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RESIDENTIAL EXPOSURES TO PESTICIDES AND CHILDHOOD LEUKAEMIA

Catherine Metayer* and Patricia A. Buffler
School of Public Health, University of California, 2150 Shattuck Avenue, Suite 500, Berkeley, CA 94720-7080, USA

Like many chemicals, carcinogenicity of pesticides is poorly characterised in humans, especially in children, so that the present knowledge about childhood leukaemia risk derives primarily from epidemiological studies. Overall, case–control studies published in the last decade have reported positive associations with home use of insecticides, mostly before the child's birth, while findings for herbicides are mixed. Previous studies relied solely on self-reports, therefore lacking information on active ingredients and effects of potential recall bias. Few series to date have examined the influence of children's genetic susceptibility related to transport and metabolism of pesticides. To overcome these limitations, investigators of the Northern California Childhood Leukaemia Study (NCCLS) have undertaken, in collaboration with a multidisciplinary team, a comprehensive assessment of residential pesticide exposure, including: (1) quality control of self-reports; (2) home pesticide inventory and linkage to the Environmental Protection Agency to obtain data on active ingredients; (3) collection and laboratory analyses of ~600 home dust samples for over 60 pesticides and (4) geographic information studies using California environmental databases to assess exposure to agricultural pesticides. The NCCLS is also conducting large-scale genotyping to evaluate the role of genes in xenobiotic pathways relevant to the transport and metabolism of pesticides. A better quantification of children's exposures to pesticides at home is critical to the evaluation of childhood leukaemia risk, especially for future gene–environment interaction studies.

INTRODUCTION

Pesticides encompass a variety of chemicals to kill or repel unwanted organisms such as insects, animals, weeds and micro-organisms from infesting lawns, gardens and crops. Hundreds of pesticides are currently used commercially including—but not limited to—organophosphates, organochlorines, carbamates, pyrethoids, triazine and phenoxy acid herbicides. Certain pesticides have been banned in developed countries for over 30 y (e.g. chlordane, dichlorodiphenyltrichloroethane (DDT) and lead arsenate), but continue to pose risks to the public as they persist in the environment. Knowledge of the carcinogenic potential of pesticides in humans is limited despite decades of toxicological and epidemiological research, which underscores the difficulty in assessing long-term health effects for 'active' ingredients and 'other' ingredients present in thousands of pesticide formulations[1–4]. Certain pesticides may be carcinogenic through non-genotoxic mechanisms (without direct effects on DNA). For example, DDT, pyrethroids and chlorinated pesticides can dysregulate the immune system[5–7], but little is known about immune-related mechanisms in the aetiology of childhood leukaemia.

There are many opportunities for a child to be exposed to pesticides in the environment at home, school and/or through dietary intake (water, food and breastfeeding). Children's exposures to pesticides at home may derive from various sources such as domestic use, drifts from nearby agricultural areas and take-home exposures from parental workplaces. Use of pesticides in and around the home is of particular interest because of young children's hand and mouth contact with surfaces potentially contaminated by various chemicals including pesticides. The current literature suggests that children can be exposed to higher levels of carcinogens than their parents and that differences in transport and metabolism of chemicals may result in different levels of toxic metabolites in foetus and young children compared with adults[8,9].

This paper focuses on residential exposure to pesticides and describes some of the challenges in characterising the 'true' exposure to pesticides in case–control studies. Note that issues related to parental occupational exposures to chemicals (including pesticides) and population-based estimates of agricultural pesticide exposure using geographic information system technology (GIS) were addressed separately at the workshop.

OVERVIEW OF THE CURRENT LITERATURE

A detailed literature review on pesticide exposure and childhood cancers was published recently by Infante-Rivard and Weichenthal[10] updating a review by Zahm and Ward published in 1998[11]. Another series of review articles has been published by Nesterlack in 2006 and 2007[12,13]. Since then, two additional studies of childhood leukaemia have reported findings on the effect of residential exposure to pesticides and

*Corresponding author: cmetayer@berkeley.edu

childhood leukaemia[14,15], leading to a total of 12 case–control studies published from 1987 to 2007[14–25] including one series of infant leukaemia[18] and one series among children with Down's syndrome[15].

Risk estimates were provided for all histological types of childhood leukaemia combined[16,17,19,21,23,25], acute lymphocytic leukaemia (ALL)[14,15,17,18,20,22]—the most common type of childhood leukaemia—and acute myeloid leukaemia (AML)[14,15,18,22,24]. Details on study populations are provided in Table 1. Characterisation of self-reported exposure to residential pesticides varies across studies as shown in Table 2, with the most similarities seen between the case–control studies in Northern California, USA[17] and Canada[20]. Home insecticides, herbicides and garden insecticides were the most frequently studied, followed by rodenticides and fungicides.

Childhood leukaemia and childhood ALL

With the exception of one series[19], previous studies[14–18,20–23,25] have consistently reported associations between any use of home or garden insecticides and childhood leukaemia overall and ALL, with risk estimates ranging generally from 1.5 to 2.5. Some studies based on small numbers of exposed children have reported 3- to 4-fold increased risks with use of specific pesticides such as pest strips[23] or Baygon/mosquitocides[18]. Statistically significant increased risks of childhood leukaemia or ALL have been reported with the use of herbicides in some[14,20], but not in all studies[15–17]. Null[19] and positive[21,22] associations were reported for garden pesticides, without specification of insecticide or herbicide use. Inconsistencies among studies examining leukaemia risk associated with garden pest products (insecticides and herbicides) may be due to differences in data collection and classification, variations in product composition over time and by country, as well as lack of statistical power. Also, pesticides used outdoors undergo degradation processes (e.g. hydrolysis and photolysis) affecting short- and long-term levels of pesticide compounds in the environment[26]. Mixed findings were reported for risk of childhood leukaemia or ALL with the use of professional pest control services[15,17,19,23], fungicides[14,16] and insect repellents[15,17,20], while no association was found with exposure to rodenticides[15,17,20]. Dose–response relationships were observed in three studies examining frequency of home insecticide use[15,17,20]. Timing of exposure to pesticides appears to be critical, as risks of childhood leukaemia or ALL tend to be higher when exposure to home insecticides occurs during pregnancy compared with early childhood[14–17,20,23]; the same observation was reported for herbicide use in some[14,16,17,20], but not all studies[15,23]. The separate or combined effects of pre- versus postnatal exposures, however, are not well characterised.

Childhood AML

A study based on 61 children with Down's syndrome and AML reported no elevated risks with exposure

Table 1. Characteristics of case–control studies on residential pesticide exposure and risk of childhood leukaemia.

Study	Location	Age	Disease	Number of cases	Sources of controls
Rudant *et al.*[14]	France	0–14	ALL; AML	646;100	RDD
Menegaux *et al.*[16]	France	0–14	Acute leukaemia	280	Hospital
Alderton *et al.*[15]	USA	0–19	ALL; AML (Down's syndrome)	97;61	Listing from primary physicians
Ma *et al.*[17]	USA	0–14	Leukaemia; ALL	162;135	State birth registry
Alexander *et al.*[18]	International[a]	Infants (0–18 months)	ALL; AML	74;49	Hospitals
Meinert *et al.*[19]	Germany	0–14	Leukaemia	1184	Community registry
Infante-Rivard *et al.*[20]	Canada	0–9	ALL	491	Government registry
Meinert *et al.*[21]	Germany	1–14	Leukaemia	173	Community registry
Leiss and Savitz[23]	USA	0–14	Leukaemia	N/A	RDD
Schwartzbaum *et al.*[22]	USA	0–14	ALL; ANLL	522;107	Hospital
Buckley *et al.*[24]	USA	1–18	ANLL	204	RDD
Lowengart *et al.*[25]	USA	0–10	Leukaemia	123	Friend or RDD

ALL, acute lymphocytic leukaemia; AML, Acute myeloid leukaemia; RDD, random digit dialling.
[a]Includes countries in Europe, Middle East, Asia and South America.

Table 2. Description of pesticide exposure variables under investigation.

Study	Products listed in the questionnaire	Combined categories for analyses	Other characteristics	Period of exposure
Rudant *et al.*[14]	Home insecticides; pet insecticides; garden insecticides; herbicides (weed killer) and fungicides	Any pesticides; any insecticides	Maternal and paternal use	Maternal use during pregnancy Paternal use since conception
Menegaux *et al.*[16]	Herbicides; home insecticides; garden insecticides; garden fungicides and treatment for pediculosis	Any garden pesticides	Maternal use only	Pregnancy, after birth
Alderton *et al.*[15]	Products to control home insects, moths fleas and ticks; rodenticides; herbicides including insecticides for plants; insect repellants and professional pest control		Frequency of use	Pregnancy, after birth
Ma *et al.*[17]	Professional pest control; professional lawn services; products to control crawling/flying insects (ants, flies or cockroaches; spiders), termites, rodents (rats, mice, gophers and moles), slug and snail baits; fleas (indoor fogger shampoos, sprays and powders) and plant/tree insect or disease; insect repellants for ticks or mosquitoes; weed killer	Any insecticides; any herbicides; indoor pesticides; outdoor pesticides; flea control products	Frequency of use	Pre-conception, pregnancy, after birth
Alexander *et al.*[18]	Pesticides (not specified)		Maternal use only	Pregnancy
Meinert *et al.*[19]	Pesticide used in gardens; use of household insecticides by parents and by pest controller		Frequency of use	After birth
Infante-Rivard *et al.*[20]	Products to control crawling/flying insects (cockroaches, ants, flies, bees, wasps, moths, mites and spiders), rodents (rats and mice); slug and snails; termites; herbicides; plant insecticides; products for trees; repellents and sprays for outdoor insects	Insecticides; rodenticides and other pesticides (except above)	Frequency of use	Pregnancy, after birth
Meinert *et al.*[21]	Pesticide used in garden			After birth
Leiss and Savitz[23]	Home extermination Yard treatment with herbicides or insecticides Pest strips			Pregnancy, after birth
Schwartzbaum *et al.*[22]	Parent gardening with fertilisers, herbicides or pesticides			Not specified
Buckley *et al.*[24]	Exposure to pesticides (not specified)			Pregnancy
Lowengart *et al.*[25]	Household pesticides; garden pesticides or herbicides		Maternal and paternal use	Not specified

to various types of pesticides[15]. In contrast, positive associations were reported in the international series of infant AML with maternal use of pesticides during pregnancy (OR = 5.08, 95% CI: 1.84–14.04) and exposure to Baygon/mosquitocides (OR = 7.82, 95% CI: 1.73–35.39); risk estimates were unstable due to limited numbers of cases[18]. Other studies not restricted to special childhood populations have shown statistically significantly elevated risks of childhood AML with maternal use of pesticides[14,24] but not herbicides or garden products[14,22]. Childhood AML remains a rare disease, and studies

with a larger sample size are required to investigate the impact of residential pesticides. Such studies will be facilitated by the newly established Childhood Leukaemia International Consortium (CLIC) with collaboration of 14 case–control studies worldwide (details available at http://clic.berkeley.edu).

Genetic susceptibility

The literature to date regarding the role of genes modulating transport and metabolism of chemicals (i.e. multiple drug resistance (*MDR1*) genes, cytochrome P450 (*CYP*) genes and glutathione-S-transferase (*GST*) genes) in the aetiology of childhood leukaemia is mixed, likely due to small sample size and limited coverage of the genes (see details in ICNIRP/WHO/BfS workshop report on genetic susceptibility to childhood leukaemia). Even fewer studies have examined how the child's genetic susceptibility may interact with exposure to pesticides. Two reports showed that children exposed to indoor insecticides and carrying the CYP1A1m1 and CYP1A1m1 mutation[20] are at high risk of childhood leukaemia, while carriers of a specific *MDR1* haplotype may be at low risk[27]. Of special interest is the paraoxonase 1/arylesterase (*PON 1*) gene involved in the metabolism of organophosphate substrates. As indicated in a recent cohort study of 130 pregnant women living in an agricultural area in California, newborns have low levels of the PON1 enzyme and may be more susceptible to the harmful effects of organophosphate pesticides[28]. No study to date has investigated *PON1* gene variants and childhood leukaemia risk. In conclusion, very little is known on how genetic susceptibility related to transport and metabolism of pesticides may affect the risk of childhood leukaemia. However, many epidemiological studies worldwide are currently incorporating molecular tools to provide answers to this important question in the near future.

PESTICIDE EXPOSURE ASSESSMENT: EXPERIENCE FROM THE NORTHERN CALIFORNIA CHILDHOOD LEUKAEMIA STUDY (NCCLS)

Because childhood leukaemia is a rare disease, the most efficient method to study its aetiology is a case–control design with retrospective ascertainment of exposure. Previous studies of childhood leukaemia have relied on self-reported exposures to pesticides at home or at the workplace for parents, which provide useful information at critical pre- and postnatal time windows of the child's development, but are limited by the lack of specificity in defining type of pesticides (active ingredients), target pest and amount of pesticide. Also, recall of previous exposure to pesticides may be different in parents of a child diagnosed with leukaemia (case) versus a healthy child (control), resulting potentially in biased estimates of effect. Interestingly, the magnitude of the associations with pesticides varies by histological type of leukaemia and other haematopoietic malignancies in several investigations[14,15,18,19], suggesting that differential recall bias may not fully explained the observed associations between childhood leukaemia and residential use of pesticides. A better quantification of children's exposures to pesticides is critical to the evaluation of childhood leukaemia risk, and even more so for evaluating interactions between genetic and environmental factors[29].

To address some of the limitations inherent in case–control study studies, a comprehensive model for chemical exposure assessment was developed in the NCCLS, in collaboration with a multidisciplinary team of environmental epidemiologists and toxicologists from the University of California at Berkeley, the US National Cancer Institute, the US Center for Disease Control and Prevention, the Northern California Cancer Center and Colorado University. The NCCLS is a population-based case–control study with a target number of 1000 leukaemia cases and 1300 controls enrolled from 1995 to 2008, of whom ~42% are Hispanic children. It covers geographic areas in California with the highest agricultural pesticide use in the USA[30]. Details for NCCLS case and control enrolment have been described elsewhere[17].

Initial in-person interviews (referred to as Tier 1) were conducted in English or Spanish by trained staff usually with the biological mother. Standardised questionnaires, show cards and calendars were used to elicit responses regarding exposure to a wide range of chemicals and pesticides used at home and at work, for critical periods of the child's development (before conception, three trimesters of the pregnancy and early years of life up to age 3 y old). More specifically, respondents were asked about the personal use of the following pesticide products and/or target pest: insect repellents; indoor foggers for fleas; other flea products; control products for crawling/flying insects (i.e. ants, flies, cockroaches, spiders and termites), rodents, slugs, snails, weeds and insects/diseases for plants/trees. The respondents were also asked whether professional services for pest control and lawn maintenance were utilised. For each of the pesticide products/professional services, additional information was collected as follows: 'what was the name of the product?' and 'how often was the product used during this time period?'. For all the NCCLS case and control participants, the full residential history was obtained from birth up to age 3 y old, and residences were geocoded for linkage with the California pesticide use report (PUR) database using GIS and global positioning system (GPS) tools. The California PUR system is a unique resource containing detailed and time-specific information on

type, amount and location of agricultural pesticide applications.

From 2001 to 2007, a second home visit (referred to as Tier 2) was conducted among children <8 y old at the time of the diagnosis for cases (and corresponding reference date for matched controls) and who lived in the same residence since diagnosis. The follow-up visit was conducted within 3–12 months following the Tier 1 visit. Age and residential criteria were selected to focus the study analyses on younger children who spend more time at home and less time at school or after school activities where their environmental exposures may differ, and because characteristics of a child's exposure to chemicals are likely to be more constant when she/he lives in the same residence as that at time of diagnosis. A total of 731 households were eligible for the refined pesticide exposure assessment and 629 (86%) agreed to participate. Assessment of exposure to residential and agricultural pesticides in the Tier 2 participants includes the following components: (1) evaluation of the reproducibility of self-reported home pesticide use by comparing responses of Tier 1 and Tier 2 questionnaire data; (2) visual inspection of pesticide products stored in the homes and records of the US Environmental Protection Agency registration numbers to obtain information on active ingredients; (3) collection of home carpet dust samples and windowsill wipes analysed for over 60 pesticides in the chemical families of organochlorines, organophosphates, pyrethroids, carbamates, triazine and other herbicides. The carpet dust was collected using two methods: a high volume sampler (HVS3) and home vacuum bag. A comparison of the two methods revealed that levels of pesticide detection were comparable for most compounds[31], confirming that the use of home vacuum bags is a time and cost effective method for case–control studies. Dust is a reservoir for persistent organic compounds such as organochlorine compounds[32–37], representing an important route of exposures to a wide range of pollutants, and a unique medium to assess past exposures to pesticides. Because one-time sampling may suffer from imprecision, the NCCLS investigators have proposed conducting repeated sampling to assess variability over time. Theses longitudinal studies are critical to evaluate how current dust measurements can provide useful information about past exposures; and (4) mapping of crops (i.e. crop field boundaries and species) around Tier 2 residences using GPS, as well as mapping of general land utilisation commonly associated with pesticide use.

Analyses are currently underway to quantify the risk of childhood leukaemia in relation to pesticide dust levels in the Tier 2 households. Methodological studies are also being conducted to compare home dust levels of pesticides with interview-based data (i.e. home pesticide use, household characteristics, socio-demographic factors and sampling season) and GIS/GPS-based estimates of exposure to agricultural pesticides. Statistical modelling is used to identify predictors of pesticide levels in the house dust, which in turn will inform risk analyses of childhood leukaemia in the entire NCCLS population. While previous reports have shown that pesticide levels measured in dust samples appear to be predictive of pesticide levels in children' s urine samples, the correlation between the two measurements remains low, suggesting that dust levels are not sufficient to characterise fully the internal dose[38–40]. The NCCLS collected blood and urine (first morning void) samples in a subset of mothers, and diagnostic pre-treatment blood in leukaemia cases, in order to conduct similar methodological studies.

CONCLUSION AND FUTURE DIRECTIONS

The current literature shows that most epidemiological (case–control) studies conducted in several countries in North and South America and Europe over the past two decades have consistently reported positive associations between self-reported home insecticide use and childhood leukaemia, while findings for garden pesticides/herbicides are mixed. Although the publication bias cannot be ruled out with underreporting of negative findings and systematic differential recall bias across all studies, consistency over time and across several geographic area points to a possible association between pesticide exposure (in a broad sense) and childhood leukaemia. Whether this observed association is causal remains under discussion as many questions are not answered to date: 'can specific agents or families of pesticides based on common chemical or toxicological characteristics be identified to clarify the observed association?'; 'what are the critical windows of exposure to pesticides (pre-conception, pregnancy or after birth)'; and 'how would these various timing interact?'. Alternative hypotheses have also been suggested mainly in the context of agricultural pesticide exposures, in that the presence of biological factors—some of which are known to be carcinogenic in animals or humans (i.e. mycotoxins[41] and animal viruses[42])—may explain the observed associations between cancers and pesticide exposures[12,13]. Critical discussions about the causal relationship between pesticides exposure and childhood cancer or leukaemia are available in several review papers[10–13].

Collection of home dust samples and exposure biomarkers have been mostly implemented in children cohort studies to date; however, these exposure assessment methods may be valuable tools to evaluate the relationship between home pesticides exposure and risk of childhood leukaemia in the

context of case–control studies. In addition to pesticide quantification, HVS3 dust samples represent a unique opportunity to measure fungi, endotoxins and allergens (e.g. to cockroaches, mites and cats), as these factors may modulate children's immune-response and may be involved in leukaemogenesis.

Childhood leukaemia is a heterogeneous disease that encompasses several molecular and cytogenetic subtypes, including rearrangement of the *MLL* gene on chromosome band 11q23 for infant leukaemia and a spectrum of cytogenetic abnormalities for older children, with common subtypes being translocation t(12;21), 12p deletions and a group of extra chromosomes (hyperdiploidy). Most studies in children to date have investigated *in utero* exposures specific to infant leukaemia with MLL rearrangements, reporting associations with maternal consumption of food that contains topoisomerase II inhibitors during pregnancy[43] and transplacental exposures to pesticides and drugs such as dipyrone[18]. It is now well established that rearrangements t(12;21), t(8;21), t(15;17) and inv(16), with the exception of t(1;19), are commonly detected in the neonatal blood spots of childhood leukaemia cases, supporting the suggestion that most childhood leukaemias begin before birth[44]. The next generation of studies will examine how maternal and perinatal exposures to chemical agents such as pesticides may lead to these distinct cytogenetic subgroups of childhood leukaemia. These studies will benefit from the CLIC to obtain adequate sample sizes.

Finally, large-scale genotyping is currently underway in several childhood leukaemia studies worldwide to characterise the genetic susceptibility to exposures to various chemicals, including pesticides.

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