Cancer Causes Control (2017) 28:1125–1132
DOI 10.1007/s10552-017-0944-5

ORIGINAL PAPER

Maternal use of household pesticides during pregnancy and risk of neuroblastoma in offspring. A pooled analysis of the ESTELLE and ESCALE French studies (SFCE)

Paula Rios[1,2,13] · Helen D. Bailey[1,2] · Brigitte Lacour[1,2,3] · Dominique Valteau-Couanet[4] · Jean Michon[5] · Christophe Bergeron[6] · Hélène Boutroux[7] · Anne-Sophie Defachelles[8] · Marion Gambart[9] · Nicolas Sirvent[10] · Estelle Thebaud[11] · Stéphane Ducassou[12] · Laurent Orsi[1,2] · Jacqueline Clavel[1,2]

Received: 23 December 2016 / Accepted: 12 August 2017 / Published online: 24 August 2017

Abstract

Purpose Neuroblastoma (NB) is an embryonic tumor that occurs almost exclusively in infancy and early childhood. While considerable evidence suggests that it may be initiated during embryonic development, the etiology of NB is still unknown. The aim of this study was to explore whether there is an association between maternal use of household pesticides during pregnancy and the risk of NB in the offspring.

Methods We conducted a pooled analysis of two French national-based case–control studies. The mothers of 357 NB cases and 1,783 controls younger than 6 years, frequency-matched by age and gender, responded to a telephone interview that focused on sociodemographic and perinatal characteristics, childhood environment, and lifestyle. Unconditional logistic regression was used to estimate pooled odds ratios and 95% confidence intervals.

Results After controlling for matching variables, study of origin, and potential confounders, the maternal use of any type of pesticide during pregnancy was associated with NB (OR 1.5 [95% CI 1.2–1.9]). The most commonly used type of pesticides were insecticides and there was a positive association with their use alone (OR 1.4 [95% CI 1.1–1.9]) or with other pesticides (OR 2.0 [95% CI 1.1–3.4]).

Conclusions Although there is the potential for recall bias due to the study design, our findings add to the evidence of an association between the household use of pesticides and NB. Until a better study design can be found, our findings

Electronic supplementary material The online version of this article (doi:10.1007/s10552-017-0944-5) contains supplementary material, which is available to authorized users.

✉ Paula Rios
paula.rios@inserm.fr

[1] CRESS-EPICEA Epidémiologie des cancers de l'enfant et de l'adolescent, Inserm, Université Paris-Descartes, Université Sorbonne-Paris-Cité, Paris, France

[2] RNCE - National Registry of Childhood Cancers-hematopoietic cancers, Villejuif, France

[3] RNCE - National Registry of Childhood Cancers-solid tumours, CHU de Nancy, Vandœuvre-lès-Nancy, France

[4] Service d'Oncologie Pédiatrique, Institut Gustave Roussy, Paris, France

[5] Service d'Oncologie Pédiatrique, Institut Curie, Paris, France

[6] Institut d'Hématologie et d'Oncologie Pédiatrique, Lyon, France

[7] Assistance Publique – Hôpitaux de Paris, Service Hématologie Oncologie Pédiatrique, Hôpital Armand Trousseau, Paris, France

[8] Service d'Oncologie Pédiatrique, Centre Oscar Lambret, Lille, France

[9] Sce d'Hématologie Oncologie Pédiatrique, Hôpital des Enfants, Toulouse, France

[10] Service d'Hémato-oncologie pédiatrique, Hôpital Arnaud De Villeneuve, Montpellier, France

[11] Service d'Oncologie Pédiatrique, Hôpital de la mère et l'enfant, Nantes, France

[12] Service d'Oncohématologie pédiatrique, Hôpital Pellegrin Tripode, Bordeaux, France

[13] UMRS-1153 Equipe 7 (EPICEA), Inserm, 16 avenue Paul Vaillant Couturier - Bat 15/16, 94807 Villejuif Cedex, France

add yet another reason why to advise pregnant women to limit pesticide exposure during the periconceptional period.

Keywords Neuroblastoma · Pesticides · Risk factors · Childhood cancer · Case–control study

Abbreviations

ESCALE	Etude Sur les Cancers et les Leucémies de l'Enfant
ESTELLE	Etude Sur les Tumeurs Embryonnaires, Leucémies et Lymphomes de l'Enfant
MYCN	N-myc proto-oncogene
NB	Neuroblastoma
RNCE	Registre National des Cancers de L'Enfant
SFCE	Société Française de lutte contre les Cancers de l'Enfant et de l'Adolescent

Introduction

Neuroblastoma (NB) is a malignant embryonal tumor of the neural crest cells that occurs almost exclusively in infancy and early childhood. Forty percent of NB cases are diagnosed before the age of one year and 85% before the age of five years [1].

The etiology of NB remains unknown. A genetic predisposition of NB has been suggested after the observation of rare familial cases (1% of NB cases) and a possible association with congenital malformations [2, 3]. Considerable progress has been made recently in the germ line and somatic genetic characterisation of patients and tumors [4]. However, genetic predisposition cannot fully explain its origin and other factors may be involved in NB development [5].

Considerable evidence suggests that NB may be initiated in utero during sympathoadrenal development [6]. The undifferentiated stem cells from the neural crest progenitors may persist in crest-derived tissues awaiting stimulation or reactivation in response to environmental or cellular cues [7]. Prenatal exposure to pesticides may be one such risk factor. A possible association between pesticides and NB was first suggested more than 30 years ago in relation to exposures to chlordane or heptachlor [8], which are active ingredients in many household and garden pesticides. An association between pesticide exposure and NB is plausible as more than 25 chemical compounds used in pesticides have been classed as potential human carcinogens [9, 10]. In addition, previous studies have showed that they pass through the placenta leading to fetal exposure [11, 12].

Literature about the subject is scarce. Only two previous studies [13, 14] have shown associations between NB and use of household pesticides during the preconception period, pregnancy, or in early childhood. Studies looking at parental occupational exposure to pesticides are heterogeneous in exposure definition and in findings. Some studies have suggested an increased risk of NB with maternal occupational exposure to pesticides during pregnancy [15] or at any time during the preconception-pregnancy period or childhood [14, 16], while a meta-analysis found no association with paternal occupational exposure to pesticides at any time [17]. A large cohort study [18] suggested an increased risk of NB in offspring of farm holders, while a registry-based study using geographic information [19] did not support an association with residence exposure to pesticides related to neighboring agricultural activities.

The aim of this study was to investigate whether the maternal use of household pesticides during pregnancy was associated with the risk of NB in her child. For these analyses, we pooled data from two large case–control studies, ESCALE and ESTELLE, which were conducted by the same investigators in France.

Materials and methods

Study population

The ESCALE and ESTELLE studies have been described in detail elsewhere [2]. Briefly, they were two nationwide population-based case–control studies, which were conducted with the support of the Société Française de lutte contre les Cancers de L'Enfant et l'Adolescent (SFCE).

The cases, which were directly identified from the French national registry of childhood cancer (RNCE), were children younger than 15 years old who lived in France at the time they were newly diagnosed with cancer. The ESCALE study included cases of NB, lymphoma, leukemia, and malignant brain tumor diagnosed in 2003–2004. The ESTELLE study included cases of NB, leukemia, lymphoma, childhood brain tumor, Wilms' tumor, and hepatoblastoma diagnosed in 2010–2011.

Overall case participation rates were 81.2% for ESCALE and 92.2% for ESTELLE. Information on the MYCN amplification subtype was obtained subsequently from the RNCE.

The population controls were children free from cancer randomly selected from the French population using quota-sampling methods who were recruited by telephone during the same time periods. The participation rates were 71.2 and 85.5%, respectively.

In both studies, the cases and the controls were ineligible if their biological mother was unavailable, did not speak French, or had a serious psychosocial problem. In

addition, 22 cases, 9 out of 248 cases under 18 months (3.6%) and 13 out of 252 cases aged 18 months or more (5.2%), were not eligible to maternal interview for ethical reasons because they had died or were in palliative care.

The present paper focuses on NB in children under six years old (91.3% of cases).

Data collection

Trained interviewers conducted standardized telephone interviews with the biological mothers of cases and controls, which lasted approximately 50 min. The interviews used similar scripts and were performed in the same conditions in the two studies. They focused on socioeconomic characteristics, prenatal and childhood environment exposures, familial and personal medical history.

In regards to pesticide exposures during pregnancy, the mother was asked if she used herbicides ("weed killers"), fungicides, or insecticides (and whether they were used indoors, for gardening or outdoors, or on pets). The mother was also asked if she was exposed to any type of pesticides in the workplace.

The ESTELLE study included additional questions about maternal pesticide use in the three months prior to conception and after birth, and whether there had been any professional pest control treatments of the home.

Data analysis

Study-specific odds ratios (ORs) and pooled ORs and 95% confidence intervals (95% CIs) were estimated by unconditional logistic regression (SAS version 9; SAS Institute Inc., Cary, NC, USA). All the models included the study matching factors: child's age and gender, and, for the pooled analyses, the indicator of the study of origin.

The socioeconomic variables tested as potential confounders were: maternal level of education, size of the urban unit of residence, maternal age at child's birth, birth order, and the type of housing during pregnancy. We also tested fetal growth, congenital malformations, and breastfeeding that were significantly associated with NB in previous analyses [2]. In the final model, only maternal age, birth order, size of the urban unit of residence, and the type of housing were retained.

Between-study heterogeneity was systematically tested by fitting an interaction term between the study and the exposure of interest.

We performed additional analyses stratified by age at diagnosis (<18 months/≥18 months), MYCN status (amplified/non-amplified), urban/rural status of the area of residence, and maternal level of education (less than baccalaureate/baccalaureate or higher).

Due to a small number of children with a congenital malformation, possible confounding was accounted for by excluding these children rather than by adjustment. Finally, sensitivity analyses were also conducted in the ESTELLE study by excluding the cases whose mother did not have a landline at home since they could not have been selected as controls (the information was not available in the ESCALE study).

Results

The pooled analysis included 357 cases (174 from ESCALE and 183 from ESTELLE) and 1,783 controls (949 from ESCALE and 834 from ESTELLE) younger than six years old (Table 1). Among cases, MYCN was amplified in 17.9% (11% of the cases under 18 months of age and in 25% of the older cases), non-amplified in 75.6%, and non-informative in 6.4%.

Case–control comparability

In both studies the cases were more likely to be younger, first born, to live in an urban area, and to have younger mothers than the controls (Table 1).

Between-study heterogeneity

Control mothers in the ESTELLE study lived more often in less populated areas and were more highly educated than those in the ESCALE study (Table 1). They were also more likely to have used pesticides at home ($p < 0.01$) (results not tabulated).

Pesticides use

Overall, maternal use of any pesticide during pregnancy was reported for 43.7% of the cases and 35.7% of the controls. Insecticides were the most commonly used (40.6% of cases and 33.9% of the controls) and they were mostly used alone. Their use was mainly reported indoors (80.0% of insecticides use in cases and 81.0% in controls). Mothers rarely used herbicides or fungicides and they often also used insecticides.

The maternal use of any type of pesticide during pregnancy was associated with the risk of NB (OR 1.5 [95% CI 1.2–1.9]). There was a positive association with the use of insecticides alone (OR 1.4 [95% CI 1.1–1.9]) or insecticides with other pesticides (OR 2.0 [95% CI 1.1–3.4]). There was no between-study heterogeneity except for herbicide use (pooled OR 2.0 [95% CI 1.1–3.7]); ESCALE (OR 3.8 [95% CI 1.8–8.0]); ESTELLE (OR 1.1 [95% CI 0.4–3.2]); p value for interaction = 0.07).

Table 1 Characteristics of the cases and controls of the ESCALE and ESTELLE studies

	ESCALE (2003–2004)				ESTELLE (2010–2011)				POOLED			
	Cases ($n = 174$)		Controls ($n = 949$)		Cases ($n = 183$)		Controls ($n = 834$)		Cases ($n = 357$)		Controls ($n = 1,783$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
MYCN status												
Non-amplified	131	75.3			139	76.0			270	75.6		
Amplified	34	19.5			30	16.4			64	17.9		
Missing	9	5.2			14	7.6			23	6.4		
Age (years)												
<1	74	42.5	187	19.7	70	38.2	188	22.5	144	40.3	375	21.0
1	36	20.7	182	19.2	37	20.2	123	14.7	73	20.4	305	17.0
2	30	17.2	153	16.1	35	19.1	148	17.7	65	18.2	301	16.9
3	13	7.5	166	17.5	21	11.5	139	16.7	34	9.5	305	17.1
4	11	6.3	145	15.3	12	6.6	131	15.7	23	6.4	276	15.5
5	10	5.7	116	12.2	8	4.4	105	12.6	18	5.0	221	12.4
Sex												
Boys	88	50.6	429	45.2	83	45.4	388	46.5	171	47.9	817	45.8
Girls	86	49.4	520	54.8	100	54.6	446	53.5	186	52.1	966	54.2
Birth order												
1	89	51.1	402	42.4	91	49.7	345	41.4	180	50.4	747	41.9
2 or more	85	48.9	547	57.6	92	50.3	489	58.6	177	49.6	1,036	58.1
Maternal age at child's birth (years)												
<25	31	17.8	80	8.4	25	13.7	86	10.3	56	15.7	166	9.3
25–29	61	35.1	314	33.1	70	38.2	250	30.0	131	36.7	564	31.6
30–34	54	31.0	360	37.9	50	27.3	293	35.1	104	29.1	653	36.6
≥35	28	16.1	195	20.5	38	20.8	205	24.6	66	18.5	400	22.4
Maternal education												
<Baccalaureate	55	31.6	319	33.6	50	27.3	203	24.3	105	29.4	522	29.3
Baccalaureate	32	18.4	195	20.5	44	24.0	192	23.0	76	21.3	387	21.7
>Baccalaureate	87	50.0	435	45.8	88	48.1	439	52.6	175	49.0	874	49.0
Missing	0	0	0	0	1	0.5	0	0	1	0.3	0	0
Size of urban unit of residence (population)												
<5,000	57	32.8	360	37.9	59	32.2	351	42.1	116	32.5	711	39.9
5,000–99.999	36	20.1	211	22.2	43	23.5	174	20.9	79	22.1	385	21.6
100.000–1.999.999	41	23.6	233	24.5	50	27.3	158	18.9	91	25.5	391	21.9
Paris unit	37	21.3	145	15.3	30	16.4	149	17.9	67	18.8	294	16.5
Missing	3	1.7	0	0	1	0.5	2	0.2	4	1.1	2	0.1
Type of housing during pregnancy												
Apartment	78	44.8	379	39.9	77	42.1	324	38.8	155	43.4	703	39.4
House or farm	96	55.1	570	60.1	105	57.3	506	60.7	201	56.3	1,076	60.3
Missing	0	0	0	0	1	0.5	4	0.5	1	0.3	4	0.2

Maternal occupational pesticide exposure during pregnancy was associated with the risk of NB (OR 2.0 [95% CI 1.0–4.0), although the frequency of exposure was low (3.6% of cases and 1.8% of controls) (data not tabulated).

The results were similar whether or not MYCN was amplified (Table 2), and when the analyses were stratified by age at diagnosis (Table 3). Among the controls, the prevalence of pesticide use varied by urban/rural status, but not by maternal level of education, and the results did not change when stratification for either of these factors was used instead of adjustment (Supplementary Table 1);

Table 2 Maternal use of pesticides during pregnancy and risk of neuroblastoma

	Controls $n = 1,783$		All NB cases $n = 357$		OR[a]	95% CI	MYCN— $n = 270$		OR[a]	95% CI	MYCN + $n = 64$		OR[a]	95% CI
	n	%	*n*	%			*n*	%			*n*	%		
Maternal use of any pesticides														
None	1,112	62.4	198	55.5	1.0	Reference	155	57.4	1.0	Reference	32	50.0	1.0	Reference
Any pesticide	636	35.7	156	43.7	1.5	1.2–1.9	113	41.8	1.4	1.1–1.9	31	48.4	1.7	1.0–2.9
Any insecticide	604	33.9	145	40.6	1.5	1.1–1.9	105	38.9	1.4	1.1–1.9	28	43.7	1.6	0.9–2.7
Any herbicide	61	3.4	20	5.6	2.0	1.1–3.7	14	5.2	1.9	0.9–3.6	3	4.7	1.8	0.5–6.5
Any fungicide	50	2.8	14	3.9	1.6	0.8–3.1	7	2.6	1.1	0.5–2.6	6	9.4	4.3	1.6–11.5
Only insecticides	537	30.1	125	35	1.4	1.1–1.9	93	34.4	1.4	1.0–1.9	23	35.9	1.5	0.8–2.6
Only herbicides	13	0.7	5	1.4	1.5	0.4–4.8	5	1.8	1.9	0.6–6.2	0	0		
Only fungicides	19	1.1	6	1.7	1.7	0.7–4.6	3	1.1	1.2	0.3–4.4	3	4.7	5.2	1.4–19.8
Insecticides + other pesticides	67	3.8	20	5.6	2.0	1.1–3.4	12	4.4	1.6	0.8–3.1	5	7.8	2.4	0.9–6.8
Only herbicides and fungicides	0		0											
Use of insecticides														
Indoor use	489	27.4	116	32.5	1.5	1.1–2.0	81	30.0	1.4	1.0–1.9	25	39.1	1.8	1.0–3.1
Gardening and outdoor use	57	3.2	13	3.6	1.3	0.7–2.5	7	2.6	0.9	0.4–2.1	3	4.7	1.6	0.5–5.8
For pets	224	12.6	49	13.7	1.3	0.9–1.9	37	13.7	1.3	0.9–2.0	10	15.6	1.2	0.5–2.8
Missing	35	1.9	3	0.8			2	0.7			1	1.6		

Pooled analyses of the ESCALE and ESTELLE studies

[a] Odds ratios (OR) and 95% confident intervals (CI) estimated by unconditional logistic regression models adjusted for children age and sex, study, maternal age, birth order, size of the urban unit of residence, and type of housing during pregnancy

Table 3 Maternal use of pesticides during pregnancy and risk of neuroblastoma by age at diagnosis

	Age <18 months						Age ≥18 months					
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI
	$n = 188$	%	$n = 544$	%			$n = 169$	%	$n = 1,239$	%		
Maternal use of pesticides												
None	114	60.6	369	67.8	1.0	Reference	84	49.7	743	59.9	1.0	Reference
Any pesticide	73	38.8	166	30.5	1.5	1.0–2.1	83	49.1	470	37.9	1.6	1.1–2.2
Any insecticide	65	34.6	155	28.5	1.4	0.9–2.0	80	47.3	449	36.2	1.6	1.1–2.3
Any herbicide	7	3.7	22	4.0	1.1	0.4–3.1	13	7.7	39	3.1	3.4	1.6–7.1
Any fungicide	5	2.7	15	2.8	1.0	0.3–3.3	9	5.3	35	2.8	2.3	1.0–5.1
Only insecticides	62	32.9	134	24.6	1.5	1.0–2.2	63	37.3	403	32.5	1.4	1.0–2.0
Only herbicides	4	2.1	7	1.3	1.4	0.3–5.9	1	0.6	6	0.5	1.6	0.2–14.7
Only fungicides	4	2.1	4	0.7	3.1	0.7–13.7	2	1.2	15	1.2	1.1	0.3–5.0
Insecticides + other pesticides	3	1.6	21	3.9	0.5	0.1–1.9	17	10.0	46	3.7	3.4	1.8–6.5
Only herbicides and fungicides	0		0				0		0			
Use of insecticide												
Indoor use	50	26.6	121	22.2	1.5	1.0–2.2	66	39.0	368	29.7	1.6	1.1–2.3
Gardening and outdoor use	8	4.3	23	4.2	1.5	0.6–3.6	5	2.9	34	2.7	1.2	0.4–3.2
For pets	23	12.2	58	10.7	1.3	0.7–2.3	26	15.4	166	13.4	1.3	0.8–2.2
Missing	1	0.5	9	1.6			2	1.2	26	2.1		

[a] Odds ratios (OR) and 95% confident intervals (CI) estimated by unconditional logistic regression models adjusted for children age and sex, study, maternal age, birth order, size of the urban unit of residence, and type of housing during pregnancy

neither did the exclusion of children with congenital malformations change the results.

Maternal use of pesticides before and after pregnancy and the use of professional pest control treatments at home were not collected in the ESCALE study. In the ESTELLE study, more than a quarter of the mothers reported pesticide use during all three time periods (29.0% of the cases and 27.6% of the controls) and very few mothers reported the use during pregnancy only (6.0% of cases and 3.5% of controls). This precluded specific analyses by time window.

No association was found with professional pest control treatments at home during pregnancy (OR 1.2 [95% CI 0.5–2.8]) (data not tabulated).

Finally, in the ESTELLE study, the results were unchanged in sensitivity analysis excluding the cases with no telephone landline.

Discussion

Our findings suggest that the maternal use of pesticides during pregnancy may be associated with an increased risk of NB.

In a large US case–control study, Daniels et al. [13] also reported modest associations (OR around 1.5) with the use of pesticides at home or in the garden during the preconception-pregnancy period or childhood. Consistent with our findings, this study showed similar estimates irrespective of the MYCN status, which does not support the potential for pesticides to act through different pathways in the two subtypes. In that study, the estimates were stronger among older children. Since the use of pesticides at home may be associated with life-patterns, the stronger associations observed in older children may reflect the effect of longer period of exposures to pesticides. Previous studies have also suggested that different etiologic factors may be specific to age at NB diagnosis [14, 20, 21]. Our study found no difference by age for the most prevalent exposures, pesticides and specifically insecticides. While there was a suggestion of differences by age with the use of herbicides and fungicides, this could be a chance finding since based on small numbers, the confidence intervals in the two groups overlapped substantially.

Another study conducted in Germany by Schüz et al. [14] found an association between NB and the use of household pesticides after the child's birth, but did not investigate pesticide exposure during pregnancy.

Consistent with our findings, associations between NB and maternal occupational exposure to pesticides were reported in two case–control studies in the USA [15, 16]. In a cohort study in Norway, an increased risk of NB was observed in offspring of parents having worked in field vegetable [18]. However, these findings should be interpreted with caution since they are based on small numbers. In two of these studies [16, 18], like in ours, estimates were based on less than ten exposed cases and could represent a chance finding. Literature on paternal occupational exposure to pesticides is not supportive of an association with NB as shown in a meta-analysis conducted by Moore et al. [17]. A large Texan case–control study estimated residential exposures to pesticides due to neighboring agricultural activities and found no association [19]. However, estimates were inconsistent between low and high level of exposure and were based on less than 15 exposed cases.

It is biologically plausible that maternal pesticide exposure during pregnancy could be associated with the risk of NB. Pregnancy represents a critical window of exposure since some explanatory hypotheses suggest that NB is initiated in utero during the sympathoadrenal development from the neural crest [6]. It has been shown that maternal exposure during pregnancy can lead to fetal exposure since these compounds pass through the placenta and can be found in cord blood, infant hair, and meconium [11, 22]. The potential underlying mechanisms are still unknown. Many pesticides are suspected to have different mutagenic or immunotoxic properties and some individual pesticides have been classed as "probable or possible carcinogens" by the International Agency for Research on Cancer [9, 10]. In addition, because of the similarity of brain biochemistry, some insecticides that target the nervous system of insects may also be neurotoxic to humans [23]. However, in our study, because the use of pesticides was correlated between time periods (preconception, pregnancy, and childhood) we cannot identify pregnancy as a true critical period of exposure. It is possible that patterns of exposure are related to lifetime habits, which are normally consistent throughout the periconceptional period and later in childhood.

A limitation of our study is that the majority of mothers who reported any pesticide use (94%) actually used insecticides, either alone or combined with herbicides or fungicides, which limited our ability to investigate associations with pesticides other than insecticides. In addition, we could not identify the active ingredients in the products used as in our study we only asked women about the category of pesticide as we thought this would be recalled with greater accuracy than the actual product name. Commercial household pesticides often contain multiple active ingredients, all which may have different properties including potentially carcinogenic actions. In our study we mainly focused on maternal use of pesticides at home. However, the mothers may be exposed to other direct or indirect sources of pesticides which we did not account for, like the paternal use of household pesticides or other sources of environmental exposure.

As expected, the proportion of cases ineligible because they had died or were receiving palliative care was smaller under 18 months of age than for those aged 18 months or more. This may have introduced a selection bias if age was related to opportunity of pesticide exposure. However, the age-stratified analyses did not provide evidence of substantial differences in the associations between NB and maternal use of pesticides. As no information on exposure was available on cases and controls that refused to participate, we do not know if these children were comparable to the study sample. To overcome these limitations, we stratified our analysis for different factors that may have been related to control participation to limit selection bias.

Finally, the study of pesticides exposure relied on maternal self-report, which may involve both non-differential and differential bias. Because of the particular distribution of NB (52.7% of the cases younger than 18 months) the lapse of time between the exposure time and the interview was short, which may have limited non-differential measurement error, and which may not be the case for other childhood cancers. In our study, trained interviewers using highly structured questionnaires conducted interviews with the aim of reducing potential differential misclassifications. Despite this, it cannot be excluded because case mothers may have tended to think more deeply about their possible exposures than control mothers. Previous studies have found consistency between self-reported pesticide treatments and pesticides concentrations in dust [24] and that agreement about pesticides exposure between parents did not differ by case–control status [13], suggesting no differential recall based on motivation of case parents. Furthermore, our findings stratified by urban status were similar, despite differences in the reported prevalence of pesticide use across these strata.

Our studies also have several strengths. The ESCALE and ESTELLE studies were designed to be pooled with uniformly defined exposures, which facilitated the pooling process, making this one of the largest investigations of NB at present. In these population-based studies, the control participation rate was high and the cases were identified from a nationwide cancer registry, which has a high degree of completeness.

In conclusion, this pooled analysis adds to the evidence of an association between NB and maternal use of pesticides during pregnancy, in household or occupation. Because data were obtained retrospectively by questionnaire, recall bias is possible, particularly for domestic use. Replication by other large epidemiological studies with different designs is important. However, until a better study design can be found, our findings add yet another reason why to advise pregnant women to limit pesticide exposure during the periconceptional period.

Acknowledgments INSERM, the Ligue National Contre le Cancer (LNCC), the Fondation de France, the Agence Françaises Sécurité Sanitaire des Produits de Santé(AFSSAPS), the Agence Française Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), the Association pour la Recherche sur le Cancer (ARC), the Agence Française Sécurité Sanitaire des Produits de Santé(ANSM), the Agence Française Sécurité Sanitaire de l'Environnement et du Travail (ANSES), the association Cent pour sang la vie, the Institut National du Cancer (INCa) and the Agence Nationale de la Recherche (ANR), the Institut National du Cancer (INCa), and Cancéropôle Ile de France. Paula Rios PhD scholarship is supported by the Interdisciplinary research program on health crisis and health protection (PRINCEPS). The authors are grateful to: Marie-Hélène Da Silva, Christophe Steffen and Florence Menegaux (INSERM U1018, Environmental Epidemiology of Cancer), Noureddine Balegroune, Sofien Ben Salha and the team of clinical research associates who contributed to the recruitment of the cases; Aurèlie Guyot-Goubin, Laure Faure and the staff of the French National Registry of Childhood Blood Malignancies, who contributed to case detection and verification; Sabine Melèze and Marie-Anne Noel (Institut CSA), who coordinated the selection of the controls and the interviews, and Catherine Tricoche (Callson), Christophe David and the team of interviewers (Institut IPSOS), who interviewed the cases and controls.

References

1. Lacour B, Guyot-Goubin A, Guissou S et al (2010) Incidence of childhood cancer in France: National Children Cancer Registries, 2000–2004. Eur J Cancer Prev 19:173–181
2. Rios P, Bailey HD, Orsi L et al (2016) Risk of neuroblastoma, birth-related characteristics, congenital malformations and perinatal exposures: a pooled analysis of the ESCALE and ESTELLE French studies (SFCE). Int J Cancer. doi:10.1002/ijc.30239
3. Menegaux F, Olshan AF, Reitnauer PJ et al (2005) Positive association between congenital anomalies and risk of neuroblastoma. Pediatr Blood Cancer 45:649–655. doi:10.1002/pbc.20263
4. Schleiermacher G, Janoueix-Lerosey I, Delattre O (2014) Recent insights into the biology of neuroblastoma 135:2249–2261. doi:10.1002/ijc.29077
5. Heck JE, Ritz B, Hung RJ et al (2009) The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol 23:125–143. doi:10.1111/j.1365-3016.2008.00983.x
6. Marshall GM, Carter DR, Cheung BB et al (2014) The prenatal origins of cancer. Nat Publ Gr. doi:10.1038/nrc3679
7. Maguire LH, Thomas AR, Goldstein AM (2015) Tumors of the neural crest: common themes in development and cancer. Dev Dyn 244:311–322. doi:10.1002/dvdy.24226
8. Infante PF, Epstein SS, Newton WAJ (1978) Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. Scand J Work Environ Health 4:137–150. doi:10.5271/sjweh.2718
9. International Agency for Research on Cancer (2015) Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos
10. International Agency for Research on cancer (1991) Occupational exposures in insecticide application, and some pesticides
11. Ostrea EM, Bielawski DM, Posecion NC et al (2009) Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure to environmental pesticides. Environ Res 109:116–122. doi:10.1016/j.envres.2008.09.004
12. Fisher M, Arbuckle TE, Liang CL et al (2016) Concentrations of persistent organic pollutants in maternal and cord blood from the

maternal-infant research on environmental chemicals (MIREC) cohort study. Environ Health 15:59. doi:10.1186/s12940-016-0143-y
13. Daniels JL, Olshan AF, Teschke K et al (2001) Residential pesticide exposure and neuroblastoma. Epidemiology 12:20–27
14. Schüz J, Kaletsch U, Meinert R et al (2001) Risk factors for neuroblastoma at different stages of disease. Results from a population-based case-control study in Germany. J Clin Epidemiol 54:702–709
15. Kerr MA, Nasca PC, Mundt KA et al (2000) Parental occupational exposures and risk of neuroblastoma: a case–control study (United States). Cancer Causes Control 11:635–643. doi:10.1023/A:1008951632482
16. Olshan AF, De Roos AJ, Teschke K et al (1999) Neuroblastoma and parental occupation. Cancer Causes Control 10:539–549. doi:10.1023/A:1008998925889
17. Moore A, Enquobahrie DA (2011) Paternal occupational exposure to pesticides and risk of neuroblastoma among children: a meta-analysis. Cancer Causes Control 22:1529–1536. doi:10.1007/s10552-011-9829-1
18. Kristensen P, Andersen A, Irgens LM et al (1996) Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 65:39–50. doi:10.1002/(SICI)1097-0215(19960103)65:1<39:AID-IJC8>3.0.CO;2-2
19. Carozza SE, Li B, Wang Q, et al Agricultural pesticides and risk of childhood cancers. doi: 10.1016/j.ijheh.2008.06.002
20. Carlsen NL (1996) Neuroblastomas presenting in the first year of life: epidemiological differences from those presenting at older ages. Cancer Detect Prev 20:251–261
21. Urayama KY, Von Behren J, Reynolds P (2007) Birth characteristics and risk of neuroblastoma in young children. Am J Epidemiol 165:486–495. doi:10.1093/aje/kwk041
22. Lewis RC, Cantonwine DE, Anzalota Del Toro LV et al (2014) Urinary biomarkers of exposure to insecticides, herbicides, and one insect repellent among pregnant women in Puerto Rico. Environ HealTH 13:97. doi:10.1186/1476-069X-13-97
23. Bjørling-Poulsen M, Andersen HR, Grandjean P (2008) Potential developmental neurotoxicity of pesticides used in Europe. Environ Health 7:50. doi:10.1186/1476-069X-7-50
24. Deziel NC, Colt JS, Kent EE, Gunier RB, Reynolds P,7, Booth B, Metayer C9 WM (2015) Associations between self-reported pest treatments and pesticide concentrations in carpet dust. Environ Health 14:27