills were affected by exposure even at levels too low to cause toxicity supporting the hypothesis that effects are present without visible toxicity effects. Their results indicate that the effects of pesticides on motor skills may not affect broader skills. This is supported by work from Handal, Lozoff, Breilh and Harlow (2007) who assessed 283 children aged 3 – 61 months living in Ecuador. Using the Ages and Stages Questionnaire, the authors found an effect of organophosphate and carbamate exposure on children's motor abilities. An effect of exposure was found with children living in the higher exposure areas who scored lower on their fine motor skills. A similar study which was also conducted in Ecuador using the Ages and Stages Questionnaire found an effect of exposure in children's fine motor skills (Handal, Lozoff, Breilh, & Harlow, 2007). Children who spent longer hours playing outside, particularly near water in areas of high pesticide use, performed lower on fine motor skill tasks. These results are also consistent with work by Dallaire et al. (2012) who found an effect of exposure on the motor development of 7-month old infants using the Brunet-Lezine test for motor development. Results indicated that prenatal exposure to organochlorines was associated with lower fine motor skills. Finally, the Boucher et al. (2013) study also found an effect on fine motor skills. This indicates that prenatal exposure to pesticides affects fine motor skills such as reaction times or hand control, as opposed to broader motor skills, such as running or jumping.

While few studies have investigated the effects of postnatal exposure on motor skills, consensus does point to an effect in children, again moderated by age. Studies by both Torres-Sánchez et al. (2009) and Llop et al. (2013) report no effect of postnatal exposure on infant motor development. As both animal (Chakraborti et al., 1993; Pope & Liu, 1997) and human (Shafer et al., 2005) studies report lower effects of chronic low level postnatal pesticide exposure in infants, it is possible that very young children's (0 – 4 years old) motor skills are not affected. This is supported by

work from Handal et al. (2007) who found an effect of exposure on motor speed in children from the age of 24 months onwards. In older children, Butler-Dawson et al. (2016) reported an effect on motor speed in children aged 5 – 12 years old living in an orchard community. Similarly Eckerman et al. (2007) reported motor skills as one of the most affected areas of functioning in farm workers aged 10 – 18 years. This is consistent with postnatal exposure having cumulative effects over time, whereby the effects seem to become greater over time. While consensus to the exact effect of chronic pesticide exposure on motor skills is still unclear, the literature on both prenatal and postnatal exposure suggests that an effect does exist, which needs further exploration.

Processing Speed

While under researched, an effect of both pre- and postnatal exposure on processing speed is suggested. González-Alzaga et al. (2015) investigated the effects of both pre- and postnatal pesticide exposure on 305 children aged six to eleven years in Spain. Scores on the WISC-IV were associated with prenatal exposure, with a larger effect in boys on processing speed; however, effects were larger when children were also exposed postnatally. This is potentially due to the cumulative nature of chronic low-level exposure, whereby effects become worse with greater duration of exposure. Processing speed forms an index of the overall Full-scale IQ (Wechsler, 2003a) and deficits in this score have been linked with pesticide exposure further suggesting that processing speed may be affected. However, an overall lack of studies investigating pesticide exposure and processing speed specifically makes this relationship unclear. As processing speed works to moderate many of the other cognitive domains, it is a crucial area for further investigation to more fully understand how neuropsychological development is affected by pesticide exposure.

Memory

The effects of chronic low level prenatal pesticide exposure on memory were investigated by Ribas-Fitó et al. (2006). Looking at the abilities of 475 children aged four years on the McCarthy Scales of Children's abilities, they found that prenatal exposure to pesticides was negatively associated with verbal, memory and perceptual performance skills. Associations were greater amongst girls. No studies were found that looked at the effects of postnatal pesticide exposure on memory. As

memory is one of the most important domains of cognitive functioning (Lezak et al., 2012), deficits in this area are likely to have serious consequences for later learning, making this an important area for further investigation.

Verbal Skills and Language

Verbal skills are an essential component of overall functioning and have been found to be affected by prenatal pesticide exposure. Handal, Harlow, Breilh, and Lozoff (2008) investigated the effects of prenatal exposure on neurodevelopment on 121 children living in Ecuador. Prenatal exposure was associated with delayed development in both communication skills and visual skills. The WISV-IV verbal comprehension domain has also been negatively linked with prenatal exposure (Viel et al., 2015). Consistent with this, the work by Ribas-Fitó et al. (2006) also found a negative association with pesticide exposure and children's verbal skills. Finally, Andersen et al. (2015) found impairments in language abilities in 6 – 11 year old female children, suggesting a possible link between exposure and language, however only in girls. While a link between prenatal exposure and verbal skills is suggested in girls, a gap exists in the literature on the effects of postnatal exposure to more fully understand the potential sex specific relationship.

Visuo-Spatial skills

The work by both Ribas-Fitó et al. (2006) and Handal et al. (2008) found an effect of prenatal exposure on visuo-perceptual skills. Visuo-Spatial skills also make up a domain of cognitive functioning and overall Full-scale IQ on the WISC-IV (Flanagan & Kaufman, 2004). Multiple studies looking at IQ in relation to exposure have found a negative effect on visuo-spatial skills due to chronic prenatal pesticide exposure (Bouchard, et al., 2011; Eskenazi et al., 2008; Rowe et al., 2016), suggesting a link between exposure and visuo-spatial skill deficits. Again, there is no available literature on the effects of postnatal chronic low-level pesticide exposure.

Working Memory

While the majority of research reports a relationship between exposure and working memory, Carier et al. (2016) found no relationship, inconsistent with other studies. The research described

above by Puertas et al. (2010) found a significant negative association between prenatal pesticide exposure and working memory skills. Exposure was associated with a five-point drop in working memory abilities on the McCarthy Scales of Children's Abilities, which is argued to present a large potential effect on children's future schooling abilities. Work by Viel et al. (2015) also suggests an effect of prenatal pesticide exposure on working memory skills on the WISC-IV working memory index at age six. Results were found for prenatal child levels of pesticide exposure; however maternal exposure levels were not significantly related to future effects. This is likely due to differences in the child's dose weight ratio compared to the mother, where any dose exposure for the child is comparatively larger. Finally as with visuo-spatial skills, working memory forms a domain of functioning in the WISC-IV Full-Scale IQ score, which has been found to be affected by chronic pesticide exposure (Bouchard et al, 2011; Eskenazi et al., 2008; Rowe et al., 2016). This indicates that, although research is mixed, working memory is likely also negatively affected by prenatal pesticide exposure. Similarly, to the other domains of functioning no literature on the effects of postnatal pesticide exposure is available.

Limitations

There are a number of limitations within the existing literature on the effects of pesticide exposure on neuropsychological development. The chief of which is the limited number of studies investigating the effects of chronic low-level pesticide exposure. This is echoed in many review studies (e.g., Eskenazi et al., 1999; Moser, 2007; Pope, 2010; Roberts & Karr, 2012; Saillenfait et al., 2015) and an even more pronounced research gap exists for postnatal exposure. Many areas of cognitive functioning, including memory, visuospatial skills and working memory have not been researched in regard to postnatal exposure. Further, in the areas of functioning where studies do exist, with the exception of attention, so very few studies make it difficult to fully understand the potential effects of postnatal exposure. This is compounded by the limited studies looking across the age ranges, with most studies looking at either very young children (below five years of age) and adolescents (age twelve onwards) leaving a large gap in the literature on the effects on children aged

six to eleven years. As a child's age has an impact on their levels of exposure, and the effects of that exposure vary due to a number of different factors, including their ability to process pesticides, it is difficult to fully understand the impact of pesticide exposure on children's functioning. Further, most children in this age range are beginning their education, and deficits during this time can have serious consequences for later learning and outcomes, making this a crucial area for investigation.

While research has focused mainly on motor skills and attention, some domains are under- or not at all represented. Two major areas of functioning, social perception and executive functioning have not been researched in regard to pesticide exposure. As attention (a closely related domain to executive functioning,) and language (closely related to social perception) have been found to have some effects it stands to reason that social perception and executive functioning may also be affected. Further, some domains such as processing speed have flow on effects on a child's other cognitive abilities, making it crucial to understand any effects on this area to better understand the overall impact of exposure on child neuropsychological development.

Finally, as the effects of chronic exposure have been found to be more subtle than acute exposure there is a strong need for the use of measures which are designed to measure small deficits. While many studies used measures such as the BARS or WISC, which have been extensively validated and are able to detect subtle effects, this is not the case for all studies. The use of parental reports or self-designed measures such as in the work by Guillette et al. (1998) are unlikely to accurately capture the more subtle potential deficits associated with exposure. This creates the need for further studies which utilise measures which are validated in their ability to detect subtle deficits in cognitive performance.

These limitations of the current literature point to a clear gap and need for further research looking at the effects of exposure in children, especially in the six to eleven years age range. As knowledge is argued to be critical in the prevention of harm (Grandjean & Landrigan, 2006), a gap in the current literature may ineffectively inform regulation and safety practices. This is particularly pertinent in the New Zealand context, as many previous studies have been conducted in countries with

a different exposure profile, leading to little knowledge about the potential effects in New Zealand. These limitations also reveal a need for further research looking at many of the under researched domains such as social perception, executive functioning and processing speed to both get a clearer picture of the effects of exposure and better understand the potential flow on effects of any deficits.

Chapter 6: Hypotheses

The literature suggests that exposure to pesticides is associated with negative effects on neuropsychological development in children. The potential effects of both pre- and post-natal to pesticides will be investigated using the hypotheses listed below. Exposure will be measured primarily using proximity which is suggested to be one of the biggest potential exposure pathways. It will be measured using dust samples, and current proximity to both agricultural and recreational areas. Lifetime exposure to agricultural areas as measured through length of time spent living on farms will also be used to investigate the potential for cumulative effects. Three main hypotheses will be examined in the current study. The first is general as follows:

1) There will be a significant negative effect of pesticide exposure on cognitive functioning in children aged six to eleven years in New Zealand.

In line with the domain cantered view of cognition hypothesis one is further broken down to include the following cognitive domains:

a) attention
b) motor speed.
c) processing speed.
d) memory
e) working memory
f) language
g) executive functioning
h) social perception

The basis for hypothesis one, is that the literature on the effects of low level pesticide exposure suggests that there is a negative association between exposure and some areas of cognitive development in children. The current study will be the first to assess the effects of pesticide exposure on children in New Zealand. Previous studies have been conducted in countries with different exposure profiles due to their different regulations, geography, and pesticides used which makes it

difficult to generalise their findings within New Zealand. While trends can be broadly applied, specific effects are difficult to translate. As research informed regulations are one of the most important factors protecting people from the potential harmful effects of pesticide exposure, it is important that up to date research within New Zealand is available. Thus, the current study will help contribute to the public health of New Zealand through providing information on the effects of pesticide exposure in a New Zealand context. Given strict regulations around pesticide use in New Zealand, it is anticipated that any effects will be smaller than those found in developing countries. However, as effects have been found in countries with tight regulations it is hypothesised that there will be a significant effect found in the current study. In the current study, based on a domain centred view of cognition (Lezak et al., 2012), cognitive functioning is divided into the following categories: attention, motor speed, working memory, processing speed, memory, language, executive functioning, and social perception. As discussed in chapter five, research has focused primarily on attention and motor speed, with few studies looking at the effects of exposure on memory, language, working memory, and processing speed. Further to this, executive functioning and social perception have not yet been investigated in relation to exposure. As cognitive development and functioning relies on the complex interplay between multiple different domains (Weiss, 2000b), this limited focus can underestimate the overall effects of pesticide exposure on cognition. The current research will extend the knowledge in this area through looking at the effects of exposure on multiple domains through examination of the following hypotheses

The second hypothesis is as follows:

Complex attention types (divided and selective attention) will be more negatively affected by pesticide exposure compared with the simpler attention types (focused and sustained attention).

The basis for hypothesis two is that attention has been found to contain four subtypes: focused, selective, sustained, and divided attention. While there is a suggestion that complex cognitive tasks are more affected by pesticide exposure, no research has investigated whether this is also replicated in attention. As part of this hypothesis, the question as to whether pesticide exposure affects visual and

auditory attention differently will also be considered as this has not been previously examined. There is some suggestion that the development of both types emerges over different developmental time periods making it important to investigate any differences in potential deficits.

The third and final hypothesis is as follows:

2) There will be a significantly stronger negative effect of exposure on cognitive functioning in children who have resided their whole lives in either rural or farming areas, with the largest negative effect being present for children residing in farming areas.

Exposure will be measured using questionnaire data gathered as part of the larger study (the questionnaire will be discussed in chapter 7) and will primarily be based on the proximity exposure pathway. Previous studies have linked the proximity pathway with increased pesticide exposure levels however research has not looked at how this specific pathway is linked with cognitive development. Exposure will be further broken down into three subcategories based on the area the child has been residing in: urban, rural, and farming. Proximity to recreational areas such as parks and sports grounds will also be used to measure proximity. As pesticide exposure has a cumulative component (Abdel Rasoul et al., 2008a; Butler-Dawson et al., 2016; Rohlman et al., 2007) it is expected that children who have lived longer in farming or rural areas will have larger deficits. As farming areas have even greater proximity—and increase the risk of exposure through drift and skin contact—it is anticipated that these areas will demonstrate the greatest effects.

In summary, the current study aims to build on the gaps in the literature by investigating the effects of pesticide exposure on the cognitive development of children aged six to eleven years. It also aims to investigate the effects of exposure on a more complete picture of cognitive functioning through examining multiple cognitive domains. Chapter 7 will describe the study design and methodology as well as provide rationales for the chosen measures.

Chapter 7 Method

Ethical Considerations

Ethical approval for the study was granted by the Health and Disability Ethics Committee (HDEC)[15] in 2013 (application ref 13/CEN/134). The ethics proposal attached in Appendix D was completed by the CPHR before the author became involved with the study. No further ethics approval was needed for the current thesis. The privacy of each participant was ensured through allocation of a code number. No personally identifying information of any kind has been used within the current thesis or the wider study. Participants were advised that they were able to withdraw from the study without reason at any stage. They were also asked for assent before participation in each of the three stages of the study. All physical copies of data were stored in a locked filing cabinet within the CPHR, with only researchers involved with the study having access to this. All electronic data was securely stored on the CPHR servers, under a password protected drive.

The BASC measure contained questions around the child's safety and mental health. It was anticipated that some profiles would contain scores on these items, henceforth referred to as critical items. Answers on these items are typically indicative of areas of concern, for example an endorsement of the child having thoughts around suicide. When critical items were endorsed, a member of the research team with clinical psychology experience contacted the parent. Information around where to access support was provided as appropriate, and if needed a referral was made to the Massey Wellington Psychology Clinic. In total 54 calls were made, 32 by the current author. The majority of phone calls did not require information or further follow up. Only one phone call necessitated a referral to the Psychology Clinic, and five phone calls resulted in information being provided on where to find support.

It was not anticipated that any of the phases of the project would cause discomfort or distress although it was anticipated that parents would be interested in their children's performance on the neuropsychological testing components from Phase II. Parents were able to indicate their interest in

[15] The Health and Disability Ethics Committees (HDECs) are Ministerial committees (established under section 11 of the New Zealand Public Health and Disability Act), whose function is to secure the benefits of health and disability research by checking that it meets or exceeds established ethical standards (Ministry of Health, 2017).

feedback on a section on the consent forms. Written feedback was provided by Professor Leathem, once all of the neuropsychological testing was completed. Participants will also be contacted and provided a summary of findings once the overall study concludes if they have indicated interest.

Cultural consultation was sought throughout the project, including when selecting the measures, with the Māori cultural advisor/Kaimatai Hinengaro Matua in the Massey University School of Psychology, Dr. Simon Bennett, who was also available for ongoing consultation and supervision throughout the project.

Research Design

Overall Project

As described in Chapter one the current thesis was conducted as part of a larger CPHR-led study and a short summary is provided here, highlighting the current author's involvement in the first two phases of the project. The overall project was divided into three phases, each with separate aims. The current author's involvement with the project began in 2015, one year after the study had commenced. In that year, ethics approval, the development of the phase I questionnaire, the recruitment of most of the Wellington-based schools, and the outline for the overall project had been already accomplished. The current author's involvement coincided with the development of the neuropsychological testing battery in early 2015. The current author was primarily involved in Phase II– recruitment, development of the refusal questionnaire and in providing conceptual and practical assistance with the BASC and the BRIEF. Tables 1 and 2. below provide a summary of the procedures in the first two phases of the larger study and highlight the current author's involvement.

Table 1

Outline of activities involved with Phase I of the larger study

Recruitment	Phase I Questionnaire	Refusal Questionnaire	BASC and BRIEF
Initial contact with principals (June 2014 – June 2016)	Initial Development (February 2014 – June 2017)	Initial Development** (August 2016)	Mailing of forms (June 2014 – March 2017)
Meeting with principals (February 2015 – June 2016) • Wellington Region (4)** • Hawkes Bay Region (10)** • Nelson Bays Region (3)** • Horowhenua Region	Mailing of questionnaire (June 2014 – March 2017)	Phone Administration (August 2016 – March 2017)	Follow up of forms (June 2014 – March 2017)
Distribution of consent forms to parents and students (June 2014 – December 2016)	Phone administration of missing items (June 2014 – March 2017)	Marking and Scoring (August 2016 – March 2017)	Phone administration of missing items (June 2014 – March 2017)
School presentations and information sessions (May 2016 – June 2016) • Wellington Region (3)** • Hawkes Bay Region (4)** • Nelson Bays Region (1)** • Horowhenua Region	Marking and Scoring (June 2014 – March 2017)		Marking and Scoring (June 2014 – March 2017)
Follow up calls for unreturned forms and questionnaires (June 2014 – March 2017)			Critical item calls (32)** (March 2015 – July 2016)
Science activities February 2016 – December 2016)			

** indicates areas in which the current author was involved in

Table 2

Outline of activities involved with Phase II of the wider study

Development of testing battery**	Neuropsychological Testing**	Scoring and Providing Feedback**
Literature Review** (April 2015 – May 2015)	School meetings and organising logistics** (June 2015 – December 2016) Test Administration (June 2015 – December 2016) • Wellington Region** • Hawkes Bay Region** • Nelson Bays Region** • Horowhenua Region	Hand scoring of tests** (June 2016 – January 2017)
Selection of measures** (May 2015)		Double scoring of tests for consistency** (June 2015 – December 2017)
Cultural consultation** (May 2015)		Creating feedback template** (August 2016)
Revision of battery** (June 2015 – July 2015)		Providing feedback to parents** (August 2016 – January 2017)

** indicates the areas the current author was involved in

Current Thesis

The study described in this thesis used a cross-sectional design. Analysis was conducted between groups with hypothesised different levels of pesticide exposure (urban, rural, farming) to assess the effects of exposure on neuropsychological functioning. A power analysis was conducted with G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) to calculate the minimum sample size needed to achieve an alpha level of 0.05. A minimum sample size of 225 participants was required to achieve a power level of 0.95 with three groups (urban, rural and farming) and eight dependent variables (the eight cognitive domains listed in the previous chapter). The current study utilises all 450 Phase II participants which will ensure that there are sufficient participants. Exclusion criteria were based on any historic factors in the child's life which are likely to impact on their cognitive functioning exclusive of pesticide exposure. Children with a diagnosed mental health condition and development disorders were excluded from the current study. As the neuropsychological tests require a reasonable understanding of English, non-English speaking individuals were not eligible to participate in the study. Two children were excluded from the current study—the first had a recent

diagnosis of ADHD and was not able to complete testing due to his hyperactivity, the second child had a diagnosis of fragile X syndrome and had severely reduced cognitive functioning.

Recruitment

Participants were recruited for the larger study through schools in the North and South Island of New Zealand. Schools were selected based on their location, i.e., on the basis of their likely exposure to pesticides. Schools were also recruited based on decile[16] (to ensure an even spread of school deciles to control for socio-economic status). Their proximity to areas associated with pesticide exposure was identified by the CPHR using the online mapping program Koordinates, which allows for an overlay of farming areas with schools in an area (Koordinates Ltd, 2015).

Initial recruitment focused on the Wellington and Hawkes Bay regions. Due to difficulties in recruiting enough participants for phase I of the study, recruitment was extended to both the Nelson Bays and the Horowhenua regions. Both regions have a high density of horticultural farms and vineyards. Schools were again recruited based on both school deciles and their proximity to areas associated with pesticide exposure. In total 30 schools participated in the study and their details are in table 3 below. For privacy reasons each school has been assigned a code number.

The principal of each school was contacted via email (accessed through school websites) by the study coordinator. Information about the study was provided (Appendix F) and principals elected to contribute. A further face to face meeting to answer questions and explain the study in more detail was arranged. One of the doctoral students and the study coordinator attended these meetings.

Once a school had agreed to participate, information packs were distributed to children at assemblies to take home to their parents. The packs contained information sheets about the study, consent forms and a postage paid return envelope. A drop off box was also provided to each school and interested parents were able to return their consent forms to this box or by mail. Once parents elected to participate they were then posted the questionnaire for the first phase of the study. The

[16] Lower deciles typically indicate lower socio-economic status.

questionnaire is 24 pages long and contained questions related to pesticide exposure, alongside collecting demographic data. A copy of the questionnaire can be found in Appendix A. The two behavioural measures, the BASC and the BRIEF, were also included in the envelope. Parents were able to return the questionnaire either by post (a postage paid envelope was provided) or in the drop off box at school. No electronic versions of the questionnaire were used.

Table 3

Demographic information about participating schools

School ID	Region	Decile	Roll
1	Wellington	10	200
2	Wellington	7	130
3	Wellington	10	84
4	Wellington	7	454
5	Wellington	4	280
6	Wellington	9	209
7	Wellington	10	163
8	Wellington	8	350
9	Wellington	4	335
10	Wellington	9	192
11	Hawke's Bay	10	550
12	Hawke's Bay	8	80
13	Hawke's Bay	5	140
14	Hawke's Bay	3	100
15	Hawke's Bay	2	283
16	Hawke's Bay	4	166
17	Hawke's Bay	5	580
18	Hawke's Bay	1	270
19	Hawke's Bay	7	230
20	Hawke's Bay	10	440
21	Horowhenua	9	234
22	Horowhenua	6	180
23	Nelson Bays	7	317
24	Nelson Bays	9	126
25	Nelson Bays	8	104
26	Nelson Bays	4	120
27	Nelson Bays	5	101
28	Nelson Bays	3	260
29	Nelson Bays	9	87
30	Nelson Bays	9	295

Due to low levels of recruitment across all schools, talks were held at assemblies and in classrooms to further advertise the study. Talks were held by one of the assessors and the study coordinator. The talks were advertised in school newsletters inviting parents to attend. A copy of the presentation can be found in Appendix G. At these talks children were also provided with a further consent form and introductory letter. Talks were five to ten minutes in length and aimed to explain the purpose of the study and were only held once at each school to minimise disruption. Two parent information sessions were also held at two schools (school 16 and 19) in an effort to increase recruitment numbers. These talks were attended by the study coordinator, Professor Douwes from the CPHR, and the author of this thesis. Attendance was two and three parents respectively. Due to low turn-out at these events, no further information sessions were held.

Parents who had submitted a consent form but not returned the questionnaire also received two reminder phone calls from the study coordinator to submit the questionnaire. This took place around one month after the consent form was received and the second call around three months after submitting the consent forms. Parents were also given the option to have the questionnaire administered via phone at this stage. No parents elected to take this route.

Parents were able to withdraw their consent at any stage. In total 275 parents withdrew from the study.Parents who did not elect to participate any further after submitting their consent forms were contacted by the study coordinator. With consent, they were administered the refusal questionnaire (found in Appendix B) over the phone. This questionnaire was developed to control for any systematic response bias and to check that the demographics of the participants who dropped out where the same as those of the study participants. The refusal questionnaire was developed by the current author and the study coordinator using a mixture of items from the BASC and BRIEF forms to screen for differences in behavioural problems in the current sample. The questionnaire took no more than five minutes to administer. Data from this questionnaire was not used in the current thesis.

Compensation

Participating schools were offered $200 in the form of a voucher to spend towards school equipment. A science activity was also offered to each school, where the study coordinator held a two hour long session with students. Science activities aimed to teach children the basics about the brain, the importance of being safe and looking after the brain and healthy eating, with an emphasis on washing fruits and vegetables. Individual children were also offered a small item of stationery (pens, pencils and erasers) for their participation in the neuropsychological testing.

Measures

Test Selection

In line with previous research and the research questions outlined in chapter six, tests were selected to assess the following cognitive domains: language, memory, attention, executive functioning, working memory, social perception, motor speed, and processing speed. Tests also needed to be suitable for administration in a variety of locations, and require little specialised equipment. They also needed to take no longer than 60 minutes to administer in total, to minimise disruption at the school. Table 4 displays the tests considered, and the final selected tests.

The tests used were selected through a committee approach. The panel consisted of the three researchers from the School of Psychology involved with the study and Professor Leathem. The committee used the following criteria when selecting tests:

a) Sound psychometric properties
b) Designed for use with children aged 6 – 11 years
c) Required very little specialised equipment
d) Measured the domains of interest – with an emphasis on attention and executive functioning
e) Together took no longer than 60 minutes to administer.

As discussed in Chapter 4, many previous studies reported a relationship between the attention domain and pesticide exposure. For this reason, attention was emphasised through the selection of multiple tests measuring this domain. Executive functioning was also emphasised.

Table 4

Tests reviewed for the testing battery

Cognitive Domains	Tests considered	Tests selected
Memory	• Rey Auditory Verbal Learning Test • Rey Complex Figure Test • Narrative Memory (NEPSY) • Memory for Faces (NEPSY)	• Narrative Memory • Memory for Faces
Language	• Comprehension of Instructions (NEPSY) • Similarities (WISC) • Vocabulary (WISC)	• Comprehension of Instructions
Attention	• Sky search (TEA-Ch) • Map Mission (TEA-Ch) • Score (TEA-Ch) • Walk/Don't Walk (TEA-Ch) • Inhibition (NEPSY) • Auditory Attention and Response Set (NEPSY)	• Sky Search • Inhibition • Auditory Attention and Response Set
Working Memory	• Spatial and Listening Recall (AWMA) • Digit Span (WISC)	• Spatial and Listening Recall*
Motor Speed	• Finger Tapping (NEPSY)	• Finger Tapping
Processing Speed	• Coding (WISC) • Symbol Search (WISC)	• Coding
Social Perception	• Affect Recognition (NEPSY)	• Affect Recognition
Executive Functioning	• Theory of Mind (NEPSY) • Animal Sorting (NEPSY) • Trail Making (DKEFS) • Verbal Fluency (DKEFS) • Tower Test (DKEFS)	• Theory of Mind • Animal Sorting

* This test was replaced with the Digit Span task after a review

Cultural input was sought during the test selection, with a focus on language that is appropriate in New Zealand. Names and some terms used were substituted for versions more commonly used in New Zealand, and can be found in Table 5.

Table 5

List of replacement terms and names used

Item	Original Term	Supplemented Term
Item 1	André	Andrew
Item 2	Mom	Mum
	Ming	Mandie
	Sheryl	Sophie
Item 5	Luz	Liz
	Brandon	Matthew
Item 7	Mom	Mum
	Reggie	Reagan
	Audrey	Ashleigh
Item 8	Fun House	Haunted House
Item 9	Eric	Aaron
Item 10	Laurie Lamb	Laura Lamb
Item 12	Recess	Morning Tea
	Denise	Daisy
Item 13	Mama	Their Mum
Item 14	Laurie Lamb	Laura Lamb
Item 11	Uncle Carlos	Uncle Charlie

Finally, the order of test administration was carefully discussed to minimise the influence of practice or interfering factors. As per the NEPSY manual (Korkman, Kirk, & Kemp, 2007a) a twenty minute gap was left between the immediate and delayed components of the Memory for Faces subtests.

In the original meeting the Spatial Recall and Listening Recall subtests from the AWMA were selected to be part of the testing battery. Overall 11 assessments with these two tests were conducted. Both tests took about 15 minutes total to administer, often bringing the total testing time to

be one hour and fifteen minutes. Further, children struggled to understand the provided recorded instructions, which often needed to be replayed multiple times.

After discussions, the Digit Span subtest from the WISC-IV was agreed as a suitable substitute for the AWMA being quicker and easier to administer, as well as being a robust measurement of working memory. The final tests were administered in the following order:

1) Sky Search
2) Memory for Faces – Immediate
3) Auditory Attention and Response Set
4) Digit Span
5) Narrative Memory
6) Inhibition
7) Finger Tapping
8) Coding
9) Memory for faces – Delayed
10) Comprehension of Instructions
11) Affect Recognition
12) Theory of Mind
13) Animal Sorting

The psychometric properties and validity of the neuropsychological testing systems the subtests were selected from are discussed below[17].

A Developmental NeuroPSYchological Assessment – II (NEPSY-II)

The NEPSY-II consists of 36 different subtests measuring different aspects of cognitive functioning in children aged 3 – 16 years (Korkman et al., 2007a) and is based on Lurian principles of functional systems (Matthews, Riccio, & Davis, 2012). Subtests in the NEPSY-II are organised around the following six domains of function which are theoretically based; Attention and Executive Functioning, Language, Memory and Learning, Visuospatial Processing, Sensorimotor and Social Perception (Korkman et al., 2007a). This ensures that the NEPSY-II assesses a wide spectrum of functioning in children. The NEPSY-II has been reported to have excellent test-retest and interrater reliability (Brooks, Sherman, & Strauss, 2010; Kemp & Korkman, 2010; Korkman, Kirk, & Kemp, 2007b; Matthews et al., 2012) indicating that it is a reliable measure of children's neurocognitive abilities.

For use in clinical settings the NEPSY-II manual recommends specific testing batteries to target specific referral questions or concerns, (Korkman et al., 2007b). For assessment in general settings the manual recommends use targeted subtests to capture areas of interest. The current study did not use any of the prescribed batteries, and instead specific subtests were chosen for their ability to assess the domains of interest for the research study.

Auditory Attention and Response Set (NEPSY-11): This subtest measures auditory sustained and selective attention through the use of an audio recording of words. In the Auditory Attention condition, the child is presented with four circles (blue, black, red and yellow) and instructed to point to the red circle whenever they hear the word red. A practice list of words is read to the child, and any wrong responses are corrected. An audio recording of a longer list of words is then played for the child. The assessor notes down the child's responses for each word on the recording. There is no early termination condition, and off task behaviours are also recorded by the assessor.

[17] All measures used scaled scores to report results to allow generalisability between ages. Scaled scores have a mean of 10, standard deviation of 3 and range from 1 to 19, On the tests used a higher scaled score indicates better performance.

The response set condition also uses the same four coloured circles, however the child is instructed to point to the yellow circle when they hear red, to the red circle when they hear yellow and the blue circle when they hear blue. A second practice list is read to the child with incorrect responses being corrected as they occur. An audio recording of a longer list of words is then played with the child's responses being noted down as in the Auditory Attention Condition. There is no early termination condition. This test is only administered to children aged seven and upwards.

Theory of Mind (NEPSY-11): This subtest measures the social component of the executive functioning domain through both a verbal and contextual component. In the verbal component children are presented with numerous scenarios which require them to think from another person's perspective. Scenarios also include common phrases such a "two peas in a pod" accompanied by a picture which require rational thinking to decipher the correct meaning. The test is terminated if the child provides four consecutive incorrect responses. There are three age related start points for children aged 5 – 6 years, 7 -8 years and 9 – 16 years. Scores on these items are totalled to calculate a score for the child's verbal theory of mind abilities.

The contextual task presents the child with seven drawings depicting a girl in different situations. Each scenario is paired with four different pictures of the child's face, and the child is instructed to choose the face that best describes how Julia is feeling in the situation. The first scenario is used as a teaching example, with incorrect responses being corrected. No feedback is given in the subsequent six trials. Scores on this component are added to the verbal component scores to obtain a total Theory of Mind score for each child.

Animal Sorting (NEPSY-11): This subtest measures the cognitive component of executive functioning through the use of a card sorting test in children aged 7 – 16 years. The child is presented with eight cards, and asked to make two groups of four cards where each set has one detail the same across them. There are 13 possible combinations. After a teaching example where the assessor demonstrates making a set of big and small animals the child is asked to make more groups. Children are given six minutes to complete this task, with the assessor stopping the time to record the sets made

by the child and then resuming the clock. The test is either self-terminated by the child when they state that they have found all the combinations, when there is no response after two minutes, or when the time has elapsed. The child's errors, either through repetition or creation of novel sets, are totalled to obtain an error score alongside their overall animal sorting score.

Comprehension of Instructions (NEPSY-11): Comprehension of Instructions assesses the child's language ability through their ability to accurately process verbal instructions. Based on the child's age they are presented two separate conditions. Children aged 6 – 16 years are presented with a sheet of differently coloured circles and crosses. Children are asked to point to the shapes that the assessor names, with instructions becoming increasingly complex. The test is discontinued after seven consecutive incorrect responses. Further to this, if children aged six and upwards do not answer the first two items correctly, items from the condition for younger children are presented until two consecutive correct responses are received. The test is then resumed from the first incorrect response. This ensures that children understand the test instructions and are making errors due to their language abilities alone.

Finger Tapping (NEPSY-11): The Finger Tapping subtest measures the child's motor speed through their speed at tapping together their fingers. In this test children are instructed to tap their index finger and thumb together as quickly as possible while being timed. The test is terminated by the assessor after 20 correct repetitions or 60 seconds have elapsed. Both the child's dominant and non-dominant hands are assessed. Children are scored based on the time taken to complete 20 repetitions.

Memory for Faces and Memory for Faces Delayed (NEPSY-11): Both tests assess visual memory, with the delayed condition assessing long term visual memory. The child is presented sixteen pictures of children's faces and asked to remember each one and identify the sex of the child. The child is then shown three photographs at a time and asked to point to the child that they remember seeing. The test terminates after all faces have been presented.

The delayed condition is administered 15 – 25 minutes after the original Memory for Faces task. Again, three photographs are shown at a time and the child is asked to identify which child they

saw earlier. Correct responses are recorded and totalled with responses on the Memory for Faces task to provide an overall score.

Narrative Memory (NEPSY-11): Narrative memory measures the child's verbal memory skills through their ability to remember a short passage. There are two versions, one for children aged 6 -10 years and one for children aged 11 – 16 years. The passage for children aged 6 – 10 years is about a young boy and his dog, and children are asked to recall as many of the details are possible. For any details missed children are presented with prompt questions. A set of twenty recognition items are then presented. Three scores are calculated: a free recall score, a combined free and question score, and a prompt question score. For children aged 11 – 16 years a longer passage about the brain is used, and children are again asked questions regarding missed details. There is no recognition condition for children in this age group.

Affect Recognition (NEPSY-11): Affect Recognition assesses a child's ability to recognise affects by presenting children with different photographs of children of differing affect (sad, happy, angry, neutral, fear, anger and disgust). Children aged 5 – 6 years begin by selecting two photographs, out of three presented, where the children look as if they feel the same way. The next condition increases the amount of children displayed to four. The third condition involves the child selecting which child, out of four options, feels the same as the child presented at the top of the page. Finally the last condition shows a face for five seconds and children are asked to remember their affect. Six new faces are then presented and children are asked to select the two children that feel the same way as the first one shown. Children aged 5 – 6 years are not presented this final task. In total there are up to 35 trials on this measure. The test continues until all items have been presented, the age relevant cut off is reached or where children answer five consecutive trials incorrectly.

Inhibition (NEPSY-11): This test is designed to assess divided attention through testing the child's ability to inhibit automatic responses and switching between responses. The test contains two conditions; shapes and arrows and each condition has three trials: Naming, Switching, and Inhibition. In the naming trial children are asked to either name the shape or the direction of the arrows. The

Switching trial involves naming the opposite direction or shape. In the inhibition trial the white shapes or arrows become opposites and the black shapes remain the same.

The child is first presented with the shapes condition, where a short teaching example is presented. They are then presented with a longer list. This process is repeated for all three trials. In the arrows condition children are presented with a teaching example and a bigger test sheet and timed. The test is terminated once the child has named all the shapes or arrows presented or after 180 seconds for the Naming trials and 240 seconds for the Switching and Inhibition trials. The assessor marks down each correct response and type of error made; either uncorrected or self-corrected, to give an overall inhibition score for each trial. There are no age specific starts, however children aged 5 – 6 years are not administered the Inhibition trial for either condition.

Test of Everyday Attention for Children (TEA-Ch)

The TEA-Ch measures attention in children along the three subtypes of attention; spatial, selective and sustained attention. It is made up of nine different tests, each requiring different skills to help eliminate bias caused by motor speed or memory (Manly et al., 2001). Studies have found the TEA-Ch to have good validity in different cultures (Chan, Wang, Ye, Leung, & Mok, 2008; Malegiannaki, Metallidou, & Kiosseoglou, 2015) and in both clinical and typical populations (Heaton et al., 2001; Manly et al., 2001; Verstraeten, Vasey, Claes, & Bijttebier, 2010).

The current study utilised the Sky Search subtest from the TEA-Ch. Attention assessment is often biased by the participant's abilities in other domains such as motor speed, which, as discussed in Chapter 4, has been found to be affected by pesticide exposure. As the current study was conducted for research purposes and required storage of data for consistency checking, each child was given paper versions of the Sky Search, as opposed to a laminated copy. All other facets of Sky Search were kept identical with the provided stimuli.

Sky Search (TEA-Ch): Sky Search is divided into a practice, test and motor control condition. Both the test and motor conditions are presented on an A3 piece of paper, while the practice condition is on a smaller A4 sheet. The practice and test conditions require the participant to find pairs of identical

space ships amongst distractor pairs. The test condition contains 20 pairs of identical ships and 108 distractors and children are instructed to find the identical pairs as quickly as they can and then self-terminate the test by ticking the complete box at the end of the test. The motor condition has all of the distractor items removed and children are instructed to circle all 20 target items as quickly as possible while being timed. Termination is again self-determined by the child. Both the motor and test conditions are timed, with times recorded. An overall score, controlling for their motor speed is then calculated. By calculating an overall attention score any influence from motor speed is minimised (Manly et al., 2001), making the Sky Search test a pure test of attention and an effective measure in the current study.

Wechsler Intelligence Scale for Children IV (WISC-IV)

The WISC-IV is a comprehensive testing kit which assesses children's intelligence and cognitive functioning along six index scales; Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, Processing Speed Index and the General Ability Index (Wechsler, 2003a). The validity and reliability of the WISC-IV are reported to be excellent (Wechsler, 2003b) While it has undergone numerous changes since its creation in 1949 the WISC-IV is one of the most widely used intelligence tests (Wahlstrom, Breaux, Zhu, & Weiss, 2012). Further to this previous studies investigating pesticide exposure have found success in using subtests from the WISC-IV (e.g., Kofman, Berger, Massarwa, Friedman, & Jaffar, 2006). The WISC is most often used as a complete measure of IQ, however individual subtests can also be used to measure specific areas of functioning (Wechsler, 2003a).

Coding (WISC-IV): The Coding subtest measures processing speed and has two separate versions, one for younger children aged 6 – 7 years and one for children aged 8 – 16 years. In the version for younger children five shapes are presented at the top of an A4 piece of paper: a star, a circle, a triangle, a cross and a square. Each shape has a unique mark inside it and below these are 64 blank shapes. The first two shapes are filled in by the assessor to demonstrate to the child the purpose of the test, and the child then completes three further practice items. After this the child is instructed to

complete the rest of the shapes in the same manner as quickly as possible. The number of correct responses within 120 seconds are then totalled.

The version for older children works in a similar manner. Nine numbers are paired with unique shapes at the top of a page, with 126 block boxes with numbers above them being placed below this. Similarly, to the younger children's' version the instructor demonstrates the purpose of the test in the first two items and after five practice items the child is instructed to complete the rest of the items as quickly as possible. Again 120 seconds are given for this with termination after the time has elapsed. One point is awarded for each correctly item.

Digit Span (WISC-IV): This subtest measures working memory and is divided into two separate trials – forwards and backwards. In Digit Span forwards children are asked to repeat back to the assessor a sequence of numbers. The sequences increase in length over multiple trials and continues until the child fails to correctly repeat back two of the repetitions of the same length. In the backwards condition children are asked to repeat sequences of numbers in the reverse order presented to them. As with the forwards condition the test is terminated when the child fails to repeat back two repetitions of the same length correctly. Both backwards and forwards scores are then summed to create an overall Digit Span score.

Materials and Apparatus

A neuropsychological testing pack containing: The Coding and Sky Search response sheets and the NEPSY-11 scoring booklet was made up for each participant, and labelled with their ID number. Assessors had a folder containing stimulus materials set out in order of administration. The Theory of Mind and Animal Sorting subtests also required separate materials: A set of two boxes with pictures of blocks on them, filled with blocks and pencils respectively, and a copy of the animal sorting cards. Two Toshiba Netbooks were used to play the audio recording for the Auditory Attention and Response Set subtests.

Assessors

As noted earlier, all assessors had completed at least five years of university education, and post graduate papers focused on neuropsychological assessment skills. Professor Leathem, acted as a supervisor for the neuropsychological testing. A distribution of the number of tests completed by each assessor is displayed in Figure 2 below.

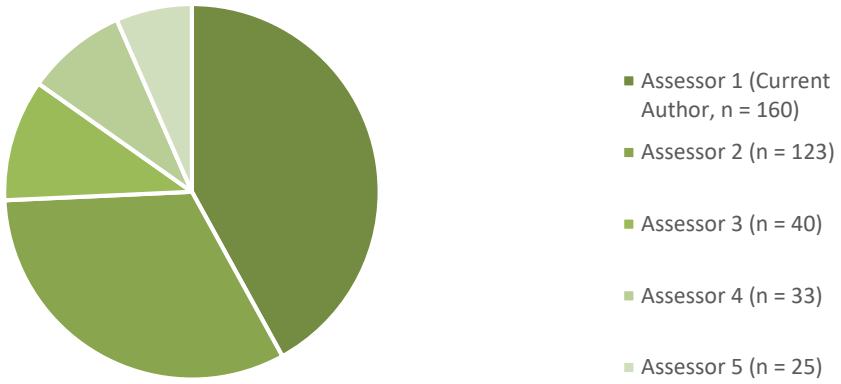

Figure 2. Distribution of neuropsychological tests per assessor

Sessions were completed with only one researcher present, however for consistency, a number of sessions (n=30) were double scored with two assessors in the room. It is acknowledged that the presence of third party assessors can influence testing scores (Howe & McCaffrey, 2010). However it is also argued that in cases where third party observation will provide a more accurate reflection of performance their use is acceptable (McSweeny et al., 1998). As the current thesis used results from multiple different assessors, double scoring was necessary for inter-rater consistency checking. Results of the double scored tests were then compared, to ensure a high degree of inter-rater reliability.

Inter-rater Reliability

Inter-rater reliability scores were calculated at two time points, after the first year of the project, and at the end of the project. The initial multivariate analysis found no effects of assessor. The second multivariate analysis found a significant effect for assessor on the motor speed task, and

this effect was subsequently controlled for in further data analysis. No significant effects were found for any other tests administered, indicating robust internal consistency. To ensure adequate inter-rater reliability 25 participants were shadow scored. Inter-rater reliability was calculated through averaging the total amount of agreement. An average inter-rate reliability score of 89.5% was found on tests from the NEPSY-11, and a score of 100% was found for tests from the TEA-Ch and the WISC-IV. This is in line with the recommended cut-offs found in the technical and administration manuals (Korkman et al., 2007b; Wechsler, 2003b).

Procedure

School Based Assessments

Testing spaces available were different from school to school depending on resources available. Commonly available spaces included resource rooms, staff rooms, and reading recovery areas. The spaces used were heterogeneous due to space restrictions at the different schools, however wherever possible settings were arranged to be consistent. Wherever possible spaces which were quiet and free from interruptions were also prioritised. Testing spaces were set out in accordance with manuals from both the NEPSY-11 and the WISC-IV.

School visits were conducted in blocks with one or two schools being visited at a time to ensure that there were no significant time gaps between interviewing children from the same school. Children were assessed with only the researcher and the child present to minimise distractions from other children and teachers where possible in line with best practice guidelines (Howe & McCaffrey, 2010). Testing sessions were arranged at least two weeks in advance to ensure that schools had ample time to brief their teachers and to lessen any disruption the research may have caused for the schools. School protocols such as signing in and out of the registrar were adhered to at all times and researchers wore clearly identifiable name badges.

An assessor would collect each participant they were assessing from their classroom. Teachers were informed where each child was assessed for safety reasons. Once the child arrived at the testing room the purpose of the session and general information around the study was provided

verbally using age appropriate language. Assent was obtained with each child before testing began. Once testing was completed the researcher returned the child to their classroom. Participants were allowed to choose a small token of appreciation (a pencil or pen from a box) as a reward for their time. For privacy reasons the researchers did not disclose any of the test results or the details of any child's performance to anyone at the schools.

Home Visit Assessments

While assessments were conducted at the child's school where possible, 15 assessments were conducted at the home either due to children having moved to a school which was not participating in the research, or where parents indicated that they would prefer a home visit. Parents were contacted either by phone or email to arrange a suitable time for the visit. In accordance with best practice recommendations (Howe & McCaffrey, 2010), children were assessed without their parents present. No child was seen without their legal guardian present at the residence. No child's results or performance were discussed on the day with the parents or other members of their family.

Similar to school based assessments, the purpose of the session and, general information around the study was provided verbally using age appropriate language. Assent was obtained with each child before testing began. For safety reasons the researcher conducting the visit sent a text upon arrival and departure of the visit to the study coordinator. All home visits for the week, including address and contact phone numbers were emailed to the study coordinator a week in advance. As the total number of home visits was less than the number of variables studied t-tests could not be conducted to investigate whether results differed (as would have been desirable as suggested by Wilson Von Voorhis & Morgan, 2007) .

Feedback

No immediate feedback on performance was given to either the participants or their parents. A summary of the participants' scores was made available to parents via email upon request. It was made clear to parents that the assessment was not a thorough neuropsychological assessment and that tests were selected for research purposes. As discussed above, the template was developed by the

current author and the principal supervisor from the psychology department and feedback was provided by Professor Leathem.

Dust Samples

In total 550 dust samples were collected in the overall study and of these 340 were involved in phase II and used in the current thesis. Dust sampling kits were returned via mail and then analysed at the University of Queensland National Research Centre for Environmental Toxicology. The following pesticides were measured: chlorpyrifos, permethrin, cypermethrin, deltamethrin and cyfluthrin. As discussed in Chapter 2 chlorpyrifos is an organophosphate commonly used in agriculture. Cypermethrin, deltamethrin, and cyfluthrin are pyrethroids recommended for outdoor use, primarily in agriculture. Permethrin is also a pyrethroid, however due to its low toxicity potential, is used primarily in the treatment of lice in humans as opposed to agricultural application. No measures of nicotinoids or carbamates were able to be conducted due to funding restrictions.

Study Sample

In total 443 participants (Female n=222, Male n=221) were involved in the current study. The average age for the total sample was 8.6 years (SD=1.6). Participants were from the Wellington (n=181), Hawkes Bay (n=178), Nelson Bays (n=52) and Horowhenua (n=30) with regions missing for two participants. Data was collected from participants either at their schools (n=433) or during home visits (n=15). Ethnicity, coded in line with recommendations from the Ministry of Health (New Zealand Ministry of Health, 2004) was listed as New Zealand European (n=349), Maori (n=42), Pacific (n=6), Middle Eastern/African (MELAA, n=9), Asian (n=18) and other (n=19). The ethnic distribution was in line with New Zealand averages for people identifying as New Zealand Europeans, but under representative of individuals identifying as Māori (Statistics New Zealand, 2015).

Schools ranged in decile from one to ten and with an average decile of 7.71 (SD = 2.3). Decile rankings provide an estimate of the socioeconomic status of residents of the surrounding region. A ranking of one typically corresponds to low socioeconomic status, while a rating of ten represents considerably higher socioeconomic status (Ministry of Education, 2017b). While the

current sample included a wide range of deciles, 77.5% of participants attended a decile six or above school. During recruitment predominantly higher decile schools agreed to participate. The main reasons given for this were lack of resources and existing participation in other research projects. Further compounding this issue, participation within higher decile schools was proportionally higher, even with additional strategies to boost recruitment in lower decile schools. In line with the disproportionate decile distribution, income was similarly skewed. Average household income for the total sample was NZ$100,000 (SD=$37,500), compared with an average New Zealand household income of NZ$90,000 (Ministry of Education, 2017b). This suggests that the socioeconomic status of the current sample is weighted higher than the likely distribution of income in New Zealand.

Data consistency

All data was hand scored by the assessors. To minimise the effects of human error when managing such a large sample the data were re-scored by a CPHR research assistant to check for any errors. Any differences in scoring were then corrected by the overall study coordinator. Data were then entered into a database by a research assistant. To check for consistency all data were then re-entered by a research assistant and any errors were corrected by the study coordinator.

Data Analysis

The data for the overall project was stored in a Microsoft Access database. For the current thesis all data were encoded using Microsoft Office Excel 365, and analysed using IBM SPSS version 25.

Exposure assessment

In line with the previous research reviewed in Chapter five, a quantitative approach was selected. Exposure was measured using questionnaire data and dust sample data. Questionnaire data is the most commonly used method to measure long term exposure, and is an effective method of measuring the effects of accumulated exposure (González-Alzaga et al., 2014). Both pre- and postnatal pesticide exposure was investigated. Prenatal exposure was measured through both maternal and paternal exposure to pesticides during pregnancy through looking at parental occupation. Initially

groups were formed based on the level of contact with pesticides: Direct handling of pesticides, handling of pesticide treated products, pesticides used in the work environment without direct handling and no pesticides being used in the workplace. However due to a lack of respondents having worked with pesticides groups were reduced to workplace exposure and no workplace exposure. Postnatal exposure was measured through the child's proximity to high pesticides use areas due to their residence and dust sample data obtained from their homes. While the main focus was on agricultural areas, as parks and sports grounds have also been linked with higher rates of exposure (Gilden, Friedmann, Sattler, Squibb, & Mcphaul, 2012) they have also been included in the current thesis.

Postnatal exposure is further broken down into current and life time exposure. Current exposure is measured through the proximity of their current residence to high pesticide use areas. Proximity to agricultural areas was further grouped into urban, rural and agricultural based on address. Exposure to sports grounds and parks was further grouped based on distance: Less than 50 metres, between 50 – 200 metres, between 200 metres and one kilometre and greater than 1 kilometre. Lifetime exposure is measured through the total time spent living next to high pesticide use areas as a proportion of the age of the child. This was calculated from demographic data provided in the phase I questionnaire found in Appendix A.

While diet and the take home pathway are also linked with exposure, investigation of these pathways was beyond the scope of the current thesis as no thorough measurements of this were included in the phase I questionnaire. Due to time constraints it was not possible to incorporate the results of the urine sampling in the current thesis.

Rationale for Regression

The current thesis involved input from both psychology and epidemiological approaches and the data analysis methods were selected after consulting with statisticians from both disciplines. Initially ANCOVA was selected for the data analysis. However after further discussion this was changed to regression to allow for a better description of effect sizes. Regression is also a more

commonly used method of data analysis within epidemiological studies as it is better suited to analysis where small effect sizes are expected. To control for the potential effects of Type I and II errors a MANCOVA analysis was also run. As there was no difference in results from the initial ANCOVA, regression and MANCOVA only the regression results are presented in the next chapter.

The data did not violate the assumptions of this test, with the exception of the finger tapping subtest. Data for this test were not normally distributed and results for this domain must be viewed with caution. Regression analysis was conducted for all other variables. All significance was measured at the $p < 0.05$ level and both standardised and unstandardized coefficients are reported. For maternal and paternal exposure, and exposure to recreational and agricultural areas, the independent variables were dummy[18] coded, and the non-exposed groups were selected as comparisons. Dummy coding was only conducted for categorical variables. For the dust sample data due to the large ranges found in the data, all results are reported as 1*SD as opposed to per unit.

[18] Dummy coding refers to the process of converting categorical variables into continuous variables able to be used in regression analysis

Chapter 8 Results

The results of the thesis are reported below, followed by a discussion of the results in Chapter 9. Univariate analysis of the potential covariate analyses are discussed first. This is then followed by the main analysis of the pre and postnatal pesticide exposure analyses.

Covariate Analyses

As discussed earlier, neuropsychological test scores are influenced by a number of variables including gender and socio-economic status. Further, child development can be disrupted by factors such as head injuries and prenatal exposure to alcohol or tobacco smoke. To ensure that any effects are due to exposure, univariate analyses were conducted to screen for potential confound variables. Variables investigated included: gender, region, assessor, decile, age, income, ethnicity, premature birth, head injuries, and prenatal alcohol and tobacco exposure.

Of the measured covariates, gender, assessor, decile, age, head injuries and prenatal tobacco exposure were found to have significant effects on the neuropsychological testing. Results are discussed by covariate below.

Gender

A significant effect of gender on the coding subtest (processing speed) was found, $F(1) = 58.188$, $p\eta^2 = 0.095$, $r^2 = 0.033$ $p = 0.04$ with males ($M = 9.71$, $SD = 2.942$) performing lower on the coding task compared to females ($M = 10.780$, $SD = 2.849$).

Assessor

A significant effect of assessor on the finger tapping subtest (motor speed) was found, $F(4) = 4.764$, $p\eta^2 = 0.054$, $r^2 = 0.058$, $p = 0.011$. As the finger tapping subtest was not normally distributed, non-parametric analysis was also conducted, with the same result found. Post-hoc analysis indicated that the scores from assessor one were significantly different to the scores from assessors two, three, and five as shown in table 6 below. Implications of this are discussed further in chapter 9.

Table 6

Descriptive statistics for the Finger tapping subtest by assessor

Assessor	Mean	SD	N
One	13.37	1.147	158
Two	12.80	1.249	124
Three	12.34	1.658	32
Four	12.97	1.432	78
Five	12.67	1.459	43
Total	12.99	1.337	435

Decile

A significant effect of decile was found on the comprehension of instructions subtest (language), $F(9) = 1.280$, $p\eta^2 = 0.074$, $r^2 = 0.053$ $p = 0.033$. Post-hoc analysis indicated that the effect was between decile four ($M = 9.65$, $SD = 2.569$) and ten ($M = 11.18$, $SD = 2.026$) schools, with a mean difference of 1.52 indicating that decile ten children performed significantly higher on this task.

Age

Descriptive statistics for all significant effects of age on the neuropsychological testing are displayed in Table 7. Age was found to have a significant effect on the coding (processing speed) subtest, $F(4) = 38.923$, $p\eta^2 = 0.100$, $r^2 = 0.129$, $p = 0.000$. Post-hoc analysis indicated that children aged six and seven performed significantly better than their counterparts aged eight to twelve. It is likely that this result is influenced by the different forms used for children aged six and seven years, and this will be discussed further in chapter 9.

Table 7

Descriptive statistics for the Coding, Finger Tapping and Narrative Memory subtests by age

	Coding			Finger Tapping			Narrative Memory		
Age	Mean	SD	N	Mean	SD	N	Mean	SD	N
Six	11.11	3.088	90	12.64	1.525	88	10.30	2.802	90
Seven	11.81	3.467	91	12.56	1.438	89	9.76	2.527	91
Eight	9.49	2.365	77	13.14	1.189	77	9.58	2.353	77
Nine	9.44	2.154	88	13.17	1.234	88	10.03	2.713	87
Ten	9.46	2.244	65	13.50	0.949	66	9.74	3.438	65
Eleven	8.82	2.855	28	13.34	1.233	29	12.64	3.841	28
Total	10.25	2.942	439	13.00	1.336	437	10.08	2.912	438

All values are based off scaled scores

Age was also found to have an effect on the Finger Tapping task, F (4) = 7.130, $p\eta^2 = 0.078$, $r^2 = 0.068$, p = 0.001. As the Finger Tapping subtest was not normally distributed non-parametric analysis was conducted, which replicated the above result. Post-hoc analysis indicates that the scores for children aged six were significantly different from those aged ten years old. They also indicated that seven-year olds performed significantly higher than their counterparts aged nine and ten years.

Finally, an effect of age on the Narrative Memory subtest was observed, F (4) = 40.671, $p\eta^2 = 0.086$, $r^2 = 0.061$, p = 0.000. Post-hoc analysis indicated that children aged eleven performed significantly lower than all other groups.

Head Injuries

Experiencing a head injury was observed to significantly affect scores on the Comprehension of Instructions subtest, F (4) = 22.552, $p\eta^2 = 0.19$, $r^2 = 0.008$, p = 0.035. Children who experienced a head injury (N = 42, M = 10.12, SD = 2.432) performed lower than children who had not (N = 392, M = 10.87, SD = 2.397). There was no relationship between the number of head injuries experienced and Comprehension of Instructions scores, r = 0.050, n = 438, p = 0.295.

Prenatal Tobacco Exposure

Exposure to tobacco prenatally was found to have a significant effect on scores of the narrative memory subtest, F (1) = 56.614, $p\eta^2 = 0.032$, $r^2 = 0.011$, p = 0.006 with children who had not been exposed to tobacco prenatally (N = 399, M = 10.17, SD = 2.914) performing better than those who had been exposed (N = 36, M = 9.06, SD = 2.848).

In summary, significant effects were found for the following covariates: gender, assessor, decile, age, head injuries, and prenatal tobacco exposure. These covariates were controlled for in the main exposure analyses. Potential explanations for these effects will be discussed in chapter 9.

Dust Sample Analysis

Univariate analysis of variance was used to investigate whether there were differences in levels of pesticides detected in dust samples based on the three exposure categories: urban, rural, and agricultural. Dust samples were measured by ng/g of pesticides, with higher values indicating greater

concentrations per gram of dust. Descriptive statistics by group are displayed in Table 8. The results of the dust sample analysis are found in Table 9. A significant effect was observed only for cyfluthrin, however as the Levene's test indicated unequal variance, results should be interpreted with caution. Tukey post hoc tests indicate that the agricultural group contained significantly higher concentrations of house dust compared to the urban and rural groups.

Table 8

Dust sample descriptive statistics by exposure group

Pesticide	Exposure Group	Mean	SD	N
Chlorpyrifos	Urban	39.51	225.13	98
	Rural	21.11	19.54	24
	Agricultural	45.45	212.93	218
	Total	42.02	208.78	340
Permethrin	Urban	28433.71	63933.57	98
	Rural	28081.87	35844.28	24
	Agricultural	26470.90	71401.43	218
	Total	27150.37	67238.46	340
Cypermethrin	Urban	1505.03	3689.71	98
	Rural	1645.71	2739.10	24
	Agricultural	1062.10	3930.46	218
	Total	1230.96	3787.56	340
Deltamethrin	Urban	433.06	1087.52	98
	Rural	79.43	208.08	24
	Agricultural	624.36	3249.97	218
	Total	530.76	2669.33	340
Cyfluthrin	Urban	1401.15	6254.15	98
	Rural	2346.09	7646.58	24
	Agricultural	189.80	984.54	218
	Total	691.16	4034.94	340

Means and Standard Deviations are derived from the total presence of pesticides found in dust samples per participant

Table 9

ANOVA dust sample results by exposure group

Pesticide	df	F	pη²	p	R²
Chlorpyrifos	2	0.156	0.001	0.855	0.001
Permethrin	2	0.031	0.000	0.969	0.000
Cypermethrin	2	0.616	0.004	0.541	0.004
Deltamethrin	2	0.541	0.003	0.583	0.003
Cyfluthrin	2	5.353	0.031	0.005*	0.031

* significant at the p > 0.05 level

Prenatal Exposure Analysis

Results of the regression analyses for maternal and paternal exposure to pesticides during pregnancy are displayed in Table 10 below. No significant effects were found for maternal exposure. A significant effect for paternal exposure was observed for the memory for faces and the memory for faces delayed tasks with exposure indicating worse performance. No other significant effects were observed.

Table 10

Paternal and Maternal exposure to pesticides regression results by cognitive domain

	Paternal Exposure			Maternal Exposure		
	No exposure	Exposure		No exposure	Exposure	
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
Attention						
Sky Search	8.90 (3.16)	8.73 (3.13)	-0.17 (-0.98, 0.64)	8.89 (3.02)	8.83 (3.56)	-0.019 (-0.98, 0.95)
Auditory Attention	10.04 (3.13)	9.49 (2.56)	-0.46 (-1.22, 0.30)	9.92 (2.92)	10.02 (3.50)	0.23 (-0.68, 1.15)
Response Set	10.60 (2.62)	10.06 (2.56)	-0.398 (-1.13, 0.34)	10.60 (2.59)	10.16 (2.75)	-0.18 (-1.06, 0.69)
Working Memory						
Digit Span	10.13 (2.72)	10.19 (2.52)	0.17 (-0.52, 0.86)	10.19 (2.62)	10.45 (2.52)	0.55 (-0.26, 1.37)
Motor Speed						
Finger Tapping	12.98 (1.34)	12.85 (1.36)	-0.07 (-0.40, 0.26)	12.98 (1.34)	13.06 (1.39)	0.015 (-0.37, 0.40)

Processing Speed						
Coding	10.23 (2.98)	10.71 (2.73)	0.58 (-0.11, 1.28)	10.25 (2.97)	10.38 (2.81)	0.29 (-0.54, 1.13)
Language						
Comprehension of Instructions	10.88 (2.62)	11.11 (2.43)	0.36 (-0.22, 0.95)	10.97 (2.27)	10.74 (2.65)	-0.06 (-0.77, 0.64)
Social Perception						
Affect Recognition	9.93 (2.86)	9.44 (2.73)	-0.59 (-1.29, 0.09)	9.90 (2.78)	9.47 (2.88)	-0.38 (-1.21, 0.44)
Theory of Mind	11.39 (2.27)	10.56 (2.43)	-0.639 (-1.87, 0.59)	11.15 (2.85)	10.13 (3.37)	-1.13 (-2.59, 0.32)
Executive Function						
Animal Sorting	8.26 (3.00)	9.16 (2.99)	0.91 (0.05, 1.76)	8.53 (3.24)	8.03 (2.85)	-0.41 (-1.43, 0.60)
Inhibition Naming	10.52 (3.24)	10.17 (3.49)	-0.25 (-1.07, 0.56)	10.34 (3.30)	10.64 (2.89)	0.37 (-0.60, 1.34)
Inhibition Inhibition	10.03 (2.93)	9.55 (3.36)	-0.29 (-1.05, 0.45)	10.01 (2.96)	9.81 (3.18)	0.07 (-0.82, 0.97)
Inhibition Switching	10.69 (2.61)	10.82 (2.75)	0.22 (-0.53, 0.98)	10.79 (2.59)	10.73 (3.01)	0.17 (-0.72, 1.08)
Memory						
Memory for faces	9.57 (2.93)	8.81 (2.57)	-0.80* (-1.52, -0.08)	9.47 (2.89)	9.43 (2.87)	-0.07 (-0.93, 0.78)
Memory face del.	9.66 (3.01)	8.73 (2.86)	-0.97* (-1.73, -0.22)	9.67 (3.05)	9.17 (2.74)	-0.35 (-1.26, 0.54)
Narrative Memory	9.92 (2.89)	10.72 (2.85)	0.66 (-0.05, 1.39)	10.08 (2.85)	10.49 (3.37)	0.43 (-0.42, 1.30)

* significant at the p > 0.05 level (Memory for Faces p = 0.012, Memory for Faces Delayed p = 0.042)
The following variables were controlled for in the analysis: age, gender, prenatal tobacco and alcohol exposure, head injuries, decile, region, school and assessor

Postnatal Exposure analysis

Current Exposure

Results of the regression analyses for current proximity to agricultural and recreational areas are displayed in Table 11 and a significant effect for current residence was only observed on the memory for faces delayed subtest. Exposure indicated worse performance with the rural group performing worse than the urban group. As per Table 12 significant effects of proximity to recreational areas were observed for the affect recognition subtest with children living 50 to 200m performing better than all other groups.

Table 11

Exposure regression for current residence proximity to agricultural areas by cognitive domain

Variable	Urban[1] Mean (SD)	Rural Mean (SD)	Difference (95%CI)	Agricultural Mean (SD)	Difference (95%CI)
Attention					
Sky Search	8.90(3.19)	8.96(3.41)	0.22 (-1.19,1.66)	8.76(3.11)	0.19 (-0.58,0.97)
Auditory Attention	10.45(2.66)	10.44(2.55)	0.35 (-0.99,1.70	9.84(3.15)	0.03 (-0.70.0.77)
Response Set	10.45(2.66)	10.10(2.94)	-0.73 (-2.03,0.56)	10.44(2.44	0.06 (-0.77,0.63)
Working Memory					
Digit Span	10.08(2.72)	10.65(2.30	0.45 (-0.76,1.66)	9.97(2.79)	0.06 (-0.59,0.73
Motor Speed					
Finger Tapping	13.06(1.33)	13.26(1.1)	-0.15 (-0.46,0.15)	12.80(1.39)	0.32 (-0.20,0.64)
Processing Speed					
Coding	10.24(2.94)	11.48(3.64)	1.09 (-0.12,2.33)	9.99(2.70)	0.23 (-0.43,0.91)
Language					
Comprehension of Instructions	10.73(2.41)	10.93(2.43	0.28 (-01.32,0.75)	10.91(2.43)	-0.01 (-0.57,0.56)
Social Perception					
Affect Recognition	9.93(2.81)	9.56(2.39)	-0.17 (-1.39,1004)	9.80(2.89)	0.23 (-0.42,0.90)
Theory of Mind	9.92(2.92)	10.29(2.50	-1.07 (-3.24,1.09)	10.84(2.28)	0.33 (-0.85,1.52)
Executive Function					
Animal Sorting	8.61(23.05)	7.00(3.25)	-0.97 (-2.47,0.52)	8.23(2.96)	0.52 (-0.29,1.34)
Inhibition Naming	10.41(3.22)	11.19(3.25)	-0.47 (-0.96.1/91)	10.36(3.28)	-0.02 (-0.80,0.76)
Inhibition Inhibition	9.83(3.04)	10.52(3.12)	-0.01 (-1.33,1.31)	9.67(2.84)	-0.49 (-1.21,0.23)
Inhibition Switching	10.85(2.64)	10.58(2.99)	0.02 (-1.20,1.34)	10.33(2.5)	0.47 (-0.25,1.19)
Memory					
Memory for faces	9.67(2.93)	9.30(3.66)	0.07 (-1.20,1.34)	9.22(2.52)	0.26 (-0.42,0.96)
Memory face del.	9.82(3.13)	8.56(2.88)	-0.64* (-1.96,0.68)	9.05(2.58)	0.71 (-0.01,1.43)
Narrative Memory	9.92(2.92	10.11(2.52)	0.04 (0-1.23,1.32)	10.41(3.00)	-0.07 (-0.77,0.62)

* significant at the p > 0.05 level

The following variables were controlled for in the analysis: age, gender, prenatal tobacco and alcohol exposure, head injuries, decile, region, school and assessor

[1] Baseline variable for the comparison with the Rural and Agricultural groups

Table 12

Exposure regression for current residence proximity to recreational areas by cognitive domain

Cognitive Domain	>1000 m[1] Mean (SD)	<50m Mean (SD)	Difference (95%CI)	50-200m Mean (SD)	Difference (95%CI)	200-1000m Mean (SD)	Difference (95%CI)
Attention							
Sky Search	8.62 (3.20)	8.98 (3.07)	0.35 (-0.76,1.48)	9.23 (3.28)	0.64 (-0.28,1.56)	8.91 (3.02)	0.33 (-0.44,1.10)
Auditory Attention	10.00 (3.06)	9.76 (3.23)	-0.08 (-1.14,0.98)	10.10 (3.05)	0.17 (-0.70.1.05)	9.74 (3.00)	-0.13 (-0.86,0.59)
Response Set	10.34 (2.72)	10.68 (2.56)	-0.44 (-0.57,1.47)	10.28 (2.54)	-0.12 (-0.96,0.72)	10.57 (2.57)	0.09 (-0.61,0.79)
Working Memory							
Digit Span	9.77 (2.790	10.48 (2.65)	0.60 (-0.35,1.55)	10.41 (2.38)	0.40 (-0.38,1.19)	9.92 (2.82)	-0.14 (-0.79,0.51)
Motor Speed							
Finger Tapping	12.83 (1.34)	13.05 (1.21)	0.13 (-0.31,0.57)	13.29 (1.14)	0.50 (-0.29,1.30)	13.00 (1.42)	0.26 (-0.04.0.57)
Processing Speed							
Coding	9.97 (2.96)	10.71 (3.28)	0.84 (-0.13,1.81)	10.64 (2.66)	0.07 (0.28,1.85)	10.21 (2.89)	-0.03 (-0.70,0.63)
Language							
Comprehension of Instructions	10.59 (2.70)	11.07 (2.18)	0.59 (-0.22,1.41)	10.73 (2.22)	0.07 (-0.60,0.75)	10.88 (2.30)	0.17 (-0.36,0.73)
Social Perception							
Affect Recognition	9.85 (2.89)	9.61 (2.93)	-0.09 (-1.04,0.86)	10.60 (2.18)	1.07* (0.28,0.51)	9.58 (3.01)	-0.01 (-0.66.0.54)
Theory of Mind	10.90 (2.24)	10.13 (3.35)	-1.24 (-2.94,0.45)	10.50 (2.14)	-0.88 (-2.28,0.51)	11.45 (2.39)	0.13 (-1.03.1.29)
Executive Function							
Animal Sorting	8.32 (2.94)	8.54 (3.57)	0.18 (-11.01,1.37)	8.10 (2.09)	-0.01 (-0.98,0.98)	8.62 (3.00)	0.43 (-0.38,1.25)
Inhibition Naming	10.08 (3.12)	10.93 (3.08)	0.86 (-0.26.2.00)	10.41 (3.33)	0.12 (-0.80,1.05)	10.58 (3.31)	0.26 (-5.00,1.05)
Inhibition Inhibition	9.60 (2.77)	10.46 (3.03)	0.75 (-0.29,1.80)	10.08 (2.86)	0.34 (-0.51,1.20)	9.92 (3.17)	0.19 (-0.11,1.32)
Inhibition Switching	10.32 (2.41)	10.66 (2.14)	0.45 (-0.59,1.50)	11.16 (2.81)	0.79 (-0.07,1.65)	10.89 (2.87)	0.60 (-0.11,1.32)
Memory							
Memory for faces	9.28 (2.68)	9.50 (2.59)	0.13 (-0.86,1.13)	9.83 (3.04)	0.65 (-0.16,1.48)	9.70 (2.96)	0.40 (-0.27,1.09)
Memory for faces delayed	9.03 (2.87)	9.03 (2.86)	0.23 (-0.86,1.13)	10.22 (3.06)	1.16* (0.30,2.02)	9.79 (2.98)	0.66 (-0.05,1.38)
Narrative Memory	10.27 (2.84)	10.13 (2.75)	0.08 (0-92,1.09)	9.62 (3.16)	-0.37 (-1.20,0.45)	10.03 (2.97)	-0.05 (-0.74,0.63)

* significant at the p > 0.05 level

[1]Baseline variable for the comparison with the <50m, 50 – 200m and 200 – 1000m groups

Table 13

*Re*gression for dust results by cognitive domain

	Chlorpyrifos Difference (95% CI)	Permethrin Difference (95% CI)	Cypermethrin Difference (95% CI)	Cyflurthrin Difference (95% CI)	Deltamethrin Difference (95% CI)
Attention					
Sky Search	0.17 (-0.18, 0.538)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Auditory Attention	0.00 (-0.34, 0.34)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Response Set	0.09 (-0.23, 0.41)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Working Memory					
Digit Span	-0.30 (-0.61, -0.01)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Motor Speed					
Finger Tapping	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Processing Speed					
Coding	-0.03 (-0.34, 0.27)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, -0.00)
Language					
Comprehension of Instructions	-0.15 (-0.41, 0.11)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, -0.00)	0.00 (0.00, 0.00)	-0.00 (0.00, 0.00)
Social Perception					
Affect Recognition	0.03 (-0.20, 0.41)	0.00 (0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (0.00, 0.00)
Theory of Mind	-0.04 (-0.53, 0.45)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)
Executive Function					
Animal Sorting	0.63 (0.26, 1.01)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	-0.00* (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Inhibition Naming	-0.34 (-0.70, 0.01)	-0.00 (-0.00, -0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Inhibition Inhibition	-0.16 (-0.41, 0.20)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)
Inhibition Switching	0.47 (0.14, 0.80)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)
Memory					
Memory for faces	-0.01 (-0.32, 0.31)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (0.00, 0.00)	-0.00 (-0.00, 0.00)
Memory face del.	-0.01 (-0.34, 0.32)	0.00 (0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00* (-0.00, 0.00)
Narrative Memory	-0.18 (-0.50, 0.14)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)

* significant at the p > 0.05 level

Difference refers to the change in outcome per unit increase of pesticide concentration.

The following variables were controlled for in the analysis: age, gender, prenatal tobacco and alcohol exposure, head injuries, decile, region, school and assessor

Regression coefficient and CI values are expressed per 1*SD

Regression results investigating the effects of pesticide residue found inside homes (as measured through house dust) on cognitive functioning are displayed in Table 13 above. Significant effects were found for cyfluthrin on the animal sorting task with increased levels of dust residue indicating worse performance.

Lifetime Exposure

Regression results investigating lifetime exposure to agricultural areas are displayed in Table 14 below. On the regression analysis, length of time lived on a farm significantly predicted scores on the memory for faces delayed subtest, with greater time indicating worse performance

Summary

In summary while the majority of the hypotheses were not supported, evidence for an effect of pesticide exposure was found for the memory domain. For prenatal exposure (as measured by paternal occupation) effects were observed on the memory for faces test. For postnatal exposure, effect of current residence and proximity to recreational areas was also observed to negatively affect scores on the memory for faces delayed test. Lifetime exposure (as measured by total time spent living on a farm) provided further evidence of an effect on facial memory scores. Finally, the results of the dust sample regressions indicate an effect of cyfluthrin on executive functioning (sorting) and deltamethrin on the memory for faces delayed subtest.

Table 14

Percentage of time lived on a farm regression results by cognitive domain

	Mean (SD	Mean Difference	95% CI	
			Lower	Upper
Attention				
Sky Search	8.86 (3.12)	0.03	-0.08	0.14
Auditory Attention	9.88 (3.03)	-0.01	-0.11	0.10
Response Set	10.43 (2.62)	-0.03	-0.13	0.07
Working Memory				
Digit Span	10.07 (2.71)	-0.02	-0.11	0.07
Motor Speed				
Finger Tapping	12.99 (1.32)	-0.01	-0.03	0.06
Processing Speed				
Coding	10.25 (2.94)	-0.05	-0.15	0.04
Language				
Comprehension of Instructions	10.80 (2.41)	-0.07	-0.15	0.01
Social Perception				
Affect Recognition	9.87 (2.81)	0.01	-0.09	0.10
Theory of Mind	11.08 (2.39)	0.01	-0.16	0.17
Executive Function				
Animal Sorting	8.41 (3.05)	-0.04	-0.16	0.07
Inhibition Naming	10.45 (3.22)	-0.03	-0.15	0.07
Inhibition Inhibition	9.89 (2.98)	-0.01	-0.10	0.10
Inhibition Switching	10.68 (2.62)	-0.04	-0.15	0.05
Memory				
Memory for faces	9.52 (2.96)	-0.01	-0.11	0.08
Memory face del.	9.52 (2.99)	-0.11*	-0.21	-0.01
Narrative Memory	10.08 (2.91)	0.05	-0.04	0.15

* significant at the $p > 0.05$ level

The following variables were controlled for in the analysis: age, gender, prenatal tobacco and alcohol exposure, head injuries, decile, region, school and assessor

Chapter 9 Discussion

The current chapter will discuss these results in the context of the hypotheses and research questions. The chapter will be divided into the following sections: summary of findings, research observations, contribution of the study to the current literature, limitations of the current study, recommendations for future research, and conclusions.

Summary of findings

Covariates

As neuropsychological testing can be influenced by a range of factors, potential covariates were investigated (gender, region, assessor, decile, age, income, ethnicity, premature birth, head injuries, and prenatal alcohol and tobacco exposure). Of these, gender, assessor, decile, age, head injuries and prenatal tobacco exposure were found to have significant effects. While a number of univariate tests were conducted, which increases the risk of type I errors, all analyses were planned (rather than exploratory) and results were in line with previous literature. The results are discussed by cognitive domain below.

Processing Speed

A significant main effect for gender on processing speed was found in the current study, with girls performing better on this measure. This finding is in line with the current literature investigating processing speed, where females have been found to outperform their male counterparts on tasks involving digits and alphabets (Roivainen, 2011).

Age was also found to have a significant effect on processing speed scores. Children aged six and seven obtained significantly higher scaled scores than children aged eight and older. This result is not typical of what would be expected, as the WISC scores are age standardised. However, children aged six and seven are given a different work sheet, where they fill in shapes rather than boxes which serve as a further prompt to reduce the cognitive load of the task. It is possible that this difference in task makes it qualitatively different and explains the current finding, however this result has not been observed in the newer version of the WISC (Dombrowski, Canivez, & Watkins, 2017) which uses a

similar task. This is an area for further investigation and will be further discussed in the recommendations for future research below.

Motor Speed

In the current study motor speed was influenced by both age and the assessor administering the tests. Further there were some concerns around the test used to measure motor speed. Scores on the finger tapping subtest were not normally distributed, and were skewed heavily towards the higher ranges. The mean score observed in the current study was 13, which is a marked deviation from the normal scaled score average of 10. The most likely explanation concerns the norms used. As discussed above norms for neuropsychological tests can become outdated over time. The NEPSY II norms were collected from 2005 to 2006 (Brooks et al., 2010). Since this time there has been a sharp rise in electronic device usage globally (Mazur et al., 2018), much of which requires finger dexterity to adequately use. There has been an observed effect of increased manual dexterity and motor speed in regular device usage (Alsafi et al., 2017; Lim, Kang, & Kang, 2017). Further research in Europe has found a similar trend, with children scoring higher than expected on the NEPSY motor speed tasks (Rosenqvist et al., 2017). This raises concerns around the ability of older neuropsychological testing norms to adequately reflect current motor speed, which will be discussed further in the recommendations for future research.

Age was found to have a significant effect on motor speed scaled scores, with children aged six performing lower than those aged ten years old, in spite of these scores being age corrected. Scores also indicated that seven-year olds performed significantly higher than their counterparts aged nine and ten years. In the literature age is found to be a significant influence on the development of motor skills (Barnett et al., 2016). However motor skills usually improve steadily from age five onwards (Bauer et al., 2011) and development begins to plateau around the twelfth year of life (Gasser et al., 2010). This makes it unlikely that age effects explain the current findings. It is more likely that the significant results are a consequence of the skewed distribution of scores on the finger tapping task, and the likely out dated norms discussed above.

There was also a significant effect of assessor on the finger tapping subtest. This was not observed during the first check conducted after the first 100 participants. Unfortunately, as no further data were entered into the database until testing had concluded no further checks occurred. There is considerable observed inter-rater variation on this subtest of the NEPSY, with agreement typically varying from around 30 – 65% (Strauss, Sherman, & Spreen, 2006). It is likely that the normal inter-rater variation on this subtest contributed to the observed effect in the current sample. This raises concerns over the reliability of this subtest for general use.

Language

In the current study children from decile four schools performed significantly worse than those from decile ten schools on the comprehension of instructions subtest. Typically, it would have been expected to also see this result for deciles one to three also, if the effect was due to decile and, by extension, socio-economic status, however this was not the case. One potential explanation is that deciles are not always an accurate reflection of socio-economic status of the children attending the school. In addition, school deciles in New Zealand were recalculated in 2014, which caused a change in funding (including more reading support programs (Ministry of Education, 2017a). Some schools experienced an inflation of their decile ranks, without corresponding rises in the surrounding socioeconomic status or the attending children. Lower socio-economic status is typically linked with poorer language skills (Hecht, Burgess, Torgesen, Wagner, & Rashotte, 2000), which may account for the present finding that decile four was worse than decile ten.

In the current study children who had sustained a head injury performed significantly lower on the comprehension of instructions subtest than children who had not. As there was no significant correlation with multiple head injuries this suggests the deficit is present even when a child has experienced only one head injury. While it must be noted that the number of children in the current sample who experienced head injuries was much lower than those who had not, this finding is consistent with the literature. Head injuries have been found to adversely affect cognitive development (Gerrard-morris et al., 2010), and even cases of mild traumatic brain injuries have been linked with language difficulties (Anderson, Godfrey, Rosenfeld, & Catroppa, 2012). While severity

of head injuries was not recorded, the current findings still contribute to the consensus of the effects of head injuries on language development.

Memory

A significant effect for age was found on the narrative memory subtest, with children aged eleven performing lower than their counterparts. There are two likely factors explaining this finding. First the eleven-year-old age group contained a much smaller sample than the other age groups, and it is possible this difference would not have been observed with a larger sample. Secondly the subtest administered for children aged eleven and upwards also differs from the one for younger children. The story read is twice as long, and contains technical information about the brain, as opposed to a story about a boy and his dog. It is possible that the increased difficulty of the task accounts for the worse performance in this age group. This raises a potential area for future research to ensure that children's memory is being adequately assessed.

A significant effect of prenatal tobacco exposure on narrative memory scores was also observed, with exposure being linked with lower scores. While there was a large difference in sample size between exposed and non-exposed children, this is unlikely to account for this finding. The finding is in line with research suggesting an effect of prenatal tobacco exposure on brain volume and development (El Marroun et al., 2014) and memory (Geng, Salmeron, Ross, Black, & Riggins, 2018). The current study further supports these findings.

Dust Sample Analysis

In the current sample pesticide residues in house dust samples were analysed to provide support for classifying children into urban, rural and agricultural groups based on address. As chlorpyrifos, cypermethrin, deltamethrin and cyfluthrin are all used in agriculture, greater quantities of these pesticides were expected in the rural and agricultural groups. Permethrin is primarily used in household pest management, such as headlice treatments, and equal quantities were expected across all groups. Only cyfluthrin was found to have significantly higher quantities in agricultural areas, however due to unequal variances, this result should be interpreted with caution. This provides some

support for increased pesticide exposure in the agricultural group. However, as dust samples were not able to be collected during the spraying seasons it is possible that the current approach undermeasured actual exposure during peak use times.

Exposure Analysis

The aim of this thesis was to investigate the potential effects of pesticide exposure in the neuropsychological development of children in New Zealand. Overall it was expected that there would be an effect of exposure, based on the literature reviewed in chapter four. It was hypothesised that there would be an effect on each of the following cognitive domains: attention, motor speed, processing speed, memory, working memory, language, executive functioning and language.

Prenatal exposure

Prenatal exposure was measured using both paternal and maternal occupation during pregnancy. Both were grouped based on whether occupation involved or did not involve pesticide use. Paternal exposure was found to have a significant effect on the memory for faces and the memory for faces delayed subtest. No other effects on memory (e.g., narrative memory) were observed. While there have been no previous studies investigating facial memory and pesticide exposure, deficits in this area are a prominent feature of foetal alcohol exposure (Wheeler, Stevens, Sheard, & Rovet, 2012). It is possible that pesticide exposure leads to similar insults to the brain. Paternal exposure is most likely to come from the take home pathway, and these results provide support for further research into this pathway as a possible avenue for exposure. Another possible factor is the influence of pesticides on sperm quality. Pesticides have been found to negatively impact sperm health, growth and structure (Perry, 2008). These abnormalities may then lead to further difficulties in childhood. This further reinforces the need for further investigation of paternal pesticide exposure.

Maternal exposure was not found to have an effect on any of the cognitive domains. This is not in line with the previous literature and it may be that higher levels of exposure for women during pregnancy are needed to have negative effects on the developing child. It is likely that New Zealand's

safety regulations around pregnant women working around potentially harmful chemicals such as pesticides (Human Rights Comission, 2005) accounts for this difference.

Postnatal exposure

Postnatal exposure was measured by the proximity of the child's current residence to agricultural areas and recreational grounds, and the dust sample data.

Hierarchical regression was selected to investigate whether there were significant differences between the urban, rural, and farming groups. A significant effect was observed only for the memory for faces delayed condition. This finding is consistent with those for prenatal exposure and the regression analysis below.

Regression analysis was also used to investigate the potential effects of proximity to recreational areas. A significant effect was observed only for the affect recognition subtest, with children living 50 to 200 metres scoring higher than all other groups. This finding is not as expected if pesticide exposure was the contributing factor and runs contrary to the other findings in this study.

Finally, the dust sample data suggests a negative relationship between cyfluthrin and scores on the animal sorting subtask, and a negative relationship between deltamethrin and the memory for faces delayed subtask. Specifically, a child's higher levels of exposure to these pesticides via proximity to recreational areas was significantly associated with a worse performance in these two subtasks. There has been no previous research investigating executive functioning and pesticide exposure, and these results indicate that further investigation of this domain in relation to pesticide exposure is warranted. The negative relationship between deltamethrin and memory for faces delayed is in line with the other findings in this study.

Lifetime Exposure

Hierarchical regression was used to investigate whether length of time lived on a farm had an effect on the cognitive domains. A significant effect was observed only for the memory for faces delayed subtest. This finding is similar to what was observed for paternal pesticide exposure and current residence in the current sample, lending further support for the argument that delayed facial

memory can be affected by pesticide exposure, both pre- and postnatally. The lack of significant effects on the other cognitive domains is not consistent with previous work suggesting a cumulative effect of exposure (Butler-Dawson, Galvin, Thorne, & Rohlman, 2016; Rohlman, Lasarev, Anger, & Mccauley, 2007). However, in the current sample overall exposure levels are likely to be low given the different exposure profile of New Zealand, suggesting that higher levels of pesticide exposure are required to achieve this cumulative effect.

Summary of Results

Significant effects of pesticide exposure were observed for the memory domain for pre- and postnatal exposure, with increased exposure being linked with lower performance on these memory tests. These findings are in line with previous literature which has also found effects on this domain, suggesting similar effects in New Zealand, and extend the literature on executive functioning and pesticide exposure. This indicates that even with a different exposure profile, results from overseas studies are still important in informing regulations in New Zealand. While it must be noted that these effects are relatively small, due to the potential of small effects to translate into large population burdens these results are still of benefit to the health sector.

Research observations

In addition to the quantitative data collected, some observations about working with this population are made.

The first observation concerns the questionnaire used. It was necessary for the larger CPHR project to collect information about general health. The researchers obtained feedback from parents at the promotional events, and from principals around the time-consuming nature and length of the questionnaire. It is likely that this contributed to a more restricted sample. It may be more useful in future to condense questionnaire measures where possible to avoid this issue.

The second observation was around the difficulties in recruitment from lower decile schools. While it was difficult to recruit lower decile schools, overall recruitment numbers from these schools were low as well. The main feedback received from principals was that families at their schools would

have benefited from an electronic version of the questionnaire. Unfortunately, this was not possible in the current study due to resourcing limitations. However future work in this area would benefit from having this method available, alongside potentially working closer with schools to have this available. This, combined with a more succinct questionnaire, may have boosted participation rates.

The third and final observation concerns the use of motor speed measurements It was not possible to foresee the skewed nature of the results; however, it is likely that including other measures of motor speed may have been beneficial. It would be useful to include measures of balance or functional skills such as threading string through a loop. This would provide a more accurate assessment of the motor control domain, considering the limitations of using finger tapping alone due to possible effects of electronic usage on this subtest.

Contribution of the Study to the Literature

In addition to the above observations the current study contributes to the literature in several ways. The thesis forms part of the first study in New Zealand looking at the potential effects of pesticide exposure on children's health. As discussed in chapter three, differing exposure profiles make it difficult to directly apply research from different countries to New Zealand. As most studies have either been conducted in third world countries or in the USA, there is a gap for countries with a similar exposure profile to New Zealand. The current thesis found some effects of exposure, in line with previous research. As the current thesis forms a component of the larger CPHR run project, results will be important in informing the wider health sector in New Zealand. It also provides support for the ability to generalise findings across countries with differing exposure profiles.

The covariate analysis also further supports the existing literature on the effects of tobacco exposure, head injuries, gender, and age on cognitive development. The covariate analysis looking at the finger tapping and coding tasks also provides evidence for the need to use up-to-date norms. The finger tapping data suggests that changes in societal usage in technology can play a role in influencing testing scores, and norms should be updated to reflect this.

Limitations

A major limitation of the current thesis was the lack of random assignment to the second phase of the study. Unfortunately, due to time and resource limitations, random assignment was not possible. This meant that all participants who had completed the Phase I questionnaire by a certain stage were selected for the second phase. While the larger study utilised a refusal questionnaire this data was not available at time of writing. This makes it possible that a biased sample was used. It is likely that parents who were most interested in the study were the first to complete their questionnaires. This was reflected in the information events, where attending parents were already very concerned about the effects of pesticides and took steps to minimise exposure in their children. As such results from the current thesis must be interpreted with caution as it is not possible to rule out bias within the sample.

The second major limitation of the study concerns the limited scope in which postnatal exposure was measured. It is common for studies to only investigate one exposure pathway. However, given the how other pathways such as diet can play an impact on exposure, this can mean the extent of exposure is missed. This is also true for the current thesis. Unfortunately, this was beyond the scope of the current thesis as data on these exposure pathways were not available at time of writing Investigating the potential effects of diet and home pesticide use is likely to have clarified the overall results.

Another limitation in the current study is the distribution of ethnicities. While the percentage of the sample identifying as New Zealand European is similar to the broader population, other ethnicities and Māori in particular, are underrepresented. This limits the extent to which the findings can be generalised to the wider population. While recruitment difficulties contributed to this underrepresentation, the project would have been strengthened by a more representative sample of individuals identifying as Māori. Further as Māori are over-represented in the healthcare system this underrepresentation may mask some health risks presented by pesticide exposure.

The measurement of motor speed presents another limitation of the study, and the skewed data was not able to be used for some of the analyses. Further the finger tapping task had low inter-rater reliability. While this is in line with previous findings, it still makes any results in this domain difficult to interpret. Given that motor speed is strongly linked with exposure in the literature, these difficulties limit some of the contribution this thesis can make in this area. A more robust and reliable measurement of motor speed, including a less subjective test and more functional measures, would have strengthened the current project.

The limited focus on only one exposure pathway was also reflected in the measurement of prenatal pesticide exposure in the current thesis. It was only possible to utilise parent occupation, which only reflects a narrow window of exposure, especially for paternal exposure. Paternal exposure likely only reflects the take home pathway. This limits the extent to which the current results can be generalised. It would have been useful to include measurements of proximity and diet in the prenatal exposure measurements, which would have provided a more inclusive picture.

The collection of the dust samples outside of spray season presents another limitation to the current study. While only one pesticide had elevated levels for the agricultural group, it is not clear whether this would have been similar during the spraying season. Aerosolised application of pesticides are used extensively in viticulture, which makes up a large percentage of agriculture in both the Nelson Bays and Hawkes Bay regions. By not collecting dust samples during this time period, it limits the measurement of the strength of the different exposure groups in the current sample.

The questionnaire used in Phase I of the wider study and for demographic and covariate information screened for prenatal tobacco and alcohol use. Other drug use including prescription drugs were not screened for. Given the literature on the effects of illicit substances and prescription drugs on cognitive development in children (Ross, Graham, Money, & Stanwood, 2015) inclusion of screening questions in this area would have strengthened the current thesis. Due to limitations on the length of the questionnaire these were unfortunately not able to be included.

A further limitation was the lack of equivalent groups. This was true for the current residence, proximity to sportsgrounds and parks, and prenatal parental exposure to pesticide groups which all ranged in size. The difficulties with recruitment and time and resource limitations discussed above made it impossible to ensure that there was equivalency across the groups. This further limits the inferences that can be drawn from the results of the analyses.

Another limitation in the thesis was the lack of testing for both nicotinoids and carbamates in the dust samples. As both types of pesticides are commonly used in agricultural settings this limits the extent to which inferences about the relationship between proximity and exposure can be made in the current sample. As nicotinoids are one of the fastest growing types of pesticides used, this is an area which will need further exploration in future studies. While carbamates make up a small percentage of overall pesticide use, and are generally used with root vegetables, limiting the potential for spray drift, they are still likely to be introduced into homes through the take home pathway.

Recommendations for Future Research

Based on the above discussion and findings from this study several recommendations for future research are made. While the use of a refusal questionnaire aimed to check for bias, random sampling would have provided a more robust measure. It will be important for future research to continue to utilise random sampling where possible, as this will provide a more effective measurement of contributing factors.

The current study utilised a broad domain centred view of cognitive functioning, as opposed to investigating only a single facet or an overall measurement such as IQ. Unfortunately, it was not possible to investigate whether this was a more robust method of measuring pesticide exposure effects due to a lack of significant findings in the current research. However, the literature on cognitive development in children strongly suggests relationships between the cognitive domains, and likely flow on effects resulting from deficits in one area. It will be useful for future research looking at the effects of exposure to toxic substances such as pesticides to utilise this domain centred view where possible.

An investigation of all the differing exposure pathways was beyond the scope of the current thesis, and it was only possible to investigate proximity. While proximity is generally the most researched pathway, there is evidence that diet is a further major contributor to pesticide exposure in children (Seurin et al., 2012). Future research should focus on also incorporating this pathway in the analysis. Further, the take home pathway is argued to potentially exacerbate the effects of proximity (Lu, Fenske, Simcox, & Kalman, 2000). A focus on this as a potential moderating variable, may further extend the current knowledge base on the mechanisms of pesticide exposure.

Future research in New Zealand would benefit from further investigating the potential for cumulative effects of pesticide exposure in New Zealand. While the current study did not found evidence of this, it is possible that this will only be observed in older children as per the previous literature (Butler-Dawson, Galvin, Thorne, & Rohlman, 2016; Rohlman, Lasarev, Anger, & Mccauley, 2007. Further research looking at the effects of exposure on adults will also be important; as per this cumulative effects hypothesis adults would demonstrate these effects increasingly over the lifespan.

Both the coding and narrative memory tasks contained separate versions for children of different ages. In the current study both tasks displayed age effects, in line with the differing versions of tests used. The coding task displayed this effect for younger children. While this effect is not reported in either the WISC IV or V manuals, the current research raises concerns around the potential for ceiling effects. It is recommended that future research is conducted to investigate this further. For the narrative memory task, the opposite trend was observed in older children who had a much longer and more technical passage to remember. The passage is more complex than similar tasks for adults, such as the logical memory task on the Wechsler Memory Scale IV (Pearson, 2018). This raises concerns as to whether the NEPSY II narrative memory task is an accurate reflection of memory in older children, and whether it suffers from floor effects. It will be valuable for future research to investigate this further.

The final recommendations for future research are around the use of norms and certain tests in neuropsychological testing. While this was not a primary focus of the current thesis, the covariate analyses raised concerns around the applicability of some of the norms used. The first was around the use of tests of motor control which emphasise manual dexterity. As discussed it is likely that changes in technology use have made older norms less valid. As many of these norms are still in use today for neuropsychological testing both in research and clinical settings, it will be important for future research to update these.

Conclusions

The aim of the current thesis was to investigate the potential effects of pesticide exposure on the neuropsychological development of children in New Zealand. effects of pesticide exposure were observed for the memory domain for pre- and postnatal exposure, with increased exposure being linked with lower performance on these memory tests. However, the majority of the hypotheses were disconfirmed. Limitations such as non-random sampling and non-equivalent groups mean these results must be viewed with caution.

The current study contributes to the current literature through providing evidence that there are effects of exposure on the memory development of children in New Zealand, in particular delayed facial memory. This study helps fill a gap in the literature by providing evidence of the effects of exposure in New Zealand. It also makes several recommendations for future research, including the need to further research whether a domain centred view of exposure is a valuable tool. Recommendations include the need to use up-to-date norms and to further investigate the validity of certain measures used in the study. Finally, a focus on the potential cumulative effects of pesticide exposure in New Zealand in adolescent and adult populations would be beneficial to further explore the potential effects of exposure.

This thesis contributes to a larger study on the potential health outcomes of pesticide exposure in children run by the CPHR. This wider project will be important in assisting regulators in continuing

to provide effective controls to protect children in New Zealand from the harmful potential effects of pesticide exposure.

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Appendices

Appendix A Pesticide Exposure Questionnaire

PESTICIDE EXPOSURE AND BRAIN FUNCTION IN CHILDREN QUESTIONNAIRE

ID NUMBER:

B	**D**					

Pesticides are chemicals that are used to kill insects and other small animals (i.e. pests), weeds, and mould. For the purpose of this questionnaire, the term "pesticide" includes all agrichemicals including herbicides, weed killers, plant growth regulators, biocides, wood preservatives, fumigants, and animal treatments.

This questionnaire is in 5 sections:

Section 1 is about your child;

Section 2 is about your child's family;

Section 3 is about the **biological mother** of the child and we therefore ask that the biological mother completes this section;

Section 4 is about the **mother (including biological) or female guardian** of the child and we therefore ask that the mother/female guardian completes this section;

Section 5 is about the **father (including biological) or male guardian** of the child and we ask that, if possible, the father/male guardian completes this section.

SECTION 1: QUESTIONS ABOUT YOUR CHILD

Part 1: Demographic details of your child

Today's date: ____ / ____ / 20_____

Child's name: _____

Child's date of birth: ____ / ____ / _____
dd mm yyyy

The person completing **Section 1** is:

- ☐ The biological mother of the child
- ☐ The biological father of the child
- ☐ Other female guardian/mother; I have lived with the child from when they were:_____[age] to: _____[age]
- ☐ Other male guardian/father; I have lived with the child from when they were: _____[age] to: _____[age]

Name of child's school: _____

School year of child: _____

Name of child's teacher:

_____

Child's sex:

- ☐ Male
- ☐ Female

To which ethnic group(s) does your child belong?

- ☐ New Zealand European/Pakeha
- ☐ Māori
- ☐ Pacific
- ☐ Other *please specify:* _____

Part 2: Residential history of your child

Please list ALL of the residential addresses for your child (including anywhere that they lived for one month or

more) starting with the address(es) during the pregnancy of the child and ending with the current address:

Home address	Full address:	From age (of child):	To age:

A (during pregnancy)			
B			
C			
D			
E			
F			

For all of the addresses listed above, please estimate the distance to the *nearest* farm or lifestyle block *(if the*

child lived on a farm or lifestyle block, this question refers to other surrounding farms/lifestyle blocks):

Please tick one box for each address

Home address	Did not live near a farm or lifestyle block	Less than 50 metres (next door)	Between 50 & 200 metres	Between 200 metres & 1 kilometre	More than 1 kilometre	What type of farm was it *(e.g. dairy, sheep, apple orchard etc.)*?
A (during pregnancy)	☐	☐	☐	☐	☐	
B	☐	☐	☐	☐	☐	
C	☐	☐	☐	☐	☐	
D	☐	☐	☐	☐	☐	

E	☐	☐	☐	☐	☐	
F	☐	☐	☐	☐	☐	

Do you know if pesticides were used on the farm(s) or lifestyle block(s)?

- ☐ Yes, pesticides were used
- ☐ No, pesticides were not used
- ☐ I am unsure whether pesticides were used
- ☐ Not applicable

For all of the addresses listed in **Question 1**, please estimate the distance to the *nearest* recreational park, golf

course, reserve or sports ground:

Please tick one box for each address

Home address	Less than 50 metres (next door)	Between 50 & 200 metres	Between 200 metres & 1 kilometre	More than 1 kilometre	Please specify if it was a park, golf course, reserve or sports ground?
A (during pregnancy)	☐	☐	☐	☐	
B	☐	☐	☐	☐	
C	☐	☐	☐	☐	
D	☐	☐	☐	☐	
E	☐	☐	☐	☐	
F	☐	☐	☐	☐	

Do you know if pesticides were used in the park(s), golf course(s), reserve(s) or sports ground(s) listed above?

☐ Yes, pesticides were used

☐ No, pesticides were not used

☐ I am unsure whether pesticides were used

Part 3: Use of pesticides at home

Please think about pesticides that have *ever* been used in and around the homes your child has lived in.

Pesticides can come in the form of sprays, bombs, poison pellets or bait, powder, chalk, traps, or ant stakes. These could have been applied by you or anyone else (including a professional pesticide applicator). Please include any pesticides used in your garden or yard and any that were used inside the home.

Examples include Raid Insect Control, Mortein Insect Control etc.

	6.1 Have pesticides been used in or around any of your child's homes to kill any of the following pests:	**6.2 What form was the pesticide(s)?** *(please tick all that apply)*	**6.3 Was the pesticide(s) *used* inside or outside the home?** *(please tick one)*	**6.4 What age was the child when the pesticide(s) was used?**	**6.5 How many times, on average, in total was the pesticide(s) applied?**

a	Rodents (rats and mice) ☐ Yes → ☐ No (go to Qb)	☐ Poison pellets/bait ☐ Poison powder ☐ Other_____ *(please specify)*	☐ Inside ☐ Outside ☐ Both ☐ Don't know	☐ During pregnancy *and/or* From_____[child's age] To _____[child's age]	_____[times per year] for _____[number of years] ☐ Don't know
b	Fleas (including pet treatment) ☐ Yes → ☐ No (go to Qc)	☐ Sprays ☐ Bombs ☐ Powder ☐ Liquid drops ☐ Other_____ *(please specify)*	☐ Inside ☐ Outside ☐ Both ☐ Don't know	☐ During pregnancy *and/or* From_____[child's age] To _____[child's age]	_____[times per year] for _____[number of years] ☐ Don't know
	6.1 Have pesticides been used in or around any of your child's homes to kill any of the following pests:	**6.2 What form was the pesticide(s)?** *(please tick all that apply)*	**6.3 Was the pesticide(s) *used* inside or outside the home?** *(please tick one)*	**6.4 What age was the child when the pesticide(s) was used?**	**6.5 How many times, on average, in total was the pesticide(s) applied?**
c	Cockroaches ☐ Yes → ☐ No (go to Qd)	☐ Sprays ☐ Bombs ☐ Powder/chalk ☐ Roach traps ☐ Gel	☐ Inside ☐ Outside ☐ Both ☐ Don't know	☐ During pregnancy *and/or* From_____[child's age] To _____[child's age]	_____[times per year] for _____[number of years] ☐ Don't know

		☐ Other_____ (please specify)			
d	Ants ☐ Yes → ☐ No (go to Qe)	☐ Sprays ☐ Powder/chalk ☐ Traps/ant stakes ☐ Other_____ (please specify)	☐ Inside ☐ Outside ☐ Both ☐ Don't know	☐ During pregnancy *and/or* From_____[child's age] To _____[child's age]	_____[times per year] for _____[number of years] ☐ Don't know
e	Other flying or crawling insects ☐ Yes → ☐ No (go to Qf)	☐ Sprays ☐ Bombs ☐ Powder/chalk ☐ Other_____ (please specify)	☐ Inside ☐ Outside ☐ Both ☐ Don't know	☐ During pregnancy *and/or* From_____[child's age] To _____[child's age]	_____[times per year] for _____[number of years] ☐ Don't know
f	Fungus, weeds, snails or slugs? ☐ Yes → ☐ No (go to Qg)	☐ Sprays ☐ Pellets ☐ Other_____ (please specify)	☐ Inside ☐ Outside ☐ Both ☐ Don't know	☐ During pregnancy *and/or* From_____[child's age] To _____[child's age]	_____[times per year] for _____[number of years] ☐ Don't know
g	Any other pests?	☐ Sprays	☐ Inside	☐ During pregnancy *and/or*	_____[times per

	☐ Yes → ☐ No (go to Q7)	☐ Bombs ☐ Powder Other_____ ☐ *(please specify)*	☐ Outside ☐ Both ☐ Don't know	From_____[child's age] To _____[child's age]	year] for _____[number of years] ☐ Don't know

IF YOU ANSWERED *'NO'* TO ALL OF QUESTION 6.1, PLEASE GO TO QUESTION 8

Was your child inside the house at the time when pesticide sprays or bombs were being used inside?

- ☐ No
- ☐ Yes, but only rarely
- ☐ Yes, sometimes
- ☐ Yes, most of the time
- ☐ Don't know

Has your child *ever* been treated for head lice (i.e. nits) or scabies?

- ☐ Yes **AT WHAT AGE(S):** _____**[ages]**
- ☐ No **PLEASE GO TO QUESTION 10**
- ☐ Don't know **PLEASE GO TO QUESTION 10**

What were the names of the product(s) that were used? *(if you are unsure, please write 'don't know')*

_____
_____

_____
_____

_____
_____

Has your child *ever* used insect repellent?

☐ Yes **AT WHAT AGE(S):**
_____**[ages]**

☐ No **PLEASE GO TO QUESTION 12**

☐ Don't know **PLEASE GO TO QUESTION 12**

What were the names of the product(s) that were used? *(if you are unsure, please write 'don't know')*

_____
_____

_____
_____

_____

_____

Part 4: Living on a farm

Has your child *ever* lived on a farm since birth?

☐ Yes

☐ No **PLEASE GO TO QUESTION 16**

For **all** of the farms that your child has lived on since birth, please state the **type** of farm and what **years** your

child lived on the farm: *(please start with first farm the child lived on and end with the most recent)*

	Type of farm (e.g. sheep, dairy, apple orchard):	*Years lived on the farm:*
Farm 1	_____	From:_____[Year] To:_____[Year]
Farm 2	_____	From:_____[Year] To:_____[Year]
Farm 3	_____	From:_____[Year] To:_____[Year]

Farm 4 _____ From:_____[Year]
To:_____[Year]

Farm 5 _____ From:_____[Year]
To:_____[Year]

Were pesticides used on any of the farms that your child lived on?

☐ Yes

☐ No **PLEASE GO TO QUESTION 16**

☐ Don't know **PLEASE GO TO QUESTION 16**

Please answer the following questions for each farm your child lived on:

Farm	15.1. What were the types and names of the pesticides used? *(e.g. type: herbicide, name: Simazine;* *type: insecticide, name: 'Viper' sheep dip).* ***If you don't know the name/type, please write 'don't know' and complete questions 15.2-15.5***	15.2. How often was your child present when pesticides were applied?	15.3. How *long* after pesticides were applied did your child usually enter the area that was treated with pesticides *(e.g. the orchard)*?	15.4. How *long* after pesticides were applied did your child come into contact with animals that were treated with pesticides?	15.5. *Where* were pesticides stored in relation to the house your child was living in?
Farm 1		☐ Pesticides weren't used in this period ☐ Never ☐ Rarely ☐ Sometimes ☐ Often	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never entered the area ☐ More than a week later ☐ 1-7 days later ☐ That day ☐ Straight away	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never came into contact ☐ More than a week later ☐ 1-7 days later ☐ That day ☐ Straight away	☐ In the home ☐ In the garage ☐ In a shed Other: _____ ☐ *(please specify)*
Farm 2		☐ Pesticides weren't used in this period ☐ Never ☐ Rarely ☐ Sometimes ☐ Often	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never entered the area ☐ More than a week later ☐ 1-7 days later ☐ That day	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never came into contact ☐ More than a week later ☐ 1-7 days later ☐ That day	☐ In the home ☐ In the garage ☐ In a shed Other: _____ ☐ *(please specify)*

			☐ Straight away	☐ Straight away	

Farm number	**What was the type and name of the pesticide(s) used** (e.g. herbicide, Simazine)?	**How often was your child present when pesticides were applied?**	**How *long* after pesticides were applied did your child usually enter the area that was treated with pesticides** *(e.g. the orchard)***?**	**How *long* after pesticides were applied did your child come into contact with animals that were treated with pesticides?**	***Where* were pesticides stored in relation to the house the child was living in?**
Farm 3		☐ Pesticides weren't used in this period ☐ Never ☐ Rarely ☐ Sometimes ☐ Often	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never entered the area ☐ More than a week later ☐ 1-7 days later ☐ That day ☐ Straight away	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never came into contact ☐ More than a week later ☐ 1-7 days later ☐ That day ☐ Straight away	☐ In the home ☐ In the garage ☐ In a shed Other: _____ ☐ *(please specify)*
Farm 4		☐ Pesticides weren't used in this period ☐ Never ☐ Rarely ☐ Sometimes ☐ Often	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never entered the area ☐ More than a week later ☐ 1-7 days later ☐ That day	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never came into contact ☐ More than a week later ☐ 1-7 days later ☐ That day	☐ In the home ☐ In the garage ☐ In a shed Other: _____ ☐ *(please specify)*

				☐ Straight away	☐ Straight away	
	Farm 5		☐ Pesticides weren't used in this period ☐ Never ☐ Rarely ☐ Sometimes ☐ Often	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never entered the area ☐ More than a week later ☐ 1-7 days later ☐ That day ☐ Straight away	☐ Not relevant to type of farm ☐ Pesticides weren't used in this period ☐ Never came into contact ☐ More than a week later ☐ 1-7 days later ☐ That day ☐ Straight away	☐ In the home ☐ In the garage ☐ In a shed Other: _____ ☐ *(please specify)*

Part 5: Visiting a farm

Has your child *ever* visited a farm *(not including the farm(s) the child has lived on)*?

- ☐ Yes, once a week or more
- ☐ Yes, two or three times a month
- ☐ Yes, once a month
- ☐ Yes, a few times a year **PLEASE GO TO QUESTION 18**
- ☐ Yes, once a year or less **PLEASE GO TO QUESTION 18**
- ☐ No, never **PLEASE GO TO QUESTION 18**

For **all** of the farms that your child has visited once a month or more, please state the **type** of farm and what

years your child visited: *(please start with first farm the child visited and end with the most recent)*

	Type of farm (e.g. sheep, dairy, apple orchard):	*Years farm was visited:*
Farm 1	_____	From:_____[Year] To:_____[Year]
Farm 2	_____	From:_____[Year] To:_____[Year]
Farm 3	_____	From:_____[Year] To:_____[Year]
Farm 4	_____	From:_____[Year] To:_____[Year]
Farm 5	_____	From:_____[Year] To:_____[Year]

Part 6: Any other contact with pesticides

Are you aware of any pesticides that your child may have been in contact with which you have not already

described above? *(e.g. city council spraying)*

- ☐ Yes **Please explain:**_____

  _____

  _____
- ☐ No
- ☐ Don't know

Part 7: Your child's diet

Please answer Questions 19 to 28 for <u>the last 12 months</u>

How many portions of **fruit** does your child eat on average (1 portion=one child's handful)?

- ☐ Never eats fruit **PLEASE GO TO QUESTION 22**
- ☐ Less than 2 portions a week
- ☐ 2 to 6 portions a week
- ☐ 1 portion a day
- ☐ 2 portions a day
- ☐ 3 or more portions a day

Is the **fruit** washed before it is eaten?

- ☐ No, never
- ☐ Yes, but only rarely
- ☐ Yes, sometimes
- ☐ Yes, almost always
- ☐ Don't know

Is the **fruit** organic?

- ☐ No, never
- ☐ Yes, but only rarely
- ☐ Yes, sometimes
- ☐ Yes, almost always
- ☐ Don't know

How many portions of **vegetables** does your child eat on average (1 portion=one child's handful)?

- ☐ Never eats vegetables **PLEASE GO TO QUESTION 25**
- ☐ Less than 2 portions a week
- ☐ 2 to 6 portions a week
- ☐ 1 portion a day

- [ ] 2 portions a day
- [ ] 3 or more portions a day

Are the **vegetables** washed before eaten?

- [ ] No, never
- [ ] Yes, but only rarely
- [ ] Yes, sometimes
- [ ] Yes, almost always
- [ ] Don’t know

Are the **vegetables** organic?

- [ ] No, never
- [ ] Yes, but only rarely
- [ ] Yes, sometimes
- [ ] Yes, almost always
- [ ] Don’t know

How often does your child eat **other organic** foods (1 portion=one child's handful)?

- ☐ Never eats other organic food
- ☐ Less than 3 portions a week
- ☐ 3 to 6 portions a week
- ☐ 7 to 13 portions a week
- ☐ 14 or more portions a week
- ☐ Don't know

How often does your child eat **canned food** (or food prepared with canned ingredients)?

- ☐ Never
- ☐ Less than once a week
- ☐ 1 to 2 times a week
- ☐ 3 to 4 times a week
- ☐ 5 to 6 times a week
- ☐ 7 or more times a week
- ☐ Don't know

How often does your child eat hot meals that have been heated or stored in **plastic containers** (both home-

cooked and take-away meals)?

- ☐ Never
- ☐ Less than once a week
- ☐ 1 to 2 times a week
- ☐ 3 to 4 times a week
- ☐ 5 to 6 times a week
- ☐ 7 or more times a week
- ☐ Don't know

How many litres of water does your child drink from a **plastic bottle**?

- [ ] Never drinks water from a plastic bottle
- [ ] Less than 1 litre a week
- [ ] 1 to 6 litres a week
- [ ] 1 to 2 litres a day
- [ ] 3 more litres a day
- [ ] Don't know

Part 8: Your child's health

How much does your child weigh? *(please choose one option)*

_____ Kilograms *OR*

_____ Stone _____ Pounds *OR*

_____ Pounds _____ Ounces

How tall is your child? *(please choose one option)*

_____ Centimetres *OR*

_____ Metres *OR*

_____ Feet _____ Inches

Was your child born prematurely? (i.e. less than 37 weeks gestational age)

- [ ] Yes **HOW MANY WEEKS PREMATURE?_____[weeks]**
- [ ] No
- [ ] Don't know

What was the weight of your child when he/she was born? *(please choose one option)*

_____ Kilograms *OR*

_____ Grams *OR*

_____ Pounds _____ Ounces

Has your child *ever* had a head injury which resulted in damage to the scalp, skull or brain?

☐ Yes **HOW MANY?** _____[Number of head injuries]

☐ No **PLEASE GO TO QUESTION 39**

At what age did your child have the head injury?

If more than one injury: Injury 2: *Injury 3:*

_____[age] _____[age]
_____[age]

As a result of the head injury, did your child lose consciousness?

If more than one injury: Injury 2: *Injury 3:*

☐ Yes ☐ Yes ☐ Yes

☐ No ☐ No ☐ No

IF YOU HAVE ANSWERED *'NO' FOR ALL,* PLEASE GO TO QUESTION 39

For approximately how long was your child unconscious?

If more than one injury: Injury 2: *Injury 3:*

_____[minutes] _____[minutes]
_____[minutes]

As a result of the head injury, did your child have any symptoms of concussion (such as appearing dazed, crying

excessively or repeated vomiting)?

If more than one injury: Injury 2: *Injury 3:*

☐ Yes ☐ Yes ☐ Yes

☐ No ☐ No ☐ No

IF YOU HAVE ANSWERED *'NO' FOR ALL,* PLEASE GO TO QUESTION 39

For approximately how long did this/these symptom(s) last?

If more than one injury: Injury 2: Injury 3:

_____[minutes] _____[minutes]
_____[minutes]

Has your child *ever* been diagnosed with any of the following *(please tick all that apply):*

Age of diagnosis: Please list the medication (if applicable):

- ☐ Attention deficit hyperactivity disorder (ADHD) or Attention deficit disorder (ADD) _____ _____
- ☐ Autism _____ _____
- ☐ Asperger's syndrome _____ _____
- ☐ Eating disorder _____ _____
- ☐ Traumatic brain injury _____ _____
- ☐ Intellectual disability _____ _____
- ☐ Reading difficulties _____ _____
- ☐ Seizures or epilepsy _____ _____
- ☐ Speech or language difficulties _____ _____
- ☐ Other learning disability _____ _____
- ☐ Nutritional deficiency _____ _____
- ☐ Mental illness _____ _____

☐ Behavioural problems _____

☐ _____

Other:_____ _____

☐ _____

(please specify)

None of the above

Has your child had wheezing or whistling in the chest in the past 12 months?

☐ Yes

☐ No

Has your child *ever* had asthma?

☐ Yes

☐ No **PLEASE GO TO QUESTION 44**

Was the diagnosis confirmed by a doctor?

☐ Yes **AGE OF DIAGNOSIS?** _____**[age]**

☐ No

In the past 12 months, has your child taken any medicines, pills, inhalers, or other medication for asthma?

☐ Yes

☐ No

Has your child *ever* had hayfever?

☐ Yes

☐ No

Has your child had an itchy rash which was coming and going for at least 6 months at any time in the past 12 months?

☐ Yes

☐ No

Has your child *ever* had eczema?

☐ Yes **AT AGE(S):** _____**[ages]**

☐ No

Part 9: Your child's early life

Was your child born in New Zealand?

☐ Yes

☐ No **WHERE WAS YOUR CHILD BORN?**

_____**[country]**

How many years has your child lived in New Zealand? _____ [years]

During the child's **first year of life,** was he/she given paracetamol (e.g. Panadol, Pamol)?

☐ Never

☐ Once in the child's first year of life

☐ A few times in the child's first year of life

- [ ] Once a month
- [ ] Two or three times a month
- [ ] Once a week or more
- [ ] Don't know

During the child's **first year of life**, how many hours per day, on average, was the child around someone

(including both parents) who was smoking?

Please include time at home, childcare, away from home, and in the car.

- [ ] Not at all
- [ ] Less than one hour per day
- [ ] One hour per day or more
- [ ] Don't know

When your child was a toddler (aged 1-3 years), did they put **non-food** items in their mouth?

- [ ] No, never
- [ ] Yes, a few times a month or less
- [ ] Yes, a few times a week
- [ ] Yes, about once a day
- [ ] Yes, frequently during the day

Did your child ever go to a childcare facility or pre-school when they were **under 5 years** of age?

- [ ] Yes
- [ ] No

Part 10: Your child's home environment

The following questions relate to the primary dwelling of your child (i.e. where they live most of the time)

What language(s) are spoken in your home around the child?

_____
____

In the last 12 months, how many hours per day, on average, was your child around someone (including both

parents) who was smoking? *Please include time at home, childcare, away from home, and in the car.*

- ☐ Not at all
- ☐ Less than one hour per day
- ☐ One hour per day or more
- ☐ Don't know

Does/did your child's home have peeling paint anywhere in the home? *(please tick all that apply)*

	Never had	At this moment	During the pregnancy	During the 1st year of the child's life	At another time	Don't know
Peeling paint inside	☐	☐	☐	☐	☐	☐
Peeling paint outside	☐	☐	☐	☐	☐	☐

Does/did your child's home have visible moisture or mould spots on the walls or ceiling, anywhere in the home?

(please tick all that apply)

	Never had	At this moment	During the pregnancy	During the 1st year of the child's life	At another time	Don't know
Moisture spots	☐	☐	☐	☐	☐	☐
Mould spots	☐	☐	☐	☐	☐	☐

IF YOU'VE ANSWERED *'NEVER HAD'* FOR BOTH MOISTURE AND MOULD SPOTS,

PLEASE GO TO QUESTION 59

Where in the home did/do these damp/mould spots occur? *(please tick all that apply)*

- ☐ Living room
- ☐ Child's bedroom
- ☐ Parent's bedroom
- ☐ Kitchen
- ☐ Bathroom
- ☐ Other

Did/does the total area affected by damp/mould spots exceed the size of one postcard?

- ☐ Yes
- ☐ No

What is the source of the water supply for your child's current home?

- ☐ Town water (i.e. water supplied by the city council)
- ☐ Roof water
- ☐ Bore or well water pumped from the property

In your child's current home, is there a water filter fitted at the tap?

- ☐ Yes
- ☐ No

☐ Don't know

What pets have been living in your child's home since their birth? *(please tick all that apply)*

☐ Dog(s)

☐ Cat(s)

☐ Other, please specify: _____

☐ Never had pets **PLEASE GO TO QUESTION 64**

How many times, on average, have the pets been treated for fleas, ticks or mites?

☐ Never **PLEASE GO TO QUESTION 64**

☐ Once a year or less

☐ A few times a year

☐ Once a month

☐ Two or three times a month

☐ Once a week or more

How was the treatment usually administered? *(please tick all that apply)*

☐ Spray

☐ Oral (i.e. mouth)

☐ Dermal (i.e. applied to their skin)

☐ Other, please specify: _____

What is your household's approximate gross (before tax, levies etc.) annual income?

- ☐ $1 – 20,000
- ☐ $20,001 – 50,000
- ☐ $50,001 - 70,000
- ☐ $70,001 – 100,000
- ☐ $100,001 – 150,000
- ☐ $150,001 or more
- ☐ Prefer not to say

Part 11: Your child's current lifestyle

About how many books does your child have?

- ☐ None
- ☐ 1 to 2 books
- ☐ 3 to 9 books
- ☐ 10 or more books

About how often does someone read stories to your child at home?

- ☐ Never
- ☐ Less than once a week
- ☐ Once a week
- ☐ A few times a week
- ☐ Everyday

About how often does your child read to him/herself for enjoyment?

- ☐ Never because my child does not like reading
- ☐ Never because my child is too young to read to him/herself
- ☐ Less than once a week

☐ Once a week

☐ A few times a week

☐ Everyday

How often does your child: *(please tick one box for each question a to e)*

	Almost never	Sometimes	Almost always
a) Make his/her own bed?	☐	☐	☐
b) Clean his/her own room?	☐	☐	☐
c) Clean up after spills?	☐	☐	☐
d) Bathe him/herself?	☐	☐	☐
e) Pick up after him/herself?	☐	☐	☐

Is there a musical instrument (e.g. piano, drums, guitar etc.) that your child can use at home?

☐ Yes

☐ No

What hobbies does your child currently have? *(please list all hobbies)*

_____

_____

_____

_____

Does your child receive special lessons or belong to a club/organisation for extra curricular activities such as

dance, sport, art etc.?

☐ Yes: please specify:
_____

☐ No

How often have you or another family member taken your child to any type of museum <u>within the last 12</u>

<u>months</u>? *(not including school trips)*

- [ ] Never
- [ ] Once or twice
- [ ] Several times
- [ ] About once a month
- [ ] About once a week

How often have you or another family member taken your child to any type of musical or theatrical performance

within the last 12 months? *(not including school performances)*

- [ ] Never
- [ ] Once or twice
- [ ] Several times
- [ ] About once a month
- [ ] About once a week

About how often does your whole family get together with relatives or friends?

- [ ] Once a year or less
- [ ] A few times a year
- [ ] Once a month
- [ ] Two or three times a month
- [ ] Once a week or more

How often do you eat dinner together as a family?

- [ ] Never
- [ ] Less than once a week
- [ ] Once a week
- [ ] A few times a week

☐ Everyday

How often does your child eat a meal in front of the TV?

☐ Never

☐ Less than once a week

☐ Once a week

☐ A few times a week

☐ Everyday

How many times in the last 7 days have you or the child's father (or guardian):

(please tick one box for each question a to c)

	Zero	Once	More than once
a) Taken away TV or other privileges?	☐	☐	☐
b) Praised your child?	☐	☐	☐
c) Shown your child physical affection like kissing or hugging?	☐	☐	☐

Think for a moment about a typical weekday for your family. How much time would you say your child spends

watching TV/DVDs or movies on a computer/phone on a typical weekday *(either in your home or elsewhere)*?

_____[hours]

Now, think about a typical weekend day (Saturday or Sunday) for your family. How much time would you say

your child spends watching TV/DVDs or movies on a computer/phone on a typical weekend day (*either in*

your home or elsewhere)?

_____[hours]

Does your child ever play on a computer/tablet or play video games like X-Box, Playstation etc.?

☐ Yes

☐ No **PLEASE GO TO QUESTION 82**

How much time does your child spend playing computer or video games?

a) on a typical weekday? _____[hours per day]

b) on a typical weekend day? _____[hours per day]

How many hours per day, on average, does your child engage in physical activity *(e.g. running around, riding a*

scooter etc.)?

_____[hours per day in Summer]

_____[hours per day in Winter]

How many hours per day, on average, does your child spend playing outside when they are not at school?

_____[hours per day in Summer]

_____[hours per day in Winter]

<u>In the past 7 days</u>, how many hours, on average, has your child spent taking part in creative activities *(outside of*

school hours) e.g. dancing, music, arts, crafts etc.?

_____[hours per week]

How many hours, on average, does your child spend playing sports *(outside of school hours)*?

_____[hours per week in Summer]

_____[hours per week in Winter]

On school days, what time does your child usually go to bed?

___ ___: ___ ___ PM

On school days, what time does your child usually wake up?

___ ___: ___ ___ AM

In the weekend or holidays, what time does your child usually go to bed?

___ ___: ___ ___ PM

In the weekend or holidays, what time does your child usually wake up?

___ ___: ___ ___ AM

SECTION 2: QUESTIONS ABOUT YOUR CHILD'S FAMILY

Part 12: Your child's family

What is your current marital status?

- ☐ Married/Civil union (not separated)
- ☐ In a de facto relationship

What age was the child when this occurred?

- ☐ Separated _____[age]
- ☐ Divorced _____[age]

☐ Widowed _____[age]

☐ Single

Which of the following best describes your child's past and present family situation? *Please tick all that apply*

Child's age:

☐ Living with biological mother and father From:_____[age] to :_____[age]

PLEASE GO TO QUESTION 94

☐ Living with biological mother only From:_____[age] to :_____[age]

☐ Living with biological father only From:_____[age] to :_____[age]

☐ Living with biological mother and partner From:_____[age] to :_____[age]

☐ Living with biological father and partner From:_____[age] to :_____[age]

☐ Living with guardian(s), _____ From:_____[age] to :_____[age]

(please specify)

☐ Other:_____*(please specify)* From:_____[age] to :_____[age]

Does your child live with you for most of a typical week?

☐ Yes **PLEASE GO TO QUESTION 94**

☐ No

Where does your child live most of the time?

☐ With their other parent/guardian

☐ With another relative (e.g. grandparents)

☐ Boarding school

☐ Other, please specify:_____

How many *older* brothers and/or sisters does your child have? (include half brothers and sisters)

_____ Brothers _____Sisters

How many *younger* brothers and/or sisters does your child have? (include half brothers and sisters)

_____ Brothers _____Sisters

Does your child live with these siblings?

- ☐ Not applicable
- ☐ Yes, all of the time
- ☐ Yes, some of the time
- ☐ Yes, but not very often
- ☐ No, never

What is the child's biological mother's date of birth: _____ / _____ / _____

dd mm yyyy

What is the child's biological father's date of birth: _____ / _____ / _____

dd mm yyyy

Part 13: Family medical history

Have any biological family members (e.g. parents, siblings, grandparents, uncles/aunts) of the child had any of

the following? If you tick a box, please specify the family member's relationship to the child.

Please tick all that apply

	Family member:		***Family member:***
☐ Alzheimer's disease	_____	☐ Alcohol/drug abuse	_____
☐ Parkinson's disease	_____	☐ Mood disorder	_____
☐ Tourette's syndrome	_____	☐ Mental illness	_____
☐ Cerebral palsy	_____	☐ Autism	_____
☐ Motor neurone disease	_____	☐ ADHD/ADD	_____
☐ Polyneuropathy	_____	☐ Intellectual disability	_____
☐ Dementia	_____	☐ Traumatic head injury	_____

☐	Suicide _____	☐	Seizures or epilepsy _____
☐	Asthma _____	☐	Reading difficulties _____
☐	Allergies _____	☐	Other learning disability _____
☐	Migraine headaches _____	☐	Speech or language difficulties _____
☐	Multiple sclerosis _____	☐	Thyroid disease _____
		☐	Other: _____
			_____
			(please specify)

SECTION 3: QUESTIONS FOR THE BIOLOGICAL MOTHER OF THE CHILD

The questions in this section relate to the pregnancy and breastfeeding period of the child. If you are not the biological mother, please go to Section 4.

Part 14: Your pregnancy

During the pregnancy**,** how often did you take paracetamol (e.g. Panadol, Pamol)?

Please tick one box for each trimester

	1st trimester	2nd trimester	3rd trimester
Never	☐	☐	☐
Once in the trimester	☐	☐	☐
A few times in the trimester	☐	☐	☐
Once a month	☐	☐	☐
Two or three times a month	☐	☐	☐
Once a week or more	☐	☐	☐
Don't know	☐	☐	☐

Did you drink alcohol while pregnant with the child?

☐ Yes

☐ No **PLEASE GO TO QUESTION 103**

☐ Don't know **PLEASE GO TO QUESTION 103**

On average, how often did you drink alcohol while pregnant?

Please tick one box for each trimester

	1st trimester	2nd trimester	3rd trimester
Less than once a month	☐	☐	☐
1 to 2 times a week	☐	☐	☐
3 to 5 times a week	☐	☐	☐
Daily	☐	☐	☐
Don't know	☐	☐	☐

Did you smoke tobacco while pregnant with the child?

☐ Yes

☐ No **PLEASE GO TO QUESTION 105**

☐ Don't know **PLEASE GO TO QUESTION 105**

What did you smoke and how many did you smoke per day during the pregnancy?

	Number smoked per day:
☐ Cigarettes	_____[per day]
☐ Cigars	_____[per day]
☐ Pipe	_____[per day]
☐ Other: _____	_____[per day]

(please specify)

During the pregnancy, did you spend more than an hour per day, on average, around someone smoking

close enough for you to smell the smoke?

- [ ] Yes
- [ ] No
- [ ] Don’t know

Part 15: Your job held during pregnancy

The following questions refer to **the job that you held while <u>pregnant</u> with the child.**

☐ Tick here if you *didn't work* during the pregnancy, then **PLEASE GO TO QUESTION 115**

106. **Period of Employment:**

From …… [year] To ……. [year]

107. How many **hours per week** did you work in this job? (on average) …… [hours per week]

108. How many **days per week** did you work in this job? (on average): …….. [days per week]

109. Did you regularly work **outside 8-5 o'clock** for this job?

Yes ☐ → ***if yes,*** please specify:……

No ☐

110. What was the **main activity** of the company or organisation you worked for?

(for example: what was produced, what service was provided)

……

……

……

……

……

……

111. What **department** did you work in?

……

112.

What was your **job title**?

……

113. Please describe the specific job in detail, including:

What did you do?

How was it done?

What **materials** were used?

What **tools** or **machinery** were used?

What type of **process** was it?

(it may help to describe what a typical day involved)

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During the pregnancy, did you *ever* carry out any activities at work that involved contact with pestcides?

- ☐ Yes, I directly worked with pesticides
- ☐ Yes, pesticides were used in my work environment **but** I didn't handle them directly
- ☐ Yes, I handled products that were treated with pesticides
- ☐ No, pesticides were not used in my work environment

Part 16: The breastfeeding period

Was your child breastfed?

- ☐ Yes
- ☐ No **PLEASE GO TO QUESTION 120**

For how many months was your child breastfed? _____[months]

For how many months was your child ***exclusively*** breastfed? _____[months]

Did you drink alcohol while breastfeeding the child?

- ☐ Yes
- ☐ No **PLEASE GO TO QUESTION 120**
- ☐ Don't remember **PLEASE GO TO QUESTION 120**

On average, how often did you drink alcohol while breastfeeding the child?

- ☐ Less than once a month
- ☐ 1 to 2 times a week
- ☐ 3 to 5 times a week
- ☐ Daily
- ☐ Don't know

SECTION 4: QUESTIONS FOR THE FEMALE GUARDIAN/MOTHER (including biological)

Part 17: Demographic details

This section was completed by:

- ☐ The biological mother of the child **PLEASE GO TO QUESTION 122**
- ☐ Other female guardian
- ☐ The biological father of the child
- ☐ Other male guardian

Please complete Section 4 for the <u>mother or female guardian</u> of the child

What is your date of birth: _____ / _____ / _____

dd mm yyyy

What is your highest level of education?

- ☐ None
- ☐ Primary school
- ☐ Secondary school
- ☐ Technical or trade school diploma
- ☐ Undergraduate university degree
- ☐ Postgraduate university degree

Part 18: Your work history since the birth of the child

123. Please list **all of the jobs held since the child was born (or if you are not the biological mother, since you have lived with the child**) in order from the first job held after the birth of the child to the most recent job held.

	Job Number	Who was your **employer**? (Name and Location) *(For example: Massey University, Wellington)*	Over what **period** did you work for this employer?	What was the **main activity** of the **company** or **organisation** you worked for? *(For example: sheep farming, selling shoes, making clothes)*	What **department** did you work in, and what was your **job title**?	Did you use pesticides in this job?

1.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No
2.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No
3.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No

4.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No
5.	Name …… Location	From: …..……[year] To: …..……[year]		Department: …….. Job title:	☐ Yes ☐ No

Part 19: Work-related pesticide exposure

IF YOU HAVEN'T WORKED ON A FARM SINCE THE BIRTH OF THE CHILD (or if you are not the biological mother, since you have lived with the child), PLEASE GO TO QUESTION 134.

For **all** of the farms that you have worked on **since the birth of the child**, please state the **type** of farm and

what **years** you worked on the farm:

(please start with the first farm since the birth of the child and end with the most recent)

Type of farm (e.g. sheep, dairy, apple orchard): Years worked on the farm:

Farm 1 _____ From:_____[Year]
To:_____[Year]

Farm 2 _____ From:_____[Year]
To:_____[Year]

Farm 3 _____ From:_____[Year]
To:_____[Year]

Farm 4 _____ From:_____[Year]
To:_____[Year]

Farm 5 _____ From:_____[Year]

To:_____[Year]

After the birth of the child (or if you are not the biological mother, since you have lived with the child), have you

ever carried out any activities at work that involved contact with pestcides?

- ☐ Yes, I have directly worked with pesticides
- ☐ Yes, pesticides were used in my work environments **but** I didn't handle them directly
- ☐ Yes, I handled products that were treated with pesticides
- ☐ No, pesticides have never been used in any of my work environments **PLEASE GO TO QUESTION 134**

The following questions ask about four different time periods: a) current; b) during pregnancy; c) during the

1st year of the child's life; and d) in the past but after the child's 1st year of life.

Please answer the questions for each of the four time periods.

If you are <u>not</u> the biological mother, please answer the questions for the time periods that are relevant to you.

Please indicate your main areas of pesticide contact *(even if you didn't work with them directly)*:

	a) Current (tick)	**b) During pregnancy** (tick)	**c) During the 1st year of the child's life** (tick)	**d) In the past but after the child's 1st year of life** (tick)
Field crops				
1. Cereals (wheat, barley, oats, rye etc.)	☐	☐	☐	☐
2. Oilseeds (oilseed rape, linseed)	☐	☐	☐	☐
3. Potatoes	☐	☐	☐	☐
4. Sugar beet	☐	☐	☐	☐
5. Grassland and/or fodder crops	☐	☐	☐	☐
6. Other field crops ……..*(please specify)*	☐	☐	☐	☐
Horticulture				
7. Orchard crops (apples, pears, plums, kiwi, etc.)	☐	☐	☐	☐
8. Soft fruits (strawberries, currants etc.)	☐	☐	☐	☐
9. Hops	☐	☐	☐	☐
10. Mushrooms	☐	☐	☐	☐
11. Outdoor vegetables	☐	☐	☐	☐
12. Glasshouse vegetables	☐	☐	☐	☐
Animal rearing				
13. Animal treatment	☐	☐	☐	☐
14. Animal house area treatment	☐	☐	☐	☐
Non-food production				
15. Gorse control	☐	☐	☐	☐
16. Wood preservative application	☐	☐	☐	☐
17. Glasshouse crops (ornamental)	☐	☐	☐	☐
18. Outdoor ornamental flowers and bulbs	☐	☐	☐	☐
19. Outdoor plant nursery	☐	☐	☐	☐
20. Golf courses, bowling greens, reserves, sport grounds	☐	☐	☐	☐
21. Amenity weed control: roads, pavements etc.	☐	☐	☐	☐
22. Forestry	☐	☐	☐	☐
23. Aquatic	☐	☐	☐	☐

24. Pest control	☐	☐	☐	☐
25. Other ……*(please specify)*	☐	☐	☐	☐
26. Other ……*(please specify)*	☐	☐	☐	☐
27. Other ……*(please specify)*	☐	☐	☐	☐
None of the above	☐	☐	☐	☐

If you ticked *any* of these boxes please complete question 127, otherwise go to question 128

For each box that you ticked for Question 126, please complete the table below for the pesticides that you had contact with:

Please list the number from question 126 in column 1 *(e.g. number 10 for mushrooms, number 22 for forestry etc.)*

N.o from Qu 126	Type and name of pesticide	What years were you exposed to the pesticide?	Weeks per year exposed	Hours per day exposed	What was the pesticide used for?	How was the pesticide applied? (e.g. backpack sprayer, aerial spraying)	How are/were you exposed to the pesticide? *(tick all that apply)*
E.g. 20.	*Herbicide,* *Round-up*	From:*2005* [Year] To:*2007* [Year]	*20*	*0.5*	*To kill weeds around the golf course*	*Backpack sprayer*	☐ **I mixed the pesticide** ☑ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**
		From:_____ [Year] To:_____ [Year]					☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**
		From:_____ [Year] To:_____ [Year]					☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment**

							☐ **I worked in an environment where it was applied**
N.o from Qu 126	**Type and name of pesticide**	From:_____ [Year] To:_____ [Year] **What years were you exposed to the pesticide?**	**Weeks per year exposed**	**Hours per day exposed**	**What was the pesticide used for?**	**How was the pesticide applied?** (e.g. backpack sprayer, aerial spraying)	☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied** **How are/were you exposed to the pesticide?** *(tick all that apply)*
		From:_____ [Year] To:_____ [Year]					☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**
		From:_____ [Year] To:_____ [Year]					☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**
		From:_____					☐ **I mixed the pesticide**

			[Year] To:_____ [Year]					☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**
			From:_____ [Year] To:_____ [Year]					☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**

What types of protective equipment do/did you usually use when you had contact with pesticides?

Please tick all that apply for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
Didn't use protective equipment	☐	☐	☐	☐
Cartridge respirator, gas mask	☐	☐	☐	☐
Dust mask	☐	☐	☐	☐
Full face shield	☐	☐	☐	☐
Hat	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Chemically resistant gloves (like neoprene or nitrile gloves)	☐	☐	☐	☐
Fabric/leather gloves	☐	☐	☐	☐
Apron	☐	☐	☐	☐
Chemically resistant boots	☐	☐	☐	☐
Cloth coveralls (complete suit)	☐	☐	☐	☐
Disposable outer clothing (like Tyvek®)	☐	☐	☐	☐
Other…… …… *(please specify)*	☐	☐	☐	☐

After having had contact with pesticides, *when* did/do you usually change into clean work clothes?

Please tick one box for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
Right away	☐	☐	☐	☐
At lunch	☐	☐	☐	☐
At the end of that work day	☐	☐	☐	☐
At the end of the next work day	☐	☐	☐	☐
Later in the week	☐	☐	☐	☐
Always used disposable outer clothing	☐	☐	☐	☐

After having had contact with pesticides, ***where*** do/did you usually clean your work clothes?

Please tick one box for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st**

				year of life
In the family washing machine	☐	☐	☐	☐
In a separate washing machine at home	☐	☐	☐	☐
In a separate washing machine at work	☐	☐	☐	☐
Always used disposable outer clothing	☐	☐	☐	☐
Other ……. *(please specify)*	☐	☐	☐	☐

After having had contact with pesticides, where do/did you usually take off your boots/shoes?

Please tick one box for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
At work	☐	☐	☐	☐
In the family home	☐	☐	☐	☐
Outside the family home	☐	☐	☐	☐
Other ……. *(please specify)*	☐	☐	☐	☐

After having had contact with pesticides, do/did you wear your work clothes into your house?

Please tick one box for each column a to d

	a) Current	b) During pregnancy	c) During the 1st year of the child's life	d) In the past but after the child's 1st year of life
No, never	☐	☐	☐	☐
Yes, but only rarely	☐	☐	☐	☐
Yes, sometimes	☐	☐	☐	☐
Yes, often	☐	☐	☐	☐

Did you ever wash the working clothes of other workers who had contact with pesticides?

Please tick one box for each column a to d

	a) Current	b) During pregnancy	c) During the 1st year of the child's life	d) In the past but after the child's 1st year of life
Yes	☐	☐	☐	☐
No	☐	☐	☐	☐
Don't know	☐	☐	☐	☐

SECTION 5: QUESTIONS FOR THE FATHER/MALE GUARDIAN

If possible, we ask that the father or male guardian completes this section.

Part 20: Demographic details

This section was completed by:

- ☐ The biological father of the child **PLEASE GO TO QUESTION 136**
- ☐ Other male guardian
- ☐ The biological mother of the child
- ☐ Other female guardian

Please compete Section 5 for the <u>father or male guardian</u> of the child

What is your date of birth: _____ / _____ / _____

dd mm yyyy

What is your highest level of education?

- ☐ None
- ☐ Primary school
- ☐ Secondary school
- ☐ Technical or trade school diploma
- ☐ Undergraduate university degree
- ☐ Postgraduate university degree

Part 21: Your job held during the pregnancy of the child

The following questions refer to **the job that the father/male guardian held during the mother's pregnancy of the child**

☐ Tick here if you *didn't work* during the mother's pregnancy OR if you were not present at all during the pregnancy, then **PLEASE GO TO QUESTION 146**

137. **Period of Employment:**

From …… [year] To ……. [year]

138. How many **hours per week** did you work in this job? (on average) …… [hours per week]

139. How many **days per week** did you work in this job? (on average): ……..…….. [days per week]

140. Did you regularly work **outside 8-5 o'clock** for this job?

Yes ☐ → ***if yes,*** please specify:……

No ☐

141. What was the **main activity** of the company or organisation you worked for?

(for example: what was produced, what service was provided)

……

……

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……

142. What **department** did you work in?

……

143.

What was your **job title**?

……

144. Please describe the specific job in detail, including:

What did you do?

How was it done?

What **materials** were used?

What **tools** or **machinery** were used?

What type of **process** was it?

(it may help to describe what a typical day involved)

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During the mother's pregnancy of the child, did you *ever* carry out any activities at work that involved contact with pestcides?

- ☐ Yes, I directly worked with pesticides
- ☐ Yes, pesticides were used in my work environments **but** I didn't handle them directly
- ☐ Yes, I handled products that were treated with pesticides
- ☐ No, pesticides were never used in my work environment

Part 22: Your work history since the birth of the child

146. Please list **all of the jobs you held since the child was born (or since you have lived with the child)**, in order from the first job held after the birth of the child to the most recent job held.

	Job Number	Who was your **employer**? (Name and Location) *(For example: Massey University, Wellington)*	Over what **period** did you work for this employer?	What was the **main activity** of the **company** or **organisation** you worked for? *(For example: sheep farming, selling shoes, making clothes)*	What **department** did you work in, and what was your **job title**?	Did you use pesticides in this job?

1.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No
2.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No
3.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No

	4.	Name …… Location ……	From: …..……[year] To: …..……[year] Total time employed: …….. *years*		Department: …….. Job title: ……..	☐ Yes ☐ No
	5.	Name …… Location	From: …..……[year] To: …..……[year]		Department: …….. Job title:	☐ Yes ☐ No

Part 23: Work-related pesticide exposure

IF YOU HAVEN'T WORKED ON A FARM SINCE THE BIRTH OF THE CHILD (or since you have lived with the child), PLEASE GO TO QUESTION 157.

For **all** of the farms that you have worked on **since the birth of your child (or since you have lived with the**

child), please state the **type** of farm and what **years** you worked on the farm:

(please start with the first farm since the birth of the child and end with the most recent)

Type of farm (e.g. sheep, dairy, apple orchard): Years worked on the farm:

Farm 1 _____ From:_____[Year]
To:_____[Year]

Farm 2 _____ From:_____[Year]
To:_____[Year]

Farm 3 _____ From:_____[Year]

To:_____[Year]

Farm 4 _____ From:_____[Year]
To:_____[Year]

Farm 5 _____ From:_____[Year]
To:_____[Year]

After the birth of the child (or since you have lived with the child), have you *ever* carried out any activities at work

that involved contact with pestcides?

- ☐ Yes, I have directly worked with pesticides
- ☐ Yes, pesticides were used in my work environments **but** I didn't handle them directly
- ☐ Yes, I handled products that were treated with pesticides
- ☐ No, pesticides have never been used in any of my work environments **PLEASE GO TO QUESTION 157**

The following questions ask about four different time periods: a) current; b) during pregnancy; c) during the

1st year of the child's life; and d) in the past but after the child's 1st year of life.

Please answer the questions for each of the time periods that are relevant to you.

Please indicate your main areas of pesticide contact *(even if you didn't work with them directly)*:

	a) Current (tick)	**b) During pregnancy** (tick)	**c) During the 1st year of the child's life** (tick)	**d) In the past but after the child's 1st year of life** (tick)
Field crops				
1. Cereals (wheat, barley, oats, rye etc.)	☐	☐	☐	☐
2. Oilseeds (oilseed rape, linseed)	☐	☐	☐	☐
3. Potatoes	☐	☐	☐	☐
4. Sugar beet	☐	☐	☐	☐
5. Grassland and/or fodder crops	☐	☐	☐	☐
6. Other field crops ……..*(please specify)*	☐	☐	☐	☐
Horticulture				
7. Orchard crops (apples, pears, plums, kiwi, etc.)	☐	☐	☐	☐
8. Soft fruits (strawberries, currants etc.)	☐	☐	☐	☐
9. Hops	☐	☐	☐	☐
10. Mushrooms	☐	☐	☐	☐
11. Outdoor vegetables	☐	☐	☐	☐
12. Glasshouse vegetables	☐	☐	☐	☐
Animal rearing				
13. Animal treatment	☐	☐	☐	☐
14. Animal house area treatment	☐	☐	☐	☐
Non-food production				
15. Gorse control	☐	☐	☐	☐
16. Wood preservative application	☐	☐	☐	☐
17. Glasshouse crops (ornamental)	☐	☐	☐	☐
18. Outdoor ornamental flowers and bulbs	☐	☐	☐	☐
19. Outdoor plant nursery	☐	☐	☐	☐
20. Golf courses, bowling greens, reserves, sport grounds	☐	☐	☐	☐
21. Amenity weed control: roads, pavements etc.	☐	☐	☐	☐
22. Forestry	☐	☐	☐	☐
23. Aquatic	☐	☐	☐	☐
24. Pest control	☐	☐	☐	☐

25. Other ……*(please specify)*	☐	☐	☐	☐
26. Other ……*(please specify)*	☐	☐	☐	☐
27. Other ……*(please specify)*	☐	☐	☐	☐
None of the above	☐	☐	☐	☐

If you ticked *any* of these boxes please complete question 150, otherwise go to question 151

For each box that you ticked for Question 149, please complete the table below for the pesticides that you had contact with:

Please list the number from question 149 in column 1 *(e.g. number 10 for mushrooms, number 22 for forestry etc)*

N.o from Qu 149	Type and name of pesticide	What years were you exposed to the pesticide?	Weeks per year exposed	Hours per day exposed	What was the pesticide used for?	How was the pesticide applied? (e.g. backpack sprayer, aerial spraying)	How are/were you exposed to the pesticide? *(tick all that apply)*
E.g. 20.	*Herbicide, Round-up*	From: *2005* [Year] To: *2007* [Year]	*20*	*0.5*	*To kill weeds around the golf course*	*Backpack sprayer*	☐ I mixed the pesticide ☑ I applied the pesticide ☐ I handled products that were treated with the pesticide ☐ I cleaned tools or equipment that were used for pesticide treatment ☐ I worked in an environment where it was applied
		From:_____ [Year] To:_____ [Year]					☐ I mixed the pesticide ☐ I applied the pesticide ☐ I handled products that were treated with the pesticide ☐ I cleaned tools or equipment that were used for pesticide treatment ☐ I worked in an environment where it was applied
		From:_____ [Year] To:_____ [Year]					☐ I mixed the pesticide ☐ I applied the pesticide ☐ I handled products that were treated with the pesticide ☐ I cleaned tools or equipment that were used for pesticide treatment

							☐ I worked in an environment where it was applied
N.o from Qu 149	**Type and name of pesticide**	From:_____ [Year] To:_____ [Year] **What years were you exposed to the pesticide?**	**Weeks per year exposed**	**Hours per day exposed**	**What was the pesticide used for?**	**How was the pesticide applied?** (e.g. backpack sprayer, aerial spraying)	☐ I mixed the pesticide ☐ I applied the pesticide ☐ I handled products that were treated with the pesticide ☐ I cleaned tools or equipment that were used for pesticide treatment ☐ I worked in an environment where it was applied **How are/were you exposed to the pesticide?** *(tick all that apply)*
		From:_____ [Year] To:_____ [Year]					☐ I mixed the pesticide ☐ I applied the pesticide ☐ I handled products that were treated with the pesticide ☐ I cleaned tools or equipment that were used for pesticide treatment ☐ I worked in an environment where it was applied
		From:_____ [Year] To:_____ [Year]					☐ I mixed the pesticide ☐ I applied the pesticide ☐ I handled products that were treated with the pesticide ☐ I cleaned tools or equipment that were used for pesticide treatment ☐ I worked in an environment where it was applied
		From:_____ [Year]					☐ I mixed the pesticide

			To:_____ [Year]					☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**
			From:_____ [Year] To:_____ [Year]					☐ **I mixed the pesticide** ☐ **I applied the pesticide** ☐ **I handled products that were treated with the pesticide** ☐ **I cleaned tools or equipment that were used for pesticide treatment** ☐ **I worked in an environment where it was applied**

What types of protective equipment do/did you usually use when you had contact with pesticides?

Please tick all that apply for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
Didn't use protective equipment	☐	☐	☐	☐
Cartridge respirator, gas mask	☐	☐	☐	☐
Dust mask	☐	☐	☐	☐
Full face shield	☐	☐	☐	☐
Hat	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Chemically resistant gloves (like neoprene or nitrile gloves)	☐	☐	☐	☐
Fabric/leather gloves	☐	☐	☐	☐
Apron	☐	☐	☐	☐
Chemically resistant boots	☐	☐	☐	☐
Cloth coveralls (complete suit)	☐	☐	☐	☐
Disposable outer clothing (like Tyvek®)	☐	☐	☐	☐
Other…… …… *(please specify)*	☐	☐	☐	☐

After having had contact with pesticides, *when* did/do you usually change into clean work clothes?

Please tick one box for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
Right away	☐	☐	☐	☐
At lunch	☐	☐	☐	☐
At the end of that work day	☐	☐	☐	☐
At the end of the next work day	☐	☐	☐	☐
Later in the week	☐	☐	☐	☐
Always used disposable outer clothing	☐	☐	☐	☐

After having had contact with pesticides, ***where*** do/did you usually clean your work clothes?

Please tick one box for each column a to d

	a) Current	b) During pregnancy	c) During the 1st year of the child's life	d) In the past but after the child's 1st year of life
In the family washing machine	☐	☐	☐	☐
In a separate washing machine at home	☐	☐	☐	☐
In a separate washing machine at work	☐	☐	☐	☐
Always used disposable outer clothing	☐	☐	☐	☐
Other ……. *(please specify)*	☐	☐	☐	☐

After having had contact with pesticides, where do/did you usually take off your boots/shoes?

Please tick one box for each column a to d

	a) Current	b) During pregnancy	c) During the 1st year of the child's life	d) In the past but after the child's 1st year of life
At work	☐	☐	☐	☐
In the family home	☐	☐	☐	☐
Outside the family home	☐	☐	☐	☐
Other ……. *(please specify)*	☐	☐	☐	☐

After having had contact with pesticides, do/did you wear your work clothes into your house?

Please tick one box for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
No, never	☐	☐	☐	☐
Yes, but rarely	☐	☐	☐	☐
Yes, sometimes	☐	☐	☐	☐
Yes, often	☐	☐	☐	☐

Did you ever wash the working clothes of other workers who had contact with pesticides?

Please tick one box for each column a to d

	a) Current	**b) During pregnancy**	**c) During the 1st year of the child's life**	**d) In the past but after the child's 1st year of life**
Yes	☐	☐	☐	☐
No	☐	☐	☐	☐
Don't know	☐	☐	☐	☐

Additional comments:

THANK YOU VERY MUCH FOR COMPLETING THE QUESTIONNAIRE! YOUR HELP IS GREATLY APPRECIATED

Refusal questionnaire

Good afternoon,

Am I speaking with_____?

Hi, my name is _____ and I'm calling from Massey University, Wellington.

I am calling you as last year you were invited to take part in a study looking at the effects of pesticides on child health. Does this sound familiar? We are aware that were not able to be part of this study because you "*did not have time*" to fill in the survey.

I'm calling you now because it's really important for us to make sure that the people who couldn't take part in the research are the same as those who could. Would you have 1 minute now to answer 6 quick questions about your child to help us work this out?

Thank you very much- it won't take long.

This research is about pesticides and children's behaviour, so I'm going to state some phrases that describe how children may act. I'd just like you to tell me whether the phrase has applies to your child in the last several months.

Is your child_____?:

1. *Is clear when telling about personal experiences* - if yes does this occur: sometimes, often or almost always
2. *Is easily distracted*
3. *Worries about what other children think*
4. *Has trouble fastening buttons on clothes*
5. *Is able to describe feelings accurately*
6. *Is sad*

Thank you very much for your time!

Appendix C Case Study

Case Study 5

Influences of doctoral research on clinical practice: A case study

A case study presented in partial fulfilment of

The degree of

Doctorate of Clinical Psychology

Yanis Brinkmann

2017

This case study represents the work of Yanis Brinkmann during his internship at Talking Point in New Plymouth in 2017. Some information within the case study has been changed to protect the anonymity of the client.

Candidate: Yanis Brinkmann…….Date:……

Supervisor: Matthew Manderson……..Date:……

Abstract

The current case study discusses the influence of my doctoral research on my clinical practice. The first component provides a summary of my thesis, including a focus on the literature review, research questions and methods. The second component is a discussion of my self reflections on how what I learned throughout conducting my thesis research has informed my clinical practice. The reflections include a focus on working with children in a clinical context, working in a team, and gaining a better understanding of how neuropsychological assessment informs clinical practice.

Doctoral Thesis Overview

My thesis looked at the relationship between pesticide exposure and neuropsychological development in children. This section will outline the development of the thesis topic. It will then include a summary of the relevant literature, research questions and methodology of the thesis.

Thesis Topic Development

The current doctoral thesis stemmed from a collaborative project between the Massey University School of Psychology and the Centre for Public Health (CPHR) looking at the effects of pesticide exposure on children aged six to eleven years. The overall study was divided into three phases.

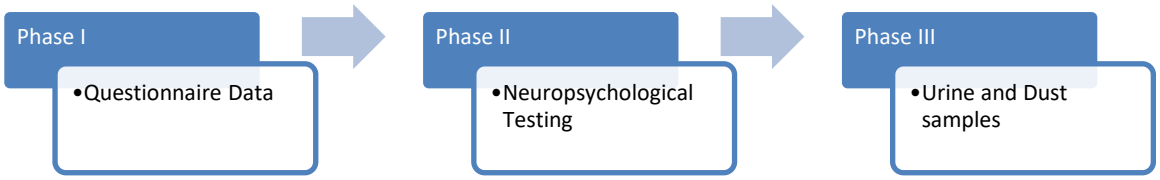

Figure 1. Outline of the overall CPHR funded study.

Phase I involved the collection of questionnaire data from 900 children from three separate populations, urban, rural and farming, with 300 children within each group. The questionnaire data collected covers off numerous lifestyle factors assessing exposure such as home pesticide use, parental occupation and proximity to high pesticide use areas. Demographics such as parental income were also collected through this questionnaire. Alongside the exposure questionnaire, two behavioural measures were also used in Phase I of the larger study; the Behaviour Assessment for

Children 2nd Edition (BASC) and the Behaviour Rating Inventory of Executive Functioning (BRIEF). The BASC uses both parent and teacher rating scales to assess the behaviour and emotions of children (PsychCorp, 2016). Both the parent and teacher forms were used. The BRIEF assesses difficulties in executive functioning through a parent report form (PAR.iConnect, 2016).

The second phase of the larger study involved the neuropsychological assessment of participating children to gather data on their current functioning and is the phase that the author was involved with. In total the larger study aimed to gather data on 450 children, evenly spread out across the three groups; urban, rural and farming. Assessments were conducted by five different assessors including the current author. Participants for this phase were selected from those taking part in Phase I, and assessments were held at their schools or homes.

The final phase of the study involved the collection of urine and dust samples from all participants from Phase II. Urine and dust samples were used in collaboration with questionnaire data in the wider study to assess the levels of pesticide exposure in the study population and collected for all participants who had undergone neuropsychological testing.

The Current Thesis

The current thesis operates within the context of this larger study through contributing to the data collection of the second phase. It also uses this data in conjunction with a proportion of the questionnaire data from the first phase to investigate the effects of pesticide exposure on children aged six to eleven years.

Rationale for Research

Children are at higher risk than adults of pesticide exposure due to a higher dose to weight ratio, age specific factors and their interactions with their environments. These factors work together to place children at greater risk of environmental pesticides by increasing the likelihood of exposure

through their behaviour across the developmental period. They also make the effects of exposure comparably greater than in adults. This is further compounded by the sensitive nature of neuropsychological development in children which can be upset by exposure through both toxicodynamic and toxicokinetic factors. This means that while low level pesticide exposure is common worldwide in both children and adults, it is likely to have a greater effect on children when compared with their adult counterparts.

While children are at higher risk of exposure a number of limitations exist in our knowledge of the effects of exposure on children. The chief limitation is the limited number of studies investigating the effects of chronic low level pesticide exposure. This is echoed in many review studies (Eskenazi et al., 1999; Moser, 2007; Pope, 2010; Roberts & Karr, 2012; Saillenfait et al., 2015) and an even more pronounced research gap exists for postnatal exposure. Many areas of cognitive functioning, including memory, visuospatial skills and working memory have not been researched in regards to postnatal exposure.

Further to this, in the areas of functioning where studies exist, with the exception of attention, there are usually only very few studies making it difficult to fully understand the potential effects of postnatal exposure. This is compounded as there are limited studies looking across the age ranges, with most studies looking at either very young children (below five years of age) and adolescents (age twelve onwards) leaving a large gap in the literature on the effects on children aged six to eleven years. These limitations of the current literature point to a clear gap and need for further research looking at the effects of exposure in children, especially in the six to eleven years age range. As knowledge is argued to be critical in the prevention of harm (Grandjean & Landrigan, 2006) a gap in the current literature may ineffectively inform regulation and safety practices. This is particularly pertinent in the New Zealand context, as many previous studies have been conducted in countries with a different exposure profile, leading to little knowledge about the potential effects in New Zealand.

Study aims, research questions and hypotheses

The current research has nine main hypotheses:

1) There will be a significant effect of exposure on children aged six to eleven years.

In the current study, based on a domain centred view of cognition (Lezak, Howieson, Bigler, & Tranel, 2012), cognitive functioning is divided into the following categories: attention, motor speed, working memory, processing speed, memory, language, executive functioning and social perception. As discussed in chapter five, research has focused primarily on attention and motor speed, with few studies looking at the effects of exposure on memory, language, working memory and processing speed. Further to this executive functioning and social perception have not yet been investigated in relation to exposure. As cognitive development and functioning relies on the complex interplay between multiple different domains (Weiss, 2000), this limited focus can underestimate the overall effects of pesticide exposure on cognition. The current research will extend the knowledge in this area through looking at the effects of exposure on multiple domains

2) There will be a significant effect of exposure and attention

The previous literature has found a strong effect of both pre and postnatal exposure on attention and it is anticipated that this will be replicated in the current sample.

Attention has been found to contain four subtypes: focused, selective, sustained and divided attention. While there is suggestion that complex cognitive tasks are more affected by pesticide exposure, no research has investigated whether this is also replicated in attention. In line with this the current study aims to investigate this:

3) Complex attention types (divided and selective attention) will be more affected by exposure compared with the simpler attention types (focused and sustained attention).

While the literature on pesticide exposure suggests an effect on attention, it is not clear whether auditory or visual attention are affected differently. There is some suggestion that the development of

both types has different milestones making it important to investigate any differences in potential deficits. The current research aims to explore the following research question.

a) Does pesticide exposure affect visual and auditory attention differently?

Previous studies have found a significant decrease in motor abilities in children who were prenatally exposed to pesticides. There is some remaining debate about the effects of postnatal exposure on motor speed, however a cumulative effect is suggested. In line with this it is predicted that children in the current sample will mirror this trend and will be measured using the following hypothesis:

4) There will be a significant effect of exposure on motor speed.

Processing speed has also been found to be affected by both pre-and postnatal exposure to pesticides (González-Alzaga et al., 2015) and in line with this a similar trend is predicted in the current study.

5) There will be a significant effect of exposure on processing speed

While previous studies have found an effect for prenatal exposure on, memory (Ribas-Fitó et al., 2006), working memory (Puertas et al., 2010, & Viel et al., 2015) and language (Handal et al., 2008, Ribas-Fitó et al., 2006 &Viel et al., 2015), post-natal effects have not been studied. Previous work has proposed a cumulative effect of exposure (Abdel Rasoul et al., 2008; Butler-Dawson, Galvin, Thorne, & Rohlman, 2016; Rohlman et al., 2007), making it likely that these domains will also be affected by long term post-natal exposure. The sixth hypothesis is as follows:

6) There will be a significant effect for exposure on the memory, working memory, and language domains

Neither social perception or executive functioning have been investigated in relation to pesticide exposure. In line with arguments around cognitive development being interlinked (Weiss, 2000) it is likely that these domains will also be affected by pesticide exposure. The current study aims to explore this gap in the current literature, using the following hypothesis:

7) There will be a significant effect for exposure on executive functioning and social perception

Exposure will be measured using questionnaire data gathered as part of the wider CPHR study (the questionnaire will be discussed in chapter 7) and will primarily be based on the proximity exposure pathway. Previous studies have linked the proximity pathway with increased pesticide exposure levels however research has not looked at how this specific pathway is linked with cognitive development. Exposure will be further broken down into four subcategories based on the area the child has been residing in: urban, rural and farming. Both the rural and farming categories will be split based on whether the child has always lived in these areas. As pesticide exposure has a cumulative component (Abdel Rasoul et al., 2008; Butler-Dawson, Galvin, Thorne, & Rohlman, 2016; Rohlman et al., 2007) it is expected that children who have lived longer in farming or rural areas will have larger deficits. As farming areas have even greater proximity, and increase the risk of exposure through drift and skin contact it is anticipated that these areas will demonstrate the greatest effects.

3) There will be a significantly higher effect of exposure on cognitive functioning in children who have resided their whole lives in either rural or farming areas, with the biggest effect being present for farming areas.

Finally the study will be the first to assess the effects of pesticide exposure on children in New Zealand. Previous studies have been conducted in countries with different exposure profiles due to their different regulations, geography and pesticides used which makes it difficult to generalise their findings within New Zealand. While trends can be broadly applied, specific effects are difficult to translate. As research informed regulations are one of the most important factors protecting people from the potential harmful effects of pesticide exposure, it is important that up to date research within New Zealand is available. Thus the current study will help contribute to the public health of New Zealand through providing information on the effects of pesticide exposure in a New Zealand context. Given strict regulations around pesticide use in New Zealand, it is anticipated that any effects will be smaller than those found in developing countries. However as effects have been found in countries with tight regulations it is hypothesised that there will be a significant effect found in the current study.

4) There will be a significant effect for pesticide exposure on cognitive development in New Zealand

Methodology

Ethics

Ethical approval for the study was granted by the Health and Disability Ethics Committee (HDEC) in 2013 (application ref 13/CEN/134). Consent forms were signed by each participating parent, and participants were able to withdraw from the study at any stage. Before commencing each assessment, assent was obtained for the child, and children were able to withdraw their participation if needed. Research data was kept anonymously and only accessed by researchers involved with the study.

Participants

Recruitment. Recruitment was managed by the CPHR. Schools in the Wellignton, Hawkes bay, Horowhenua and Nelson Bays regions were approached. Initial meetings with the principals were used to discuss the research and its processes, before they elected to participate in the study. Following this invitation letters were sent to parents. In total 32 schools participated in the research.

Exclusion Criteria. As research focused on the effects on typically developing children, mental health disorders which were likely to impact on their testing scores such as intellectual disabilities or ADHD were grounds for exclusion.

Neuropsychological assessment

As the effects of pesticide exposure have been linked with many different cognitive abilities, assessment aimed to focus on the following cognitive domains: executive functioning, attention, memory, motor speed, processing speed, language, social perception. Tests were selected both for

their ability to measure a domain, and for the time taken to administer as the entire testing session needed to take no more than 60 minutes, to minimise disruption at the child's school. The order of test administration was carefully discussed to minimise the influence of practice or interfering factors. The tests used were selected through a committee approach.

Subtests were chosen based on the following criteria:

- Sound psychometric properties
- Designed for use with children aged 6 – 11 years
- Required very little specialised equipment e.g. tablets
- Measured the domains of interest – with an emphasis on attention and executive functioning
- Together took no longer than 60 minutes to administer

Tests selected were from the Test of Everyday Attention for Children (TEA-Ch), the Wechsler Intelligence Scale for Children (WISC-IV) and the Neuropsychological Development measure (NEPSY-II). All assessments were completed by the end of December 2016.

Procedure

Recruitment was managed by the CPHR, and involved meetings with principals. Recruitment letters, information sheets and consent forms were then sent to parents of participating schools. Parents who elected to participate were sent a copy of the questionnaire. Once the questionnaire was returned they received an additional letter inviting them to participate in the second phase of the study. Testing was mostly conducted at school during school hours, and children were removed from their classrooms for around one hour. A small number of children were tested at home, again for around one hour. All assessments were conducted one on one with one of the assessors.

Clinical Psychology Internship

The following section discusses my self reflections across my yearlong internship at TalkingPoint Psychology and Tui Ora. The internship was split across both services with me working two days a week at each. TalkingPoint is a private practice which accepts both private and ACC referrals. The ACC referrals were mainly focused on chronic pain, neuropsychological assessment and interventions for trauma. Private referrals included individuals experiencing low mood, anxiety, relationship difficulties and grief. Tui Ora is a community based health and social services provider aiming to enhance whānau health and wellbeing. Referrals from Tui Ora commonly included individuals experiencing low mood, anger, anxiety and substance abuse difficulties.

Self-reflection

Working with children

While I conducted well over 100 hours of assessments with children for my thesis, due to our exclusion criteria these were all children without any significant mental health difficulties. Further none of the children had an intellectual disability or experienced recent head trauma. This proved to be a big contrast in my clinical work, conducting impairment assessments, concussion screens and neuropsychological assessments with children. On reflection I had not considered the large differences I might find, both in ability and motivation on the tests. This necessitated me thinking on my feet much more than I was used to in my thesis work. It also required an additional level of focus and vigilance. For example during one impairment assessment I spoke with the child's mother for around a minute to set up the next appointment time, and during this time the child had found a pen and drawn over both the testing materials and table. This highlighted to me that I needed to adjust my approach, and fortunately this occurred early on in my time assessing children on my internship. Following this event I made sure to be more aware of both the child and where my own attention was placed.

During my thesis testing was conducted one on one and no interviews were conducted with parents. Assessments in my clinical practice differed as parents would attend the interview component with their children. This required building rapport with both parties and juggling the need for both parties to feel heard alongside gathering the required information. This was an initial challenge for me as I was used to building rapport with just the children initially and required some supervision and further study. I found it helpful to set explain the purpose of the interview to both parents and child and outline the need for both people to get a chance to talk at the first meeting. This allowed us to navigate the space easier. On reflection this initial challenge proved very useful in my later work in situations where adult clients wanted to bring a support person or their partner to the initial interview. I found the similar principle of outlining the boundaries helpful and made the sessions run much smoother, something I may not have learned so quickly without the contrast between thesis and clinical work.

Working as part of a team

My thesis involved working with both the school of psychology and the CPHR and included many meetings where the overall project was discussed. On reflection these were similar to multi-disciplinary team (MDT) meetings which I have been involved in during my internship. I was able to draw on the experiences obtained as part of my thesis during the MDT meetings on my internship. I feel this gave me a greater sense of how to use my voice, and to how to navigate discussions where people are not in agreement. It also prepared me more on the value of being prepared and having a plan of what my aims and goals for the meeting were which I feel let me advocate more successfully for my clients.

Working alongside four other assessors underneath an overall supervisor during thesis also prepared me well for working alongside another intern and my supervisor during my internship. My thesis illustrated the value in brainstorming with others around complex cases. An example of this was around planning on how me and the other intern were going to approach an upcoming

immigration assessment. We adopted a similar style to what worked during my thesis where we brainstormed ideas together, created a plan and then consulted out supervisor which proved effective.

I also found that preparing for supervisor meetings during my thesis taught me valuable skills in working with my current supervisor. The approach that I learned during my thesis involved having established topics to discuss and an overall goal for each session. This proved to be a very time effective method of using the supervision time, both during the thesis and in my internship.

Conducting neuropsychological testing

I was very fortunate for the significant exposure to neuropsychological testing with children I had during my thesis. I felt this prepared me very well for my work at TalkingPoint. The experience of thinking about which tests to include in the thesis prepared me well for selecting the right tests to use during a neuropsychological assessment. It also engrained in me the approach of having robust clinical rationale (e.g. extra memory tests to fully understand the presentation of a memory deficit following a head injury) which proved invaluable with ACC work. I also noticed that my confidence in neuropsychological testing was comparatively higher than my confidence in other areas. On reflection this was largely due to the amount of hours spent conducting assessments during my thesis. This confidence was very helpful in reducing my stress levels and letting me think on my feet well, something that was especially helpful during the concussion screening assessments. Individuals would often become symptomatic (e.g. headaches, nausea, dizziness) during assessments, which necessitated both an awareness of the client's state aswell as making judgement calls on when to terminate testing due to this. This is something I feel was much easier for me due to the confidence with materials letting me think on my feet better.

Observing so many different children also highlighted to me the prevalence of normal variations in testing performance and how all individuals have strengths and weaknesses across the cognitive domains. This was again valuable during concussion screens, where individuals often displayed a weakness on a specific test, even though they appeared recovered in every area. My

experience let me appreciate both a pathological and normal explanation for the scores more easily which helped in my formulation of the individuals.

The value of cognitive assessments in clinical practice

For my literature review I looked at the cognitive domains in detail, which on reflection gave me a thorough understanding of the practical implications of deficits in each area. This helped inform my clinical practice by giving me a solid grounding for my recommendations. It also let me appreciate the difficulties people were likely to face if they had a deficit in a specific area. For example, one individual sustained eleven concussions before seeing me and had difficulties with processing information. My knowledge of processing speed influencing the other cognitive domains allowed me to make a more accurate recommendation around how his psychological interventions would best be structured. It also allowed me to provide useful feedback to his physiotherapist around tailoring the speed of information presented to this client's need.

In summary my thesis provided me with a solid groundwork to begin my clinical practice from. On reflection it increased my confidence, knowledge base and gave me a flexible approach to conducting assessments which I am very grateful for.

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Appendix D Ethics Proposal Application

Pesticide Exposure and Neuropsychological Effects in Children – Study Protocol

Rationale for Research

In the past few decades there has been considerable concern about the health effects of pesticide exposure, particularly with regards to acute toxic effects, as well as effects of chronic exposure on mortality and cancer. Recent research, including a study conducted by the applicants,[1] has identified associations between exposure and neurological effects.[2] These effects (i.e. neurodegenerative diseases, neurobehavioural deficits and suicide) have been found in occupationally exposed farmers and farm workers,[3-5] but children may also be at risk due to residential use of pesticides, proximity to pesticide-treated agricultural areas and - to a lesser extent - through the food supply and drinking water.[6]

Children are uniquely vulnerable to these exposures, because the dose per bodyweight is likely to be greater and they have a lower capacity for detoxifying pesticides.[5-9] Also, their brains are still rapidly developing, making them more vulnerable to the neurotoxic effects of pesticides.[9] The health effects of low, but repetitive and combined exposures experienced by children are still largely unclear.[6] However, an increasing number of epidemiological studies have shown positive associations between pesticide exposure and childhood cancer (in particular leukaemia and brain tumours),[10-14] neurodevelopmental and behavioural effects,[15-23] and effects of physical development,[24,25] although the results have not always been consistent. Endocrine effects,[26,27] and effects of pesticide exposure on asthma[28] have also been reported but the evidence in children is weak.

Pesticides are a broad group of chemicals - applied to kill or control insects, unwanted plants, animals or microorganisms - and the wide range of potential health effects is reflective of the diversity of toxicological and immunological properties represented by these chemicals.[5,6] The focus of this application is on pesticides with neurotoxic properties. Most insecticides are neurotoxins, and humans are also at risk because they have nervous systems similar to those of insects.[5,6] Worldwide, the most commonly applied insecticides are organophosphates (OPs), carbamates, pyrethroids (PYRs) and organochlorines (although many organochlorines have now been phased out in most high income countries including New Zealand). OPs and carbamates are cholinesterase inhibitors while the main mode of action of PYRs and organochlorines is modulation of voltage gated ion channels in nerve cells.[5] Many other pesticides also have neurotoxic properties targeting the same or other biochemical and molecular targets within the nervous sytem.[5,29]

Neurotoxic effects of pesticide exposures have been well established in animal models and some studies have shown the potential for pesticides to affect brain development at levels well below the threshold for systemic toxicity.[30] Nonetheless, despite the potential risks, relatively few studies in humans have been conducted, and most of these have been in occupationally exposed populations. Studies in children are rare and most have been in low income countries (characterised by relatively high exposure levels) and the US. These have shown associations with developmental disorders,

delays in cognitive development, attention deficits, behavioural problems, poor short-term memory and motor skills, longer reaction time and reduced IQ.[5,6,15-23] Effects have been shown both for prenatal and postnatal exposures. Two cross-sectional studies in prenatally-pesticide-exposed school age children in Ecuador showed consistent deficits for motor skills and visuospatial performance and visual memory.[22-23] These deficits corresponded to a developmental delay of 1.5-2 years. Data from the US NHANES study showed an association between urinary OP metabolites and attention deficit hyperactivity disorder (ADHD) in children aged 8-15.[31] This was confirmed in a prospective study in Mexican-American children in rural California which showed that both pre- and post-natal exposure to OPs were associated with attention problems, including ADHD, with the strongest effects occurring at older ages.[16] A longitudinal study in children in New York found that prenatal exposure to OPs was inversely associated with cognitive development from 12 months to 6-9 years, with the strongest effects in children with PON1 Q192R QR/RR genotype (related to a key enzyme in the metabolism of organophosphates).[20] Another study in the US showed brain anomalies in children exposed prenatally to OPs.[30] These recent US-based studies suggest that neurodevelopmental effects are not restricted to highly exposed children in low income countries, but also occur in high income countries with relatively low exposure levels as may be more typical for New Zealand.

The neurotoxic effects observed in these studies are of major concern since they impact on learning and achievement, the ability to develop peer relationships, and other social competencies. As demonstrated in the Dunedin birth cohort study[32-34], and other studies[35], these effects are likely to have life-long consequences for physical and mental health and wellbeing. These concerns have been acknowledged by several international agencies, including the US Natural Resource Defence Council which considers pesticides to be one of the top five environmental threats to children's health, with the highest risk being for farm children.[36] The US National Institute for Occupational Safety and Health has also expressed concern about pesticide exposure particularly among children of farmers.[37] Also, a recent study of children's exposures to chemicals placed (organophosphate) pesticides second after lead in terms of the neurodevelopmental burden.[38]

The food supply is a well-known source of pesticide exposure for the general population, with international (US) monitoring programmes showing detectable levels in a significant proportion of food samples tested with the highest levels measured in fruit, vegetables, dairy and grain products (58%, 35%, 29% and 19% respectively for 2008).[39] The 2009 New Zealand total diet study conducted by the Ministry of Agriculture and Fisheries showed that, of the 982 food samples screened, 437 (45%) were found to contain detectable residues of pesticides, although all levels were below the relevant Acceptable Daily Intake (ADI).[40] Consistent with international studies, the New Zealand study estimated that exposures were highest in young children through eating fruit, potatoes and vegetables; however, no actual exposure measurements in children were conducted. Although levels measured on food products are generally low, there is evidence from one intervention study that consumption of organic food (free of pesticides) significantly reduces the concentration of urinary OP metabolites in children,[41,42] suggesting that exposure through children's diets is not negligible and can be avoided. Contamination of drinking water with pesticides has also been found in international studies, particularly in rural areas,[43] but levels are generally low. One study of pesticide levels in drinking water in New Zealand showed that high levels of contamination may occur in some situations, e.g. one of 82 wells tested contained 37 mg/m^3 atrazine herbicide[44] which exceeded the US EPA advisory limit for drinking water of 3 mg/m^3. However, the levels for most other samples were

generally low or non-detectable. Proximity to pesticide-treated agricultural areas, or living with household members who apply or work with pesticides, represent other sources of exposure, which are likely to be greater than those generally resulting from diet and drinking water. In particular, several studies in the US have found that pesticide levels in house dust and pesticide metabolites in urine of residents (including children) increased with (self-reported) proximity of homes to orchard fields and during the pesticide spraying season.[45-47] Similarly, studies in the US have reported that children of farmers or farm workers are exposed to higher levels of pesticides - as shown by elevated pesticide levels in house dust and urine – through parental "take-home" exposures or other mechanisms including spray drift, playing in the field, or participation in work that involves contact with pesticide-treated foliage.[45,48] Residential use of pesticides may also be an important source of exposure as has been shown for PYRs in a small US based study.[49] No studies have been conducted in New Zealand to assess exposure levels in residents in close proximity to pesticide-treated areas or in farmers' children (who are expected to have the highest exposure levels) and/or in residents using indoor insecticides.

Very few studies have assessed exposure levels in children, and most have focussed on rural and/or farmers' children with suspected high exposures (see above). However, one recent study in South Australia compared urine OP and PYR metabolite levels in 115 urban (Adelaide), 111 periurban (Adelaide Hills) and 114 rural children (no health effects were measured).[50] This reported widespread chronic exposure to OPs and PYRs in all subgroups, although higher levels of specific pesticides used in agriculture were observed in rural and periurban children. Also, higher urine metabolite levels were observed in children whose parents reported occupational exposure to pesticides and children living within 50m off an agricultural activity. No difference between subgroups was found for insecticides used commonly in agriculture and domestic settings, emphasising the relative importance of residential exposures (in addition to exposures related to agricultural activities). Widespread exposure to OPs and other pesticides in urban populations have also been shown for adults, including pregnant women.[51]

Agriculture is the largest sector of the New Zealand economy, and pesticides are widely applied throughout the industry. The extensive mixed agricultural land use pattern of New Zealand suggests that there is potential for significant pesticide exposure in the general population including children. OPs and carbamate insecticides are most commonly used and despite restrictions on some OPs and carbamates in New Zealand,[52] most are still commonly applied, with annual sales remaining stable during 1994-2004 at 200,000 kg and 40,000 kg respectively (OP and carbamate 2004 sales figures: diazinon, 93 tons/yr; methamidophos, 19 tons/yr; chlorpyrifos, 17 ton/yr; fenamiphos, 11 tons/yr; pirimiphos-methyl, 8 tons/yr; phorate, 6 tons/yr; carbaryl, 16 tons/yr).[53] PYRs are less commonly used in agriculture (5,000 kg/yr), but they are frequently used in the residential environment and, as noted above, home use of PYRs may be a significant source of exposure for the general population.[49] However, despite the extensive use of pesticides, no data for pesticide exposure in children (or adults) is available for New Zealand. Also, no previous studies have been conducted in New Zealand into neurodevelopmental effects of pesticide exposure in children (or adults). Moreover, relatively few studies have been conducted internationally, with only a handful of studies (all from the US) with exposure levels more comparable to the New Zealand situation.

We therefore propose to conduct the first study of pesticide exposure and neurodevelopmental effects in New Zealand children. We will study three distinct groups with an expected wide range of exposure levels i.e. children on horticulture farms (high exposure), rural non-farmers' children (intermediate exposure) and urban children (low exposure). The proposed study will address several limitations of previous studies by: 1) collecting more comprehensive exposure information (most studies have relied on questionnaire data or on a single urine spot sample, a marker of only acute exposure and characterised by high variance); 2) the use of objective measures of neurotoxic effects (most previous studies relied only on questionnaire data); and 3) the inclusion of both farmers' and non-farmers' children (most previous studies exclusively focussed on farmers' children with suspected high exposures). This study will use robust exposure assessment methods and both subjective and objective measures of neuropsychological effects. It will therefore contribute to risk assessment in both farmers' children who are at greatest risk of pesticide exposure and in children in the general population who are exposed at lower levels through spray drift, residential use of pesticides, diet, and drinking water. The proposed study will be one of only a handful conducted in children in high income countries, which have very different exposure profiles than those in low income countries.

Hypotheses

The hypotheses to be tested include:

1) The highest average exposures to OP and carbamate pesticides are in farmers' children, followed by rural children not living on a farm, and by urban children;
2) Average exposures to PYRs are similar for rural and urban children, but exposure levels vary widely within subgroups;
3) Distance to farm activities, residential pesticide use and parental use of pesticides are associated with exposure levels in children;
4) The level, duration and intensity of exposure to pesticides affect the prevalence and magnitude of neuropsychological symptoms in children in a dose-dependent manner;
5) The neurotoxic effects of pesticide exposures are not restricted to farmers' children, but can also be detected in rural children not living on a farm, and in urban children;
6) Environmental exposure to pesticides is an important and preventable risk factor for neuropsychological disabilities in New Zealand.

Aims

We propose to study neuropsychological effects of pesticide exposure in New Zealand children using robust exposure assessment methods and both subjective and objective measures of neuropsychological outcomes. The specific study aims are to assess:

1) The level and extent of exposure to neurotoxic pesticides in New Zealand children;
2) The key determinants associated with neurotoxic pesticide exposures in New Zealand children;
3) Whether pesticide exposure is associated with neuropsychological outcomes;
4) Whether the association between pesticide exposure and neuropsychological effects shows a dose-response relationship;
5) Whether associations between pesticide exposure and neuropsychological effects are detectable in all groups of children (farm, rural non-farm, and urban children);

The overall aim of the study is to contribute to the development of improved control options to reduce pesticide exposures in children and thereby reducing their risk of neurotoxic effects (and other potential health effects associated with pesticide exposures).

Design and Methods

Study design

We will use a cross sectional study design to assess OP, carbamate and PYR insecticide exposures and their potential neurotoxic effects in 300 farmers' children, 300 rural non-farmers' children from the same area, and 300 urban children, all aged 6-11. These groups are expected to represent children with a wide range of insecticide exposures including those at highest (farmers' children), intermediate (rural non-farmers' children) and lowest risk (urban children) of exposure.[45,50] This will allow dose-response associations to be studied and risks to be assessed for *all* children exposed to pesticides including those in urban settings (a group often not included in these types of studies). We have chosen children aged 6-11 because previous studies have shown the strongest effects in this age group, compared to younger children, and neurotoxic effects are easier to establish in this group. Farmers' children will be recruited from horticulture farms, which are known to use large amounts of OPs and carbamates, and to a lesser extent PYRs. We will use standardised questionnaires to assess neuropsychological symptoms. In randomly selected subgroups of farm (n=150), rural non-farm (n=150), and urban children (n=150) we will also use computer-administered and other neuro-psychological tests. In the same subgroups, we will collect urine samples for pesticide metabolite analyses during (acute exposure) and outside the spraying season (background exposure). We will assess long-term exposure by analysing pesticides in house dust combined with questionnaire data on current and historic exposures. We will compare exposures and symptoms between the three groups of children and assess exposure determinants. Based on the level, duration and intensity of exposure we will also assess dose-response associations across all groups. Exposure information collected in subgroups will be used to estimate exposure for all children including those for whom we do not have dust and urine samples.

Recruitment

Horticulture families living in the lower half of the North Island will be randomly selected from a national database of farms (Agribase), including horticultural enterprises. We have previously successfully recruited 1,200 farming families (including children) for another study[54] and expect no problems recruiting 300 conventional (non-organic) horticulture farm children for this study using the same approach. We will work with Horticulture NZ (which represents 6,000 fruit and vegetable growers) to facilitate recruitment. Due to the heavy use of pesticides in apple and carrot growing we will initially focus on these groups, but we will include other horticulture groups if required. To ensure optimal comparability, rural non-farm children will be recruited through schools attended by our target population of horticulture children. Urban children will be recruited through schools in Wellington and Palmerston North. We have considerable experience recruiting children through schools (including the International Study on Allergies and Asthma in Childhood (ISAAC)) and we have built excellent relationships with primary schools in Wellington, Palmerston North, the Wairarapa and Hawkes Bay.

We expect the response rate to be similar (about 75%) to those in previous studies in New Zealand children of a similar age conducted by CPHR including the ISAAC study[55] and a study of farming families.[54] In those who decline participation we will complete a short questionnaire asking for the reasons for non-participation and a few key questions of the BASC-2 and BRIEF questionnaires used to assess neuropsychological symptoms (see below). This will allow us to assess whether response bias may have occurred.

Exposure and confounder assessment

Questionnaires: Parents of all 900 participants will complete postal questionnaires on behalf of their children. We will follow up by telephone to increase response rates and offer clarifications where required. We will record demographic information (age, sex, ethnicity); a full work history of the parents (to assess pre and post natal exposures of the child); parental use of pesticides; frequency, intensity and types of insecticides used in the residential environment; general housekeeping in relation to pesticide application; distance to nearest farm activities and type of farm activities; fruit and vegetable consumption and whether fruit is washed prior to consumption; and consumption of organic foods. We will geocode the addresses of all participants and combined with the highly detailed land-use database produced by New Zealand Landcare Research we will be able to assess distance to nearest agricultural activities providing additional information on exposures from spray drift. For farmers' children we will also record spraying methods, exposures of the mother during pregnancy, activities of the child during and after spray episodes, and potential for tracking of pesticides into the house by the parents due to contaminated clothes/shoes. We will also obtain copies of spray diaries maintained by the farmer. We will collect information on potential confounders such as social economic position; family history of behavioural problems, neurological conditions, depression or anxiety, mental illness; preterm birth; place of residence; tobacco smoke; medication and co-morbidities; and recent and past stressors.

Urine and dust samples: In addition to exposure information obtained by questionnaire, we will, in a randomly selected subset of children (150 farm, 150 rural non-farm and 150 urban children), collect spot urine samples to measure OP, carbamate and PYR pesticide metabolites. We will collect urine samples during two-week periods when insecticides are being applied (mostly in spring and summer) and in winter when no or very little pesticides are being applied. To reduce intra-individual variance[56,57] we will collect a minimum of five urine samples per child per periods. Samples will be collected on separate days equally spread over the two week period. Samples for each child will be pooled for each period to reduce cost for laboratory analyses. Study participants will be sent sterile containers for self-collection of a minimum of 5 ml of urine per sample. Samples will be sent back to CPHR in a pre-paid return parcel (following the regulations for shipment of biological UN 3373 Biological Substance, Category B) and stored frozen (-20°C) until pooling and analysis. For farmers' children, we will ensure that urine samples are collected at a time during active spraying of OP and/or carbamate insecticides; similarly, we will ensure that the second set of urine samples is collected at a time between spray periods with a minimum of 6 weeks after the last spraying episode. Individual spray programmes and spray diaries maintained by the farmer will facilitate this process. We will also collect house dust from the family home. As pesticides in house dust are relatively stable (up to

several years) these provide a time-integrated measure of exposure as opposed to urine samples which provide a measure of more acute exposures (half-lives of most urine insecticide metabolites range from 24-48 hours). Dust samples will be collected by the participating families using a protocol developed by the applicants which has been extensively used in asthma studies in New Zealand and overseas.[58] Nylon dust collection devices to be used with the participants' own vacuum cleaner will be provided together with a prepaid envelope to send the samples back to CPHR. Dust samples will be sieved and stored frozen (-20°C) until analysed. Aliquots of dust and urine will be stored for future analyses of other relevant environmental chemicals including lead and persistent organic pollutants (not part of current application).

Urine samples will be analysed by the Centers for Disease Control and Prevention (CDC), Atlanta, USA. The analytical methods involve automated solid phase extraction followed by isotope dilution-high performance liquid chromatography-tandem mass spectrometry.[59-61] We will measure up to seven OP metabolites, two carbamate metabolites and five pyrethroid metabolites which cover the most commonly used OPs, carbamates and PYRS in New Zealand. All urine concentrations will be adjusted for creatinine concentration and specific gravity level. Synthetic urine will be used as blanks. Dust samples will be analysed by Battelle Memorial Institute (Columbus, Ohio, USA) using hexane/acetone extraction, solid phase extraction and gas chromatrography mass spectrometry.[62]

Assessment of neuropsychological and behavioural effects

Symptoms: Neuropsychological and behavioural symptoms will be assessed in all 900 children using the "behaviour assessment system for children, second edition" (BASC-2) and the "behaviour rating inventory of executive function" (BRIEF).[63-66] The BASC-2 is a global measure of a child's adaptive behaviour and attention problems[63,64] and the BRIEF is designed to assess children's executive functioning in the home.[65,66] These are standardised and well validated questionnaires, and are commonly used (either on their own or in combination) for both research and clinical purposes. In particular, BASC-2 and BRIEF have previously been used to show associations between adverse child behaviours and executive functioning and environmental contaminants such as pesticides, phthalates and bisphenol.[67,68] Both postal questionnaires will be completed by the parents and the children's teacher, and each takes 15-20 minutes to complete. The BASC-2 questionnaire contains 134 items and is composed of the following clinical scales: activities of daily living, aggression, anxiety, attention problems, atypicality, conduct problems, depression, functional communication, hyperactivity, leadership, social skills, somatisation, and withdrawal. The BRIEF questionnaire contains 86 items and is composed of the following eight clinical scales: inhibit (inability to control impulses); shift (the ability to transition between situations); emotional control; initiate; working memory; plan/organise; organisation of materials; monitor (assess personal performance and the effect of one's own behaviour on others), and two validity scales: inconsistency and negativity. BASC-2 and BRIEF will be supplemented with questions regarding study skills and learning problems, and growth and development during the first few years of life. Both aggregate and individual age and sex standardised scores will be used in the analyses. To identify children most suggestive of possible ADHD we will also create a composite ADHD variable based on BASC-2 and BRIEF and the computer-assisted test and NEPSY II described below.

Neuropsychological tests: In the same subset of children in which we will collect urine samples (150 farm, 150 rural non-farm and 150 urban children), we will use a validated set of computer-administered neuropsychological assessments specifically developed for use in children aged 4-11 by Prof Sunyer (CI) (a scientific paper describing the methods and its application in children has been submitted for publication). The test will be conducted on a touch screen computer (tablet) and includes tests of working memory, visual memory, attention, sustained attention, reaction time, response speed and tracking. The test system is comparable to the Behavioural Evaluation for Epidemiologic Studies (BEES) test battery[69] which we are currently using in adults to assess neurobehavioural effects of solvent exposure. All participants will first be subjected to a practice run prior to starting the actual test. The computer-assisted tests will be supplemented with subtests of the NEuroPSYchological Assessment second edition (NEPSY II) test[70] from the following four content domains: language, sensorimotor, social perception and visuospatial processing. Prof Leathem (CI) has extensive experience with the NEPSY II test and will train the nurses involved in conducting the neuropsychological tests. All test results will be age-standardised. All tests can be conducted in less than 60 minutes (including short breaks between tests). Test and questionnaire results will be provided in a summary report to the parents and evaluated by a clinical psychologist (Prof Janet Leathem). If deemed necessary, we will contact the parent(s) and offer to send a copy of the results to their family doctor.

Data analysis

Standard descriptive statistical methods (means, standard deviations, and 95% CIs) will be used to summarise the exposure, symptom and neuropsychological test data stratified by subgroup (farm, rural non-farm and urban). Neurobehavioural outcome measures (obtained by questionnaire and neurobehavioural tests) will initially be dichotomised based on "at risk" and "clinically significant" thresholds in case of BASC-2 and BRIEF as previously described in the literature[63-68] or arbitrary cut points (i.e. 90-percentile) in case of the neuropsychological tests. As a consequence, the initial analyses will involve prevalence odds ratios using logistic regression. We will subsequently also analyse continuous outcome measures using linear regression. For BASC-2 and BRIEF data we will use overall, aggregate (per domain) and individual age and sex-adjusted scores. We will also assess associations with a composite ADHD variable (see above). We will conduct both unadjusted and confounder adjusted analyses; confounders that will be considered include age, sex, ethnicity, social economic position, medical history, stressors, and other factors noted above.

We will first analyse the differences between the three subgroups and we will subsequently make comparisons based on estimated pesticide exposure (controlling for subgroup i.e. farm, rural non-farm and urban). In particular, we will estimate prevalence odds ratios and regression coefficients comparing high, medium and low/non-exposed children. Exposure measurements conducted in the three subgroups (n=150 in each) will be used to estimate exposure levels for all 900 children. For this, we will analyse exposure determinants using linear regression analyses to predict exposure levels in those children for whom we do not have measured exposure levels. The regression analysis will involve urine and dust concentrations as independent variables and factors such as, farm, rural non-farm, and urban residence; distance to farms; residential use of pesticides; occupation of the parent; (organic) fruit and vegetable consumption; spray diaries; child activities during and after pesticide spraying; and exposures to pesticides during pregnancy as dependent variables. We will assess dose-

response associations for all three pesticide exposures (OPs, carbamates, PYRs) combined, but will also conduct analyses for individual groups of pesticides (mutually adjusted for each other). We will assess dose-response associations for boys and girls combined and separately.

The analyses to assess major determinants of exposure as described above will not only provide exposure estimates for those children for whom we did not collect urine and house dust, but will also guide the development of improved control options to reduce pesticide exposures in New Zealand children.

Study size and power

The overall study will include 900 children (300 in each sub-group). If we assume 300 children in each exposure group (low, medium, high) and 5% of the non-exposed group will have neuropsychological symptoms then we have 95% power to detect a three-fold difference (i.e. 5% vs 15%) between exposure groups and 65% power to detect a two-fold difference (i.e. 5% vs 10%) between exposure groups. Using only two exposure categories (50% high and 50% low) the study will have >80% power to detect a two-fold difference. For analyses within subgroups (n=300) we will have 83% power to detect a three-fold difference. The power will be greater using individual and aggregated scores (rather than dichotomised outcomes). From previous surveys we know that in a population sample of children with motor speed function (a particular aspect of the neuropsychological tests) of 34 units, the standard deviation is about 35.[23] Then if we assume 150 children in each exposure group (i.e. neuropsychological tests are conducted in half of the participating children) the study will have 93% power to to detect a reduction of 40% in motor speed function between the exposure groups and 72% to detect a reduction of 30%. For analyses within subgroups (n=150) we will have 67% power to detect a reduction of 40%. The power is similar for other neurological tests.

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Pesticide exposure and brain function in children

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What is this study about?

We are inviting you and your child to take part in a study looking at how much children are exposed to pesticides and whether this exposure has any effects on their brain development.

There is some concern that exposure to pesticides may affect brain function and behaviour. These effects have been found in exposed farmers and farm workers, but children may also be at risk due to the use of pesticides in the home, living close to pesticide-treated farming areas, the occupation of the parents, and to a lesser extent, through the food supply and drinking water.

This study aims to assess the level of exposure to pesticides in New Zealand children and whether this exposure has any effects on the brain and mental functions, and behaviours. To do this, we are inviting 900 children aged 5-11 years to take part in this study.

What would participation in this study involve for me?

Phase I: *All participants*

Your participation will involve completing three postal questionnaires on behalf of your child. The first questionnaire will ask questions about your work history, your use of pesticides, your child's diet, and your family's health. The other two questionnaires will ask questions about your child's behaviour. All three questionnaires should take no more than about 1 hour to complete. If you are interested in taking part in the study, please complete the enclosed reply form and return it to us in the freepost envelope provided. If you agree to participate, we may also ask your child's teacher to complete the two behavioural questionnaires so that we have information about your child's behaviour at school. With your permission, we will also ask your child's school to provide us with some measures of your child's academic achievements including whether they are meeting the National Standards for reading, writing, and mathematics.

If you are *not* interested in taking part, please return the reply form indicating your refusal.

For selected participants:

Phase II: *Selected participants*

Later we will contact half (randomly chosen) of the children/parents again and ask the children to undergo neuropsychological tests of memory, attention and reaction time, as well as their language skills and visual processing skills. Tests will normally take place at school (but they can be done in your home if you prefer) and will be conducted by a trained researcher. The tests can be completed in less than an hour. Our research nurse will also ask your child to collect urine samples during and outside the spraying season and will ask you to collect a house dust sample. The collection of these samples will be used to examine pesticide exposure and will be fully explained by our research nurse.

What will happen with my personal information?

We will treat all of the information from the questionnaires and the information from the school about your child as <u>strictly confidential</u>. Each questionnaire and the results of the other tests will be entered into a database using ID numbers. The questionnaires and tests will be seen by named researchers only and when the study is completed all questionnaires will be locked away in filing cabinets which will be the responsibility of the Director of the Centre for Public Health Research. When the study has been completed, we will analyse the information, *e.g.* compare the prevalence of the effects on the brain and mental functions and behaviours in those who are exposed to pesticides compared with those who are not exposed. At the end of the study the urine and house dust samples may be tested for different chemicals related to this research. The results of the study will be published in scientific journals and a summary of the results will be provided to all study participants that have requested it. **No individual information or names will be published.**

This project has been reviewed and approved by the Central Health and Disability Ethics Committee (application ref 13/CEN/134). If you have any concerns about the conduct of this research, please contact 0800 4 ETHICS (438 442).

You have the right to:

decline to participate

decline to answer any of the questions

withdraw from the study or parts of the study at any time

be given access to a summary of the study findings when it is completed

Please contact us at the Centre for Public Health Research to discuss any queries or concerns about the study.

Thank you very much for your time in considering this study.

Study team:

Professor Jeroen Douwes (Director), Dr Andrea 't Mannetje (Senior Research Fellow), Dr David McLean (Senior Research Fellow), Dr Amanda Eng (Research Fellow), and Jean Feary McKenzie (Research Assistant), Centre for Public Health Research, Massey University, Wellington.

Professor Janet Leathem, Professor of Neuropsychology, School of Psychology, Massey University, Wellington.

Kathryn McLennan, Doctoral Student, School of Psychology, Massey University, Wellington.

Professor Neil Pearce, Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine, London, UK

Professor Jordi Sunyer, Joint Scientific Director and researcher, Centre for Research in Environmental Epidemiology, Barcelona, Spain.

Professor Jochen Mueller, ARC Future Fellow, National Research Centre for Environmental Toxicology, University of Queensland, Coopers Plains, Australia.

Professor Brenda Eskenazi, Director, Center for Environmental Research and Children's Health (CERCH), University of California, Berkeley, USA.

Dear Parent

RE: Pesticide exposure and brain function in children study

We are inviting you and your child to take part in an important health research study looking at how much New Zealand children are exposed to **pesticides** and whether this exposure has any effects on their brain and mental functions, and behaviours. To do this, we are inviting 900 children aged 5-11 years from different schools to take part in this study.

This project is funded by the Health Research Council and has been reviewed and approved by the Central Health and Disability Ethics Committee (application ref 13/CEN/134).

Taking part in the study will involve completing three brief postal questionnaires on behalf of your child. The first questionnaire will ask about potential sources of pesticide exposure as well as questions about your diet, home environment, and your family's health. The other two questionnaires will ask about your child's behaviours. There is also a second phase of the study which will involve neuropsychological testing and we will invite *selected* participants to take part in this phase.

If you are interested in taking part in the study, please read through the included information sheet and complete the enclosed reply form. **Please return the completed reply form to us in the freepost envelope provided**. Children may sign the form if they want to, but a parent must also sign it. **If you are *not* interested in taking part, please return the reply form indicating your refusal.**

The information in the questionnaires will be confidential to the research team and at no time will individual information or names be made public.

Please note that you have the right to:

decline to participate

refuse to answer any particular questions

withdraw from the study at any time

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If you have any queries or concerns about the study you can contact us at the Centre for Public Health Research.

Thank you very much for your time.

Yours sincerely,

Jeroen Douwes, PhD

Professor of Public Health

Director

Centre for Public Health Research

Janet Leathem, PhD

Professor of Neuropsychology

Director, Clinical Psychology Training

School of Psychology

Dear Parent

REMINDER LETTER

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RE: Pesticide exposure and brain function in children study

Last year we sent you a letter inviting you and your child to take part in an important health research study looking at how much New Zealand children are exposed to **pesticides** and whether this exposure has any effects on their brain and mental functions, and behaviours.

We are writing to you again to remind you to please return the reply form to us *if you haven't done so already*:

If you are interested in taking part, please return the completed reply form to us in the freepost envelope provided;

If you are *not* interested, please return the reply form to us anyway indicating your refusal;

<u>If you have already returned the form to us</u>, thank you very much for your response.

It is very important for the study that we hear from everyone! If you would like us to re-send the full information pack to you, please contact us on 0800 990 053.

Taking part in the study will involve completing three brief postal questionnaires on behalf of your child. The first questionnaire will ask about potential sources of pesticide exposure as well as questions about your diet, home environment, and your family's health. The other two questionnaires will ask about your child's behaviours. There is also a second phase of the study which will involve neuropsychological testing and we will invite *selected* participants to take part in this phase.

The information in the questionnaires will be confidential to the research team and at no time will individual information or names be made public. This project is funded by the Health Research Council and has been reviewed and approved by the Central Health and Disability Ethics Committee (application ref 13/CEN/134).

Please note that you have the right to:

decline to participate

refuse to answer any particular questions

withdraw from the study at any time

If you have any queries or concerns about the study you can contact us at the Centre for Public Health Research.

Thank you very much for your time.

Yours sincerely,

Jeroen Douwes, PhD

Professor of Public Health

Director Training

Centre for Public Health Research

Janet Leathem, PhD

Professor of Neuropsychology

Director, Clinical Psychology

School of Psychology

Pesticide exposure and brain function in children

Parent Reply Form

On behalf of my child:…….. [Full name of child]

Name of child's school: ……..……..
Year:……

☐ **We wish to participate in the study** **OR**

☐ **We do not wish to participate in the study** *(please skip to the section at the end of this form)*

We have read the Information Sheet and understand that we may ask questions at any time.

We understand that we have the right to withdraw from the study at any time and to decline to answer any particular questions.

We understand that no individual information or names will be published.

We understand that the information provided will be used only for this research and publications arising from this research project.

We understand that at the end of the project the samples may be tested for different chemicals related to this research.

We would like to be sent a summary of the study results and our child's individual results:

☐ yes ☐ no

We consent to the investigators contacting our child's GP if any abnormal results are found:

☐ yes ☐ no

Name of parent/guardian: .....

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Signed (parent/guardian): .....

Signed (child, optional): ……

Date: .....

Postal address: .....

.....

Contact phone number: (..…).....

Name and address of General Practitioner: .....

.....

If you are <u>not</u> interested in taking part, it is helpful for us to know the reason: *(please tick a box)*

☐ I am not interested ☐ I don't have time ☐ I feel that my English is not good enough to be able to complete the questionnaire

☐ Other, please specify_____

PESTICIDE EXPOSURE AND BRAIN FUNCTION IN CHILDREN

Dear Teacher,

Centre for Public Health Research

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a.j.eng@massey.ac.nz

We have invited children at your school to take part in an important health research study examining how much New Zealand children are exposed to pesticides and whether this exposure has any effects on the brain and mental functions, and behaviours. To do this, we are inviting 900 children aged 5-11 years from different schools to take part in this study.

We have sent a letter, information sheet, and consent form home with each child to their parents. For a small number of participants, we would like to ask you to complete two brief confidential questionnaires about the child's behaviour at school. The parents of the child have already completed a questionnaire about potential sources of pesticide exposure as well as questionnaires about the child's behaviour at home; however, it is important for the study to also collect information about the child's behaviour at school.

This project is funded by the Health Research Council and has been reviewed and approved by the Central Health and Disability Ethics Committee (application ref 13/CEN/134).

If you are interested in taking part in the study, please read through the included information sheet and complete and return the enclosed consent form.

The information in the questionnaires will be confidential to the research team and at no time will individual information or names be made public.

Please note that you have the right to:

decline to participate

refuse to answer any particular questions

withdraw from the study at any time

If you have any queries or concerns about the study you can contact us at the Centre for Public Health Research.

Thank you very much for your time.

Yours sincerely,

Jeroen Douwes, PhD

Professor of Public Health

Director

Centre for Public Health Research

Janet Leathem, PhD

Professor of Neuropsychology

Director, Clinical Psychology Training

School of Psychology

Teacher Consent Form

- I wish / do not wish to participate in the study (please delete one).
- I have read the Information Sheet and understand that I may ask questions at any time.
- I understand that I have the right to withdraw from the study at any time and to decline to answer any particular questions.
- I understand that no individual information or names will be published.
- I understand that the information provided will be used only for this research and publications arising from this research project.

I would like to be sent a summary of the study results: ☐ yes ☐ no

Name:……

Signed: .....

Name of school: .....

Class year:……

Date: .....

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Pesticide exposure and brain function in children

Teacher Information Sheet

What is this study about?

We have invited children at your school to take part in a study looking at how much children are exposed to pesticides and whether this exposure has any effects on their brain development.

There is some concern that exposure to pesticides may affect brain function and behaviour. These effects have been found in exposed farmers and farm workers, but children may also be at risk due to the use of pesticides in the home, living close to pesticide-treated farming areas, the occupation of the parents, and to a lesser extent, through the food supply and drinking water.

This study aims to assess the level of exposure to pesticides in New Zealand children and whether this exposure has any effects on the brain and mental functions, and behaviours. To do this, we are inviting 900 children aged 5-11 years to take part in this study.

What would participation in this study involve?

Phase I: *All participants*

We have sent a letter, information sheet, and consent form home with each child to their parents. We would really appreciate it if you could encourage your class to remind their parents to return the form to us indicating whether they would like to take part or not. For a small number of participants, we would like to ask you to complete two brief confidential questionnaires about the child's behaviour at school. The parents of the child have already completed a questionnaire about potential sources of pesticide exposure as well as questionnaires about the child's behaviour at home; however, it is important for the study to also collect

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information about the child's behaviour at school. The questionnaires that we will ask you to complete should take 15-20 minutes per child. If you are willing to take part, please complete and return the attached consent form. With parental consent, we will also ask your school to provide us with some measures of the child's academic achievements including whether they are meeting the National Standards for reading, writing, and mathematics.

For selected participants:

Phase II: *Selected participants (not teachers)*

Later we will contact half (randomly chosen) of the children/parents again and ask permission for their child to undergo neuropsychological tests of memory, attention and reaction time, as well as their language skills and visual processing skills. Tests will be conducted by a trained researcher and will normally take place at school. This phase of the study will not require any teacher involvement beyond releasing the children from class. At this time, our research nurse will ask the child to collect urine samples and their parents to collect a house dust sample. The collection of these samples will be used to examine pesticide exposure and will be fully explained by our research nurse to the children and their parents.

What will happen with the personal information?

All of the information collected from the questionnaires that you are asked to complete is strictly confidential. Each questionnaire and the results of the other tests will be entered into a database using ID numbers. The questionnaires and tests will be seen by named researchers only and when the study is completed all questionnaires will be locked away in filing cabinets which will be the responsibility of the Director of the Centre for Public Health Research. When the study has been completed, we will analyse the information, *e.g.* compare the prevalence of the effects on the brain and mental functions and behaviours in those who are exposed to pesticides compared with those who are not exposed. At the end of the study the urine and house dust samples may be tested for different chemicals related to this research. The results of the study will be published in scientific journals and a summary of the results will be provided to all study participants that have requested it. **No individual information or names will be published.**

This project has been reviewed and approved by the Central Health and Disability Ethics Committee (application ref 13/CEN/134). If you have any concerns about the conduct of this research, please contact 0800 4 ETHICS (438 442).

You have the right to:

decline to participate

decline to answer any of the questions

withdraw from the study or parts of the study at any time

be given access to a summary of the study findings when it is completed

Please contact us at the Centre for Public Health Research to discuss any queries or concerns about the study.

Thank you very much for your time in considering this study.

Study team:

Professor Jeroen Douwes (Director), Dr Andrea ‘t Mannetje (Senior Research Fellow), Dr David McLean (Senior Research Fellow), Jean Feary Mckenzie (Research Assistant) and Dr Amanda Eng (Research Fellow), Centre for Public Health Research, Massey University, Wellington.

Professor Janet Leathem, Professor of Neuropsychology, School of Psychology, Massey University, Wellington.

Kate Ross-McAlpine &Yanis Brinkmann, Doctoral Students, School of Psychology, Massey University, Wellington.

Professor Neil Pearce, Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine, London, UK

Professor Jordi Sunyer, Joint Scientific Director and researcher, Centre for Research in Environmental Epidemiology, Barcelona, Spain.

Professor Jochen Mueller, ARC Future Fellow, National Research Centre for Environmental Toxicology, University of Queensland, Coopers Plains, Australia.

Professor Brenda Eskenazi, Director, Center for Environmental Research and Children’s Health (CERCH), University of California, Berkeley, USA.

Appendix F School Presentation

Slide 1

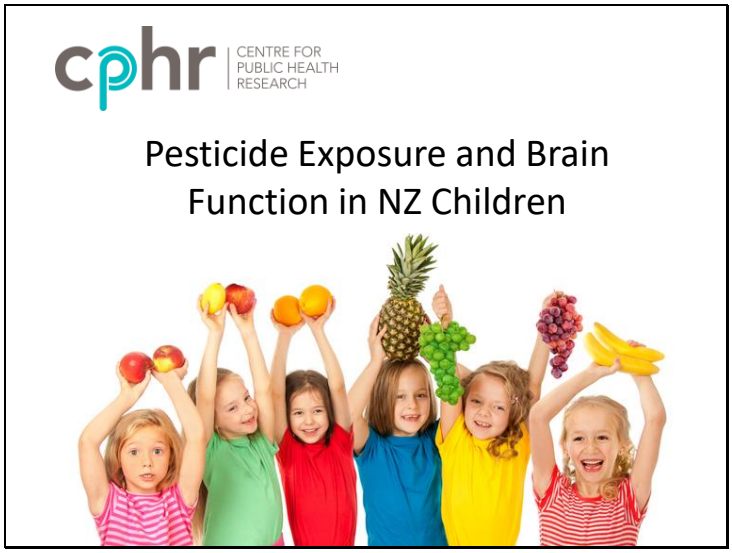
Hello _____ school!
My name is _____, and this is _____ and _____, and we are researchers (for the Centre for Public Health Research) at Massey University.
We are here today to talk to you about a study we are conducting at your school, and at 9 other schools around Wellington. (This study aims to investigate the possible effects of pesticides on the brain development of New Zealand children.)

First of all, I would like to thank you for allowing us to talk at your school today, and I would also especially like to thank those parents and students who have already agreed to take part in our study. Your help is greatly appreciated.

However, unfortunately at the moment we do not have enough people signed up to the study to complete it. Therefore, we need a lot more parents and children, like you, to take part. We do understand that you are all very busy and it is sometimes difficult to find the time to participate in research like this. However, hopefully today we can convince you that this research is a very important and worthwhile activity to take part in. We would really appreciate your help.

Now _____ will tell you a bit more about the study.

Slide 2

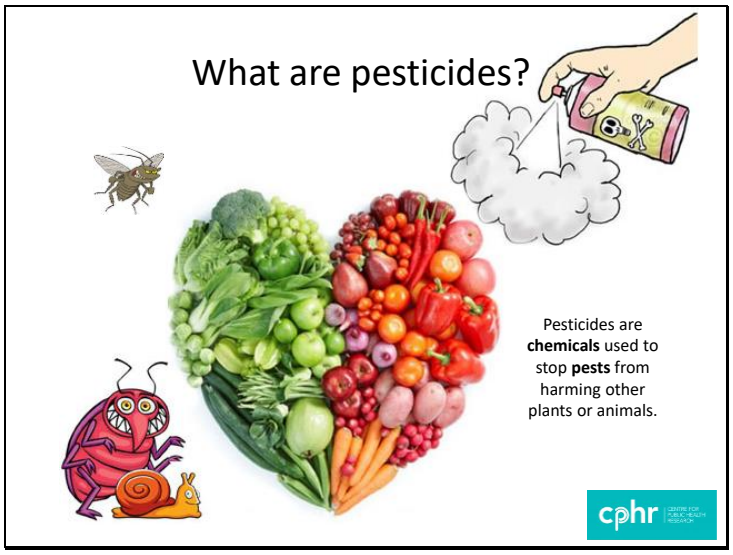


Thank you _____.

Hello everyone!
My name is _____, and I am going to talk to you a bit more about the study that you could be taking part in.

This study is investigating the possible effects of **pesticides** on the **brains** of New Zealand children.

Slide 3

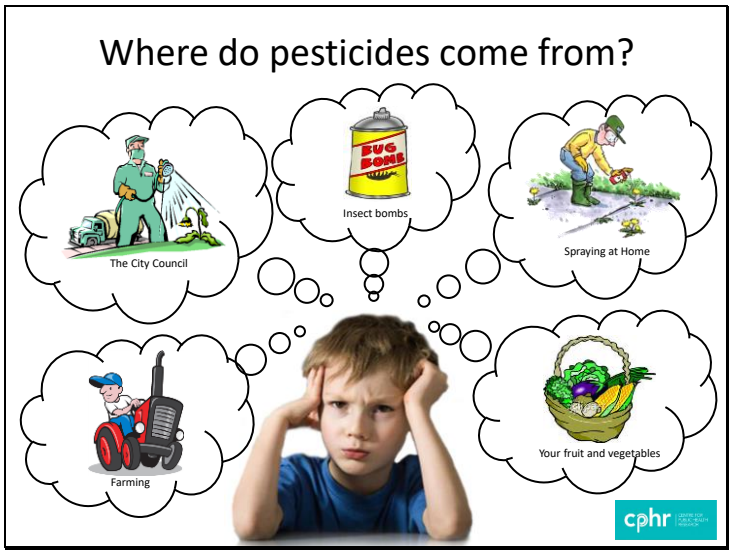


In our study we are looking at the effects of **pesticides**.

So, what are pesticides?

Pesticides are chemicals used to prevent, destroy, or repel pests to stop them from harming other plants or animals.
For example, a farmer may spray his vegetable fields with a pesticide to stop bugs from eating all of his tomatoes or carrots.

Slide 4

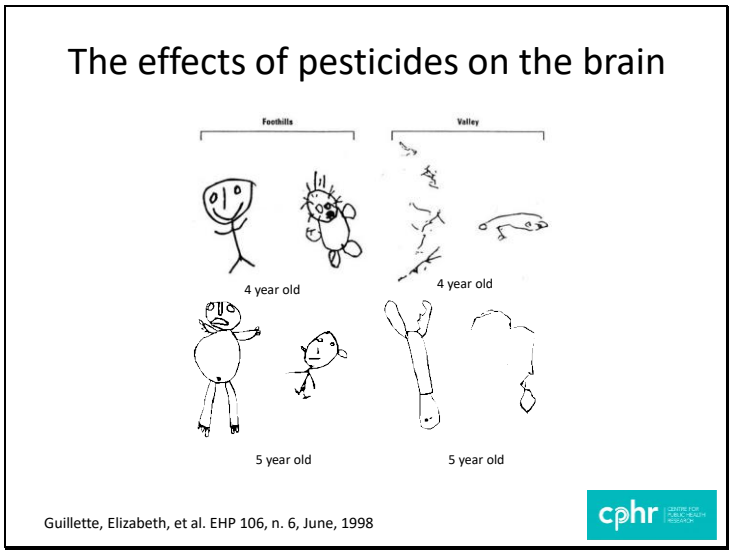


Pesticides can come from many different places.

For example, your city council may spray pesticides such as Roundup around your streets to control pests, your family may use insect bombs, your parents may spray your lawns at home, or pesticides may be used on a farm that you have access to. Pesticides may also be on your fruit and vegetables from when a farmer used pesticides on his fields. (Which is why it's always good to wash your fruit and vegetables before eating them). (Pesticides could also be sprayed on trees and shrubs around your school).

Pesticides are very useful and good in all these areas to control dangerous pests. However, some researchers have found that if **you** touch, eat or inhale high levels of pesticides they can be bad for your brain!

Slide 5



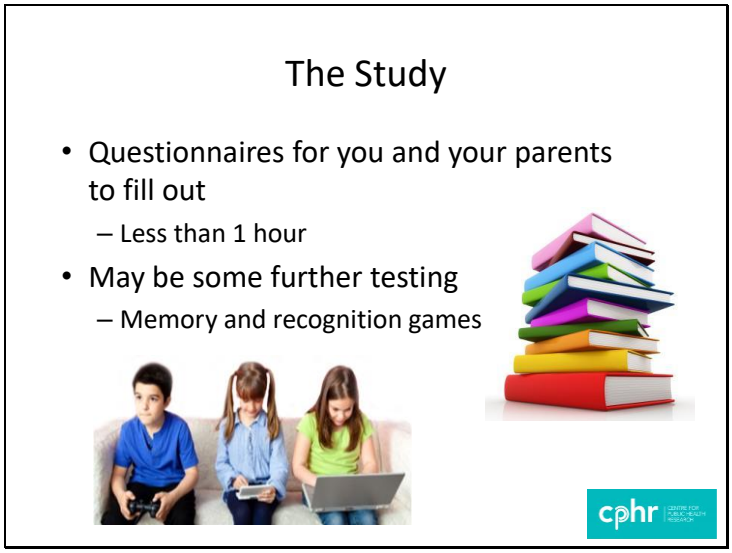
This picture comes from a study of some children in Mexico. The children were asked to draw a picture of a person.
The pictures on the left are done by children who were **not** exposed to pesticides, and the pictures on the right were done by children who were exposed to **high levels** of pesticides.

Can you see the difference?
The ones on the right, who were exposed to pesticides appear to be a Less well formed, right?
This study found that children exposed to pesticides were a lot worse at drawing a person, had decreased stamina, hand-eye coordination and had impaired memory compared to the children who were not exposed to pesticides.
This suggests that when the children in Mexico were exposed to very high amounts of pesticides it changed their brains. This can have long term serious effects for the children.

In our study we want to know if this effect happens in children in New Zealand.
At the moment we don't know much about the levels of pesticides that New Zealand children could be exposed to, and whether they can cause any health effects for children.

Our study is the first New Zealand study to look at this and we hope that this research can contribute to the creation simple policies and cost effective strategies to make the environment safer for you! With your help we can help stop other children from damaging their brains and developing serious diseases.

Slide 6



To take part in the study you and your parents will be asked to complete three questionnaires.

The first questionnaire will ask you about your lifestyle and pesticide exposure. The second two questionnaires will ask you about your behaviour.
The questionnaires will take under an hour to complete in total.

After this some children may be asked to come and play some games, which will assess memory and recognition skill.

All of this information will be kept private and anonymous.

Slide 7

We need large numbers of people to take part in this study, so we need your help!

If you are interested in taking part then you can come and talk to me or our other friendly researchers after this assembly, and we will take down your contact details.
Or if you want to have a think about it first, you can contact us later via the contact details provided on your information pack.

We will provide you all with an information pack about the study as you leave the assembly today.

Slide 8

So finally I would like to thank you all for your cooperation and we look forward to talking with you soon!