International Journal of Hygiene and Environmental Health 219 (2016) 742–748

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Passive exposure to agricultural pesticides and risk of childhood leukemia in an Italian community

Carlotta Malagoli[a], Sofia Costanzini[b], Julia E. Heck[c], Marcella Malavolti[a], Gianfranco De Girolamo[d], Paola Oleari[e], Giovanni Palazzi[f], Sergio Teggi[b], Marco Vinceti[a,*]

[a] Environmental, Genetic, and Nutritional Epidemiology Research Center – CREAGEN, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
[b] Department of Engineering "Enzo Ferrari", University of Modena and Reggio Emilia, Modena, Italy
[c] Department of Epidemiology, UCLA Fielding School of Public Health, Box 951772, Los Angeles, CA, United States
[d] Unit of Epidemiology and Risk Communication, Local Health Unit of Modena, Modena, Italy
[e] Information and Communication Technology Department, Local Health Unit of Reggio Emilia and IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy
[f] Division of Pediatric Oncology-Hematology, Policlinico Hospital, Modena, Italy

ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form
16 September 2016
Accepted 20 September 2016

Keywords:
Childhood leukemia
Pesticides
Rural area
Crop density

ABSTRACT

Background: Exposure to pesticides has been suggested as a risk factor for childhood leukemia, but definitive evidence on this relation and the specific pesticides involved is still not clear.
Objective: We carried out a population-based case-control study in a Northern Italy community to assess the possible relation between passive exposure to agricultural pesticides and risk of acute childhood leukemia.
Methods: We assessed passive pesticide exposure of 111 childhood leukemia cases and 444 matched controls by determining density and type of agricultural land use within a 100-m radius buffer around children's homes. We focused on four common crop types, arable, orchard, vineyard and vegetable, characterized by the use of specific pesticides that are potentially involved in childhood induced leukemia. The use of these pesticides was validated within the present study. We computed the odds ratios (OR) of the disease and their 95% confidence intervals (CI) according to type and density of crops around the children's homes, also taking into account traffic pollution and high-voltage power line magnetic field exposure.
Results: Childhood leukemia risk did not increase in relation with any of the crop types with the exception of arable crops, characterized by the use of 2.4-D, MCPA, glyphosate, dicamba, triazine and cypermethrin. The very few children (n = 11) residing close to arable crops had an OR for childhood leukemia of 2.04 (95% CI 0.50–8.35), and such excess risk was further enhanced among children aged <5 years.
Conclusions: Despite the null association with most crop types and the statistical imprecision of the estimates, the increased leukemia risk among children residing close to arable crops indicates the need to further investigate the involvement in disease etiology of passive exposure to herbicides and pyrethroids, though such exposure is unlikely to play a role in the vast majority of cases.

1. Background

Leukemia is the most common cancer type in children, representing 30% of all childhood cancers (American Cancer Society, 2014). Childhood leukemia (CL) annual rates in Italy are 5/100,000 inhabitants, an incidence comparable to other Western countries (AIRTUM, 2012). The etiology of this disease unfortunately remains largely unknown, though epidemiological studies have identified a number of potential genetic and environmental risk factors. Pesticide exposure is among the latter, but despite several epidemiologic studies carried out during the latest three decades on this possible relation, definitive evidence on their involvement in CL onset is still lacking (Ntzani et al., 2013). Most investigations found an increased risk of disease associated with *in utero* (Menegaux et al.,

* Corresponding author at: Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, 41125 Modena, Italy.
E-mail address: marco.vinceti@unimore.it (M. Vinceti).

http://dx.doi.org/10.1016/j.ijheh.2016.09.015
1438-4639/

2006) or postnatal (Ma et al., 2002) pesticide exposure through household use or parental occupational exposures (Wigle et al., 2009; Turner et al., 2010; Van Maele-Fabry et al., 2010, 2011; Ntzani et al., 2013; Bailey et al., 2015; Chen et al., 2015). Very few studies have investigated consequent pesticide exposure from over-spray or off-gassing of crops that are situated near resident homes (Lu et al., 2000; Curwin et al., 2005; Rull et al., 2009), despite the tendency of children spending more time outdoors, and increasing their exposure risk, when playing on the floor, ground, lawn and frequently putting hands and objects in their mouths (Freeman et al., 2005).

Under this perspective, crop density (*i.e.* the percentage of land planted with crops) around the residence may be a proxy for environmental exposure to agricultural pesticides (Walker et al., 2007; Carozza et al., 2008; Booth et al., 2015), as also suggested by the correlation between acreage crops nearby the house and pesticide concentrations in home dust (Lu et al., 2000; Fenske et al., 2002; Ward et al., 2006; Harnly et al., 2009; Gunier et al., 2011), or pesticide metabolites in biological samples (Loewenherz et al., 1997; Lu et al., 2000).

Several pesticide categories have been associated with CL risk, including insecticides such as organophosphate, organochlorine and pyrethroid, fumigants, herbicides and fungicides (Reynolds et al., 2002, 2005; Rudant et al., 2007; Rull et al., 2009; Ding et al., 2012). These compounds might favor CL onset through oxidative stress, genotoxicity, endocrine disruption, or cholinesterase inhibition (Perry and Soreq, 2004; Williams et al., 2004; Vidal, 2005; Phillips and Foster, 2008; Androutsopoulos et al., 2013; Hernandez et al., 2013; Mrema et al., 2013; Vakonaki et al., 2013; Choi and Joas, 2016; Hernandez and Menendez, 2016), effects to which children are more susceptible than adults (Au, 2002; Roberts et al., 2012).

Here we report the results of a population-based case-control study in an Italian community investigating the possible etiologic role of residence in proximity to agricultural fields, as an indicator of passive exposure to pesticides, on CL risk.

2. Methods

2.1. Study population

Using an already described study design and population (Malagoli et al., 2010, 2015; Vinceti et al., 2012), through the Italian hospital-based registry of childhood malignancies managed by the Italian Association of Paediatric Haematology and Oncology we identified all cases of CL newly diagnosed in children aged 0–14 residing in the Modena and the Reggio Emilia provinces (total population around 1,200,000) of the Northern Italy Emilia-Romagna region. For the present study, we considered CL cases diagnosed from 1998 to 2011. For each case, we randomly selected four population controls among all residents with the same year of birth, sex, and province and calendar year of residence. Residence address was collected at time of diagnosis for cases and at the corresponding year for matched controls. To verify the residential stability of our study population, we reconstructed the lifetime residential history of a sample of children and we found that the occurrence of address changes was unlikely (only 18% during the entire first 5 years of age), ensuring that our subjects are characterized by low mobility (Malagoli et al., 2010; Vinceti et al., 2012).

Socio-economic status was assessed by paternal income for the index year, collected from the Ministry of Finance.

We modeled air concentration of two pollutants from vehicular traffic, benzene and particulate matter $\leq 10\,\mu m$ (PM_{10}), at the home of residence as described in a previous study (Vinceti et al., 2012), with the exception of the few subjects residing in sparsely populated mountain municipalities.

Magnetic field induction in the proximity of high-voltage power lines ($\geq$132 kV) located in the territories of both provinces was calculated as described in a previous study (Malagoli et al., 2010), so as to identify three 'exposed'corridors surrounding the power lines, with increasing magnetic field intensity ($0.1 \leq B < 0.2$, $0.2 \leq B < 0.4$, $B \geq 0.4\,\mu T$).

2.2. Pesticide exposure assessment

We georeferenced residences of case and control children in a Geographical Information System (GIS) according to the Rome Monte Mario Italy 1 reference system, using Arc-GIS software (version 10.1, ESRI, Redlands, CA 2012). We retrieved the satellite coordinates of the residences from the institutional database of the Modena and Reggio Emilia Provinces and, for addresses not included, through *in loco* measurement with a portable GPS device (GPSmap 60CSx, Garmin Int. Corp., Olathe, KS).

Agricultural use land density (crop density) around the children's residence was used as a proxy for environmental exposure to agricultural pesticides. We assessed the land use type in proximity to each geocoded home according to The Land Use Map 2003 (available at geoportale.regione.emilia.romagna.it/it) for both Modena and Reggio Emilia provinces, containing GIS-based information including multispectral ortophotos with ground resolution of 50 cm, collected by the Emilia-Romagna Region Agency by remote sensing in 2003 (Ward et al., 2000). The Land Use Map 2003 contains a detailed description of land use with the specifications of Corine Land Cover (Bossard and Otahel, 2000). Roads, including names, technical and administrative classification were also obtained from the cartographic archive of Emilia-Romagna Region Agency. With a coupled GIS/Python procedure, we defined a circular buffer with a 100-m radius around each child's home.

For crop-type identification analysis, we used the predefined land use subtype named 'Rural area' present on The Land Use Map 2003. 'Rural area' comprises territories allocated to agriculture with various crop fields, dedicated to different cultivations. We determined crop density within the 100-m buffers for total agricultural land and for the four specific categories of crops available for type broad crop category: arable, orchards, vineyards and vegetables.

2.3. Pesticides

Provinces of Modena and Reggio Emilia are located in the Padana Plain, a flat area in Northern Italy which is very intensively cultivated. Almost 46% of both provinces' surfaces (approximately 640.676 acres) is devoted to agriculture and local farms are estimated to use approximately 1400 t of pesticides every year. Among the pesticides extensively used there with suspected leukaemogenic properties are categories such as phosphorganics, triazoles, phenylalanines, neonicotinoids, phenoxyacetic acids and pyrethroids, and compounds such as dicamba and glyphosate. With the help of the technicians of the public Agricultural Department of the Emilia-Romagna Region, which is in charge of overseeing farmers activities including pesticide use, we estimated and validated the use of pesticide categories or specific compounds for the most common crop types (Table 1). For the purposes of this study, these technicians assessed actual pesticides in a sample of 118 local farms in 2003, by scrutinizing the 'Registers of treatments', which according to the Italian rules each farm must maintain and in which all the details about type, timing and amount of pesticide use has to be recorded.

In the recent years an increasing number of farms located in the Emilia-Romagna Region was certified as being 'pesticide-free', though to date no more than 5% of farms in Modena and Reggio Emilia provinces – around 3% of agricultural land – does not use