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The effects of pesticide use on the paediatric population: a Canadian perspective

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It is increasingly being recognised that pesticides may have an adverse effect on the health of children. There have been several case control studies that have suggested an association with exposure to pesticides and the subsequent development of disease. Studies have suggested that pesticides may result in malignancies, neurological deficits, immunosuppression and disruption of endocrine function. Alongside studies that have suggested an association, there have been numerous studies that have failed to demonstrate a link between pesticide exposure and disease. Many of the studies were poorly designed. There does, however, appear to be a link between pesticide exposure and the subsequent development of malignancies in children. Health professionals need to be aware of the possible associations between pesticides and health.

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Introduction

This paper aims to provide an overview of research regarding the effects of pesticide exposure on Canadian children. Currently, there are no set recommendations for Canadian or American paediatricians regarding the impact of pesticide exposure in children. In a 2004 statement by the American Academy of Pediatrics, they acknowledged the debate regarding the potential health hazards of chronic low dose exposure to pesticides but did not develop a policy[1]. Whereas some researchers emphasise the consistency and relevance of observations relating pesticide exposures to decreased health in children, others highlight the paucity of direct conclusive evidence[1,2]. With much of the data through case control studies, research has shown an association between chronic low dose pesticide exposure and chronic illness. There have been very few studies, however, in which a causal link has been established or in which researchers were able to show any dose-response relationships[3,4]. Investigations have demonstrated that exposure to chemicals can lead to increased systemic levels, and have further linked exposures to adverse health effects[5-7], yet no data was found linking the increased systemic levels to any specific illness. With obvious barriers to randomised controlled trials in paediatric research, it seems unlikely that there will ever be research that will conclusively demonstrate a positive dose-response association between low dose chemical exposures and chronic illness. Within all the scientific discussion, the physician is caught trying to decide how to treat and counsel their patients.

There is no debate as to the paediatrician's role in recognising and treating symptoms of acute

pesticide poisoning; however the importance of monitoring for the subtle effects of low-dose exposure is unknown. It is unrealistic to expect that individual physicians will be able to differentiate cause and effect from low level exposures to pesticides versus other potential causes[1]. The question remains how strongly paediatricians should try to encourage parents to prevent exposures. The "Precautionary Principle" states that a lack of full scientific evidence does not justify the abandonment of measures that may reasonably improve the health of children[1,8]. On the other hand, it is important to remember that pesticides have several important public health benefits, such as decreasing food and vector borne illnesses as well as increasing food production productivity[2]. To complicate matters, it is not proven that risk is lowered with a change to organic food products, since the decrease in pesticides is replaced by exposure to fungal toxins[9]. Furthermore, it would be detrimental to children, especially as Canada fights against the rising obesity of its youth, should they be encouraged to avoid outdoor activity due to pesticide exposure. There are no indications to recommend decreasing time spent playing outside, especially since pesticides are found ubiquitously in our environment and often in higher amounts inside homes.

The ubiquity of chemical exposures is a major concern for those who feel that they are harmful. Pesticide exposure can come from a variety of sources, including children's food and water, indoor domestic use, as well as outdoor agricultural and domestic use[2,10,11]. It is difficult to identify a single harmful agent because exposure is often to a variety of pesticides. For instance, parental occupational exposure in agriculture is to a multitude of agents. In addition, exposure doses cannot be objectively measured to develop dose-response relationships[8]. Because of their ubiquity and the scientific knowledge of their mechanism of action it is difficult to dismiss case studies arguing that they are harmful. For example, the most commonly used pesticides, organophosphates (OP), are known to target the central nervous system and have been associated with increased occurrence of childhood brain cancers[12]. Despite the paucity of clear data, many feel that knowledge of mechanisms and the gravity of the illnesses caused are sufficient to implement policy and ban use. Advocates argue that simply because illness is not being discovered through the current research methods, this does not indicate that it is not occurring.

It has been theorised that the reason studies have not been able to conclusively show causality between pesticide exposure and illness is due to subclinical toxicity. This theory states that in the dose-response continuum of toxic effects, exposures generally only provide a mild individual effect. This insignificant individual effect has huge implications for the health of a society[13]. These implications are important for health policy development; however they are not practical in helping individual paediatricians manage their patients.

Paediatricians need to develop a means of risk-stratifying patients while developing differential diagnoses. One suggested method is to assess children in terms of the nature of the contaminant, the type of exposure, and the vulnerability of the exposed child[14]. Assessment by paediatricians can be done using the following risk assessment questions:

1. Questions regarding the nature of the contaminant
   a. Is the chemical toxic to tissues?
   b. What dose is needed to cause damage?
   c. How toxic is the chemical?
   d. What is the toxic effect that is likely to occur?
2. Questions regarding the type of exposure
   a. How was the child exposed – inhalation, ingestion, dermal contact?
   b. What "dose" did the child receive?
   c. How much and at what concentrations?
   d. How long was the child exposed?
   e. Were co-factors present?
3. Questions regarding the susceptibility of the child
   a. What age or developmental stage is the child?
   b. Does the child have a co-morbid condition?

These questions delineate the importance of pesticide exposure, thus allowing stratification of pesticides within differential diagnosis. With such debate on the topic, it would be prudent to keep pesticides exposure as a topic for discussion by making parents aware of the potential effects.

Certainly more epidemiological and toxicological research regarding the risk of environmental toxins is necessary before any definite conclusion will be reached. Perhaps the most important advice for paediatricians is to keep an open mind to the concept that environmental exposures may play a role in children's health and include exposures as part of their routine history[14].

Why are children at risk?

Evidence shows that infants are more susceptible to environmental toxins due to exposure mechanisms, physiological immaturity, and early

exposure allowing manifestation after a long latent period[15]. Despite the widely held belief that children are likely to have increased exposure and be more susceptible to these chemicals, there is a paucity of data delineating children's low-level, chronic exposures and their significance in terms of health outcomes with the exception of chronic lead exposure[6].

Exposure mechanisms

The unique behaviours that children engage in, such as crawling, increased hand to mouth activity, soil ingestion, and outdoor play put them at risk of proportionally greater chemical exposures. Mechanisms of this exposure include dermal routes, inhalation, and ingestion[2,6-8,10,14,16,17].

Crawling, along with a greater surface area to body ratio, puts children at increased risk for dermal contact and, consequently, for the adverse health effects of pesticide exposure[2]. Young children are closer to the ground, where chemicals tend to be denser, allowing for a relatively greater exposure as compared to adults[2,8,10,14,16,17]. Children are additionally at increased risk of airborne toxins due to their higher metabolic and respiratory rates. Respiratory rates are further increased in children who are, in general, more active than adults[2,7,16,17].

The risk of low-level food exposure is amplified by children's greater intake of food per kilogram body weight. This is exacerbated by their higher intake of fruits and vegetables with the associated increased transmission of pesticides. Breastfed children may ingest pesticides that have accumulated in the high fat content of maternal milk[2,7,13,14,16,17].

High risk populations include children of minority or urban populations living in areas where they have increased exposure to high levels of polycyclic aromatic hydrocarbons (PAH), diesel exhaust particulate (DEP), benzo(a)pyrenes (BaP) and residential pesticides such as organophosphates (OP)[7,15,16] as well as children living or going to school in rural/agricultural areas where there is increased exposure to pesticides[10,18].

Physiological immaturity

Children's metabolic pathways and organ systems are immature[13]. For instance, lung maturity does not occur until the 6th-8th year of life[8,15]. Children have rapid brain growth during infancy with neuronal migration and myelination of the brain (completed at 2 years of age). In theory, this brain immaturity allows for a 'leaky' blood brain barrier and potentially greater neuronal exposure to chemicals[2]. Low levels of chemical exposure, specifically OP contact, during neurological development have been shown to have subtle but permanent neurochemical and behavioural effects[8,15]. Although children are thought to be less well able to metabolise and clear OPs (since they lack the enzymes necessary for breakdown), it is believed that they are better equipped to handle other chemicals such as PAHs[13]. While levels of the more lipophilic chemicals are highest in adults due to bioaccumulation, children have higher levels of systemic pesticides such as OPs[5].

Theoretically, teenagers have increased risk due to rapid growth spurts, especially in sexual development and body mass index. These rapidly developing tissues become susceptible to pesticide exposure[14].

Early exposure

Many illnesses caused by environmental chemicals require decades to develop[13]. Exposure at a young age allows time for latency periods to pass and for the development of disease[2]. With the relatively new array of pesticides being used, the latent effects of these chemicals may not be known for decades. Only then might children who are currently being exposed show the effects of illness processes that will have been latent since contact[13]. There are further concerns that early chronic exposures will bio-accumulate leading to toxicity related adverse health effects such as cancers and birth defects in future generations[7]. With the debate ongoing, perhaps only time will tell if pesticide exposure truly is harmful.

Vulnerability *in utero*

Evidence shows an increased risk of genetic damage and a potential increased cancer risk with fetal exposure to environmental toxins. Studies suggest that clearance of toxins by fetuses is less efficient than in adults, leading to an increased systemic level and potential for elevated genetic damage with resultant cancer risks[7,14,15]. For each phenotypic event, there appears to be a window of critical exposure[7]. Maternal levels of organophosphate (OP) chlorpyrifos correlated with levels in umbilical cord blood in newborn babies, demonstrating the passage of chemicals to the fetus. An inverse relationship between levels of OPs in the neonates' plasma and birth weight and length was shown[19].

Cancer

Suggesting an association

There have been several *case-control* studies that have suggested an association with exposure to pesticides either by the child or by their parents and the subsequent development of cancer. Children of parents with occupational exposure to pesticides have an increased risk of leukaemia as well as non-Hodgkin's lymphoma[7,8]. Children exposed to maternal home insecticide use *in utero* and during childhood as well as fungicide use during childhood were significantly more likely to develop acute leukaemia[20]. Parental exposures and home use of insecticides were linked to childhood brain cancers (one study specifically astrocytomas) and soft-tissue sarcomas[7,12]. An association had been found between neuroblastomas, nervous system tumours, Wilms' tumour, Ewing's sarcoma and paternal pesticide exposure[7,12]. In a literature review by Health Canada's Pest Management Regulatory Agency, non-Hodgkin's lymphoma, leukaemia, and sarcomas were all found to be associated with chlorophenoxy herbicides. This same review noted a doubling of intractable childhood neuroblastoma with the domestic use of landscaping pesticides[21].

Inconclusive studies

There have also been several *case-control* studies that have suggested an increased risk for some malignancies but have failed to demonstrate an association with other malignancies. One case-control study demonstrated that children of parents with occupational exposure to pesticides as well as those in homes with domestic pesticide use may have an increased risk for the development of childhood leukaemias[8]. This was examined again several years later and demonstrated elevated odds ratios for leukaemias associated with exposure to chemicals classified as probable and possible carcinogens and with agricultural use of organochlorines and OPs during pregnancy[4]. The study, however, failed to demonstrate any association between central nervous system tumours or all cancer sites combined and pesticide use[4]. Furthermore, despite confirming the risks for leukaemia, the few positive results in this study are consistent with chance, giving the high number of comparisons made. Girls who developed germ-cell tumours were more likely to have had postnatal exposure to pesticides through their mothers. There was a non-significant positive association with dysgerminomas and maternal pesticide exposure. On the contrary, children who developed germ-cell tumours were less likely to have fathers with occupational pesticide exposure[22]. Sample sizes were small and results need to be confirmed.

There have also been several *case-series* studies. An overall increase in childhood cancer risk was found among children whose fathers were pesticide applicators. Specifically, there was double the risk of developing lymphoma. Authors, however, were unable to establish a dose-response relationship or identify a specific pesticide that increased risk, allowing for speculation regarding confounding factors[23]. One study examining the development of cancer in children living in areas of high agricultural use found no overall association[17]. These results stand in contrast to case-control studies done examining the same relationship. The authors did find an association between leukaemia and use of the pesticide propargite; however no dose response was established.

One group showed elevated risk of astrocytomas in children with paternal exposure to four different classes of pesticides (insecticides, herbicides, and nonagricultural and agricultural fungicides) and maternal exposure to three classes (all except agricultural fungicides)[24]. They demonstrated an increase in neuroectodermal tumours with paternal herbicide exposure yet no increase with maternal exposure. The authors concluded that parental exposures were unlikely to have an impact on childhood brain cancer since most of the risk estimates in this second study were around unity and no dose response was found[24].

High parental occupational exposure to pesticides did not significantly increase the incidence of childhood brain cancers (specifically astrocytoma and neuroectodermal tumours)[1]. Authors propose environmental factors as one of the reasons that testicular cancers have increased by 68% within the past thirty years[13]. While this suspicion is present, there are no studies found testing the hypothesis.

Neurological deficits

Several *case-control* studies have suggested that pesticide exposure is associated with neurological problems. A case-control study of exposure to chronic low concentrations of OPs affected acquisition of performance as well as response speed (finger tapping) and latency in Latino children of agricultural workers when compared to race, age, and sex matched controlled children of non-agricultural workers[10]. Delays in physical stamina, gross and fine hand-eye coordination, and short-term memory were found among Mexican and Indian children living in areas of extensive pesticide use[2,7,8].

A study of illegal exposure to pesticides in Ohio and Mississippi in the USA demonstrated inconsistent evidence of diminished short-term memory and attention span. Parents reported that their children had more behavioural and motor skill problems. These results were not consistent over the two study locations and, therefore, cannot be considered conclusive of harm from exposure[25]. Lawn pesticides were associated with several neurological illnesses such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Notably, in children, it was associated with increased autism and attention deficit disorder[26].

Respiratory problems

A Lebanese study found a significant correlation, with dose-response, between childhood exposure to pesticides and development of chronic respiratory symptoms and disease (most significantly asthma). In this study, exposure was conclusive for parental occupational exposure, residential exposures and domestic use of pesticides[27]. A study of adult farmers showed an association between insecticides and herbicides and increased wheeze. The wheeze was exacerbated by pesticide exposure within the previous year[28]. It is unknown whether these effects of pesticides on adults can be assumed in children. Another study of acute exposure to sprayed Malathion and Resmethrin did not find any significant increase in asthma rate/severity or hospital admissions through the emergency department as compared to days without pesticide spraying[29].

Immune and endocrine function

Case-series suggest that there is limited evidence to prove, one way or another, the impact of pesticides on the immune system. There have been associations made between hypersensitivity reactions, immunosuppression, autoimmune responses and chronic exposure to pesticide use[8]. Studies in laboratory animals or wildlife have shown an association between environmental chemicals and childhood endocrine disorders[7,13,30]. Scientifically, PCBs are known to be toxic to the thyroid gland and it is theorised that OPs and other pesticides may lead to a disruption in thyroid function, precocious puberty, and possible cryptorchidism[7,30]. Studies have suggested a window of vulnerability to pesticides from three months before conception through the first month of pregnancy[2]. Overall, links between environmental toxins and endocrine effects are more speculative than based on specific data[30].

Acute illness

Children less then six years of age in the USA represent more than half of the reported acute pesticide poisonings, with the majority being less then three years old. Most commonly, poisonings occur through accidental ingestion or dermal contact of OPs or carbamate pesticides[7]. It is accepted that children can have OP and carbamate poisoning leading to a variety of non-specific symptoms including a depressed level of consciousness[1]. Exposure to pesticides applied to school grounds or through pesticide drift from neighbouring agricultural areas led to a low incidence of mild acute illness in children[31]. Because of the low incidence, it is unclear what the impact of such exposures have on a societal level and how they offset the benefits of pesticide use.

Topical pesticide exposure

Adult contact exposure to pesticides and fungicides has the potential to penetrate the skin and become systemic. Contact is a major cause of irritant and allergic dermatitis in adults. There were no studies found discussing dermatological manifestations of pesticide exposure specifically in children. The risk of using diethyltoluamide (DEET) for children older than 2 months is low provided a topical concentration of 10-30% is used. The rate of potential adverse reactions (including hypotension, hypotonic reaction, syncope, death) is approximately 0.1%[26].

Discussion

This literature review found several case-control and case-series studies that demonstrated an association between pesticide exposure and the development of childhood cancers (especially leukaemias and brain cancers), neurological delays, respiratory illness, and immunological conditions as well as neonatal effects with exposure. Epidemiological studies have linked pesticide exposure to several paediatric cancers, with the most evidence for leukaemia, CNS tumours, and neuroblastomas[22]. These studies, however, are contrasted by others. The majority of research on this subject has found inconclusive results. A further set actually showed safety with exposure to pesticides. For instance, even with the potential reporting bias, several studies were found that showed exposure to pesticides did not increase children's risks of brain cancer, respiratory illness or topical illness. The only available data linking pesticides and endocrine illnesses are based on laboratory animal and wildlife studies. Overall, the literature is fraught with controversy and there is a need for more research.

Many of the available studies are plagued by design flaws that allow for questioning of results. Studies were limited by insufficient power, potential recall and/or response biases, and confounding factors. Several of the studies showing a positive finding had multiple comparisons, thus increasing the likelihood that the few positive results were due to chance. However, if this is the case, it is curious that there was so much similarity in the results. As mentioned, several papers found a positive association between childhood exposure and risks of blood malignancies such as leukaemia and lymphoma, as well as brain cancers. Unfortunately, due to inherent differences in the studies, meta-analysis is not possible.

In examining the literature, there was also an obvious reporting bias. Of the studies cited, each showed a minimum of one positive association, even when they concluded that overall there was no risk. There may be unpublished research that found no associations between pesticide exposure and illness.

For clinicians in Canada, the data may be assumed to be applicable but there is no guarantee of generalisability. Most of the studies on pesticide use were conducted outside of Canada. In reviewing the data, there is an assumption that Canadian pesticide use and exposures are similar. Although many epidemiological studies demonstrate effects of pesticide exposure on adults with associated increase in cancers and dermatological illnesses, it is unclear how this relates to paediatric illness. Earlier exposure theoretically increases risk of consequences.

The complexity of pesticide exposure on the health of children lays at the "interface between scientific data evaluation, pragmatic decision making, governmental policy, and the concerns of the general public"[32]. As such, it is the responsibility of paediatricians, as advocates for their patients, to be engaged at all these levels to help ensure the continued health of children. Although the data conflicts, it is clear that paediatricians should be mindful of the possible harm and discuss with parents the potential long term effects of environmental exposures.

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