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Review

Residential exposure to pesticides and childhood leukaemia: A systematic review and meta-analysis

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ABSTRACT

Objective: To conduct a systematic review of published studies on the association between residential/household/domestic exposure to pesticides and childhood leukaemia, and to provide a quantitative estimate of the risk.

Methods: Publications in English were searched in MEDLINE (1966–31 December 2009) and from the reference list of identified publications. Extraction of relative risk (RR) estimates was performed independently by 2 authors using predefined inclusion criteria. Meta-rate ratio estimates (mRR) were calculated according to fixed and random-effect models. Separate analyses were conducted after stratification for exposure time windows, residential exposure location, biocide category and type of leukaemia.

Results: RR estimates were extracted from 13 case-control studies published between 1987 and 2009. Statistically significant associations with childhood leukaemia were observed when combining all studies (mRR: 1.74, 95% CI: 1.37–2.21). Exposure during and after pregnancy was positively associated with childhood leukaemia, with the strongest risk for exposure during pregnancy (mRR: 2.19, 95% CI: 1.92–2.50). Other stratifications showed the greatest risk estimates for indoor exposure (mRR: 1.74, 95% CI: 1.45–2.09), for exposure to insecticides (mRR: 1.73, 95% CI: 1.33–2.26) as well as for acute non-lymphocytic leukaemia (ANLL) (mRR: 2.30, 95% CI: 1.53–3.45). Outdoor exposure and exposure of children to herbicides (after pregnancy) were not significantly associated with childhood leukaemia (mRR: 1.21, 95% CI: 0.97–1.52; mRR: 1.16, 95% CI: 0.76–1.76, respectively).

Conclusions: Our findings support the assumption that residential pesticide exposure may be a contributing risk factor for childhood leukaemia but available data were too scarce for causality ascertainment. It may be opportune to consider preventive actions, including educational measures, to decrease the use of pesticides for residential purposes and particularly the use of indoor insecticides during pregnancy.

Contents

Abbreviations: AL, acute leukaemia; ALL, acute lymphocytic leukaemia; AML, acute myelogenous leukaemia; ANLL, acute non-lymphocytic leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MA, meta-analysis; mRR, meta-rate ratio estimate; OR, odds ratio; RR, relative risk; UI, uncertainty interval.

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1. Introduction

For years, pesticides have been widely used against insects, fungi, rodents, noxious weeds, etc. that can damage crops, property and human health. As with any biologically active agents, pesticides may, however, have unwanted side-effects, including cancer.

Children can be exposed to pesticides from various sources at different levels than adults under the same exposure scenario.

The first possible source of exposure to pesticides in childhood is indirect contamination from parental occupational exposure. Children can also be directly exposed to pesticides from indoor uses (in homes, schools, and other buildings), from outdoor uses (garden, playing areas/public lands, agricultural application drift, overspray or off-gassing), through contaminated food and drinking water, by handling treated or contaminated pets or others (e.g. through the use of insecticidal shampoos for lice infestation) (Zahm and Ward, 1998).

Children may be especially vulnerable to adverse health effects of pesticides due to both developmental (physiological) and behavioural factors that can increase the dose and toxicity as compared with adults who live in the same environment (Bearer, 1995; Bruckner and Weil, 1999; Karr et al., 2007; Moya et al., 2004). Air concentrations of pesticides have been found to be higher closer to the floor (Fenske et al., 2000). As children are low to the ground, they may have greater exposure to volatile pesticide vapours. Their metabolism is also significantly different from that in adults, resulting in different levels of toxic metabolites in foetus and young children compared with adults (Garry, 2004; Weiss et al., 2004). Their immune system is also less mature.

It has long been recognised that childhood leukaemia is not a homogeneous disease. Acute leukaemia deriving from the lymphocytic or from the myeloid lineage are by far the most frequently observed among children. The most common type is acute lymphocytic (or lymphoblastic or lymphoïd) leukaemia (ALL) which accounts for 75–80% of all cases of childhood leukaemia. Acute myeloïd (myelocytic, myelogenous or non lymphoblastic) leukaemia (AML), also termed acute non lymphoblastic leukaemia (ANLL), is less frequent (about 20%). The chronic forms, chronic myeloïd leukaemia (CML) and chronic lymphocytic leukaemia (CLL), are rarely seen during childhood (Belson et al., 2007; Onciu and Pui, 2006). This major morphological division is supplemented by the identification of a range of subsets based on gene expression, antigens that delineate cell type or differentiation status, and chromosomal and molecular abnormalities. Leukaemia is a clonal disease (originating in a single cell) evolving by the accrual of mutations within a clone. There is now compelling evidence that the first or initiating event in leukaemia is a chromosome translocation occurring during foetal development but one or more additional postnatal genetic alterations are needed for leukaemia development (Greaves, 2002).

The aetiology of childhood leukaemia remains largely unknown. The difficulty arises from the fact that paediatric leukaemias, like most cancers, have multifactorial aetiologies involving the interaction between various aspects originating from the environment as well as human genetics. In addition, the investigation of childhood leukaemia requires cognizance of the timing of exposure, regardless of its environmental and molecular origins (Buffler et al., 2005). Epidemiological studies on acute leukaemia in children have examined possible risk factors including genetic, infectious and environmental factors (e.g., ionizing radiation, non-ionizing radiation, electromagnetic fields, cigarette smoking, alcohol consumption, hydrocarbons, and pesticides). So far ionizing radiation has been the most significantly linked with either ALL or AML. The strongest evidence of an association with AML has been found for benzene and cytotoxics (alkylators and topoisomerase II inhibitors). Most other factors have been weakly or inconsistently associated with either forms of childhood leukaemia (Belson et al., 2007; Eden, 2010; Linet et al., 2003). Among environmental chemicals, pesticides have been specifically scrutinized. There is growing evidence in support of an association between pesticides exposure and childhood leukaemia. Most of the studies evaluating exposure to household pesticides suggest that an increased risk is associated with *in utero* and postnatal pesticide exposures, although the subtype of leukaemia, definition of exposure, and exposure period at risk differ among these studies (Buffler et al., 2005).

Several literature reviews on pesticides exposure and childhood cancers have been published recently (Infante-Rivard and Weichenthal, 2007; Metayer and Buffler, 2008; Nasterlack, 2006, 2007). These authors considered that investigating in the acquisition and critical review of exposure information was a crucial step for establishing causal association. Suggestions for future work on chemical risk factors and childhood leukaemia included the need of pooling data and analyses as well as carrying out in-depth reviews of studies with the goal of understanding the reasons for discrepant results (Infante-Rivard, 2008). In the last months, systematic reviews and meta-analyses have been conducted with regard to childhood leukaemia and parental occupational exposure to pesticides (Van Maele-Fabry et al., 2010; Wigle et al., 2009). Both meta-analyses concluded that the strongest evidence of an increased risk of childhood leukaemia comes from maternal occupational exposure to pesticides, the associations with paternal exposure being weaker and less consistent.

The purpose of the present study is to perform a systematic review and meta-analysis of published studies that have examined the association between residential exposure to pesticides and leukaemia among children with the aim to enhance our understanding of the potential involvement of such exposure in the aetiology of childhood leukaemia. To this end, our review focuses on several exposure issues