RESEARCH ARTICLE

REVISED Pesticide exposure and lung cancer risk: A case-control study in Nakhon Sawan, Thailand [version 3; peer review: 2 approved with reservations]

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Abstract

Background: Pesticide exposure might increase risk of lung cancer. The purpose of this study was to investigate the association between the historical use of pesticides commonly found in Thailand, and lung cancer.

Methods: This case-control study compared a lifetime pesticide exposure of 233 lung cancer cases, and 447 healthy neighbours matched for gender, and age (± 5 years). Data on demographic, pesticide exposure and other related factors were collected using a face-to-face interview questionnaire. Associations between lung cancer and types of pesticides as well as individual pesticides were analyzed using logistic regression adjusted for gender (male, female), age (≤ 54 , 55-64, 65-74, ≥ 75), cigarette smoking (never smoked, smoked $< 109,500$, smoked $\geq 109,500$), occupation (farmer, non-farmer), cooking fumes exposure (yes, no), and exposure to air pollution (yes, no).

Results: It was found that lung cancer was positively associated with lifetime use of herbicides and insecticides. Compared to people in the nonexposed groups, those in Q3-Q4 days of using herbicides and insecticides had an elevated risk of lung cancer, with odds ratio (OR) between 2.20 (95% confidence interval (CI) 1.24-3.89), and 3.99 (95% CI

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1. Ann C Olsson, International Agency for Research on Cancer, Lyon, France

1.62-7.11) ($p < 0.001$). For individual pesticides, those presenting a significant association with lung cancer were dieldrin (OR = 2.56; 95% CI 1.36-4.81), chlorpyrifos (OR = 3.29; 95 % CI 1.93-5.61), and carbofuran (OR = 2.10; 95% CI 1.28-3.42). It was also found, for the first time, carbofuran, glyphosate, and paraquat to be strongly associated with lung cancer.

Conclusions: The results showed that lung cancer among Thai people in Nakhon Sawan province is associated with previous pesticide use. In addition to dieldrin and chlorpyrifos, we also found carbofuran, glyphosate, and paraquat to be strongly associated with lung cancer. These issues should receive more attention since these chemicals are used widely.

Keywords

Lung cancer, Pesticides exposure, Herbicides, Insecticides, Fungicides

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2. **Matthew R Bonner**, University at Buffalo, Buffalo, USA

Any reports and responses or comments on the article can be found at the end of the article.

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Association of individual pesticide and lung cancer were further analyzed. A cumulative exposure days of individual pesticide was calculated, and then, the association between lung cancer and the category of exposure days was determined. The updated results found glyphosate and paraquat in Q3 and Q4 to significantly associate with lung cancer. The issues were further discussed and more references were provided.

Any further responses from the reviewers can be found at the end of the article

Introduction

Lung cancer is a common and deadly type of cancer. In 2018, there were 2.1 million people around the world diagnosed with lung cancer, and 1.8 million died of the disease¹. In 2018, Thailand had 170,495 incidences, and 114,199 deaths of lung cancer². Besides genetic factors³, a major risk factor of lung cancer is cigarette smoking^{4,5}. However, lung cancer was also related to other risk factors, including asbestos, crystalline silica, radon, polycyclic aromatic hydrocarbons, diesel engine exhaust particles, chromium, and nickel^{6,7}. Previous studies have also linked cooking fumes to lung cancer⁸.

Pesticide exposure might also cause lung cancer⁹. The association between pesticides and lung cancer were presented around 50 years ago among grape farmers¹⁰. A large study in the United States found that lung cancer cases increase with the number of years working as a licensed pesticide applicator¹¹. Another study in USA reported an increased risk of lung cancer among acetochlor herbicide users (RR = 1.74, 95% CI 1.07-2.84)¹². In Pakistan, a study also found a strong association between pesticide exposure and lung cancer (OR = 5.1, 95% CI 3.1-8.3)¹³.

Some studies can also link individual pesticides to lung cancer. In the USA, a study evaluated 50 pesticides and found that seven—dicamba, metolachlor, pendimethalin, carbofuran, chlorpyrifos, diazinon, and dieldrin—to be positively associated with lung cancer¹⁴. Another study also showed a significantly increased risk of lung cancer among applicators who had been exposed to dieldrin¹⁵. Jones *et al.*¹⁶ reported an increased lung cancer incidence among male pesticide applicators with the highest exposure category of diazinon (odds ratio (OR) = 1.6, 95% confidence interval (CI) 1.11-2.31). Other individual pesticides that had been associated with lung cancer were chlorpyrifos¹⁷, diazinon¹⁸, and pendimethalin¹⁹.

To our knowledge, the association between lung cancer and pesticides has never been studied before among Thai people. The objective of this study was to investigate associations between pesticide exposure and lung cancer among people living in Nakhon Sawan province, Thailand. The results can be used for the prevention of lung cancer, and to support the global literature.

Methods

Study participants

This study is a population-based case-control study. Cases referred to people diagnosed with primary lung cancer during the period of January 1, 2014 to March 31, 2017, and having at least ten years residence in Nakhon Sawan province, Thailand. Cases were selected from the database of Thai Cancer Based Program (TCB) operated by Thai National Cancer Institute²⁰. The TCB program requires every hospital to register cancer patients and to provide related information, e.g. types of cancer, diagnostic method, treatment information, etc.

From 299 living cases registered during the study period, 32 died during the year, 20 cases were in stage IV (undifferentiated) cancer, and the other 14 not willing to participate in the study. After exclusion of those cases, 233 (participation rate = 77.9%) were contacted in person, and participated in this study. From 233 cases, 126 were confirmed by Computerized Tomography scan (CT scan)/ Magnetic Resonance Imaging (MRI)/ ultrasound of the whole abdomen/ Chest X-ray (CXR), 62 by histology of primary or metastasis, 21 by cytology of haematology, and 24 by history and physical exam.

Controls were neighbours who did not have lung or any other cancer, but were of the same gender, and age (± 5 years) as the cases. In each case, two controls were selected by the interviewer using convenience sampling. In this study, data from 458 controls were used as a comparison group.

The minimum sample size was determined to be 229 for cases and 458 for controls using Kelsey's formula²¹ (unmatched population base case-control study). The assumptions used were as follows: proportion of case with pesticide exposure was 0.5²², proportion of control with exposure was 0.4²³, and the ratio of case to control was 1:2²⁴.

Questionnaire

Data on pesticide exposure and other risk factors were collected using a questionnaire previously used in a study on pesticide exposure and diabetes²⁵. The questionnaire has two major parts (provided as *Extended data* in English)²⁶. Part 1 is about demographic data. We collected data on gender, age, marital status, education, occupation, living duration in the community, distances between home and farmland, exposure to air pollution (i.e., cooking smoke, working in a factory with air pollution; asbestos, diesel engine exhaust, silica, wood dust, painting and welding exposure). Data on smoking status, number of cigarettes smoked per day, and the total number of years smoked was also collected. Number of cumulative cigarettes smoked over a life time was calculated by multiplying the number of cigarettes smoked per day by the number of years. Those who smoked <109,500 cigarettes were considered a light smoker, while those who smoked $\geq 109,500$ cigarettes were a heavy smoker²⁷.

In Part 2, information on the historical use (mix or spray) of pesticides were collected. In this study, pesticides were categorized into five groups: insecticides (organochlorine, organophosphate, carbamate, and pyrethroid), herbicides, fungicides, rodenticides, and molluscicides. For each groups of pesticides, we collected data on the numbers of years and days using pesticides. The data of lifetime pesticide exposure days were then computed by multiplying the total years of exposure by the number of days per year. This study also collected data on the use of 35 individual pesticides commonly found in Thailand.

Pesticide exposure data were collected by the researcher and two village health volunteers working full-times for the project. Both case and control were interviewed by the same interviewer. Prior to data collection, all interviewers were trained on how to interview and properly use the questionnaire.

Statistical analysis

Collected data were analysed using IBM SPSS Statistics (version 25) and OpenEpi (version 3.5.1). P values <0.05 were considered statistically significant. Demographic data was analyzed using descriptive statistics. The associations were determined between lung cancer and groups of pesticides (herbicides, insecticides, fungicides, and molluscicides), between lung cancer and 17 individual compounds. Data were analyzed with conditional and unconditional logistic regression but the results were similar, and thus, only the results from the unconditional logistics regression are reported. Both crude and adjusted ORs with 95% confidence intervals (CIs) were presented. Adjusted ORs were analyzed using multiple logistic regressions

controlled for gender (male, female), age (≤ 54 , 55–64, 65–74, and ≥ 75), cigarette smoking (never smoked, smoked < 109,500, smoked $\geq 109,500$), occupation (farmer, non-farmer), cooking fumes exposure (yes, no), and exposure to air pollution i.e., working in factories with air pollution (yes, no). In addition to the fundamental confounding factors, variables with statistically difference between cases and controls were included in a regression model.

Cumulative exposure days on groups of pesticides were categorized into either quartiles (Q1-Q4; Q1 being the lowest exposure and Q4 the highest) or tertile (T1-T3), depending on the number of subjects in each group. The lung cancer risk was then predicted, using nonexposed group as a reference.

Ethical considerations

This study was approved by the Ethics Board of Naresuan University (project number 550/60). Written informed consent was obtained from each subject before the interviewing process.

Results

Demographic information

In this study, most of study participants were male with a mean age of around 65. Both cases and controls have similar gender, age, marital status, education, occupation, period of residence, distances, pollution exposure, and cigarette smoking. More detailed demographic data among case and control groups were in [Table 1](#) and in *Underlying data*²⁸.

Lung cancer and pesticide exposure

After adjusting for confounding factors, lung cancer was positively associated with historical exposure of study

Table 1. General characteristic of the case and control groups.

Characteristic	Case		Control		P value**
	n	%	n	%	
Total (any) (N = 680)*	233	100.0	447	100.0	
Gender					0.693
Male	135	57.9	266	59.5	
Female	98	42.1	181	40.5	
Age (years)					0.891
≤ 54	34	14.6	71	15.9	
55–64	72	30.9	128	28.6	
65–74	72	30.9	146	32.7	
≥ 75	55	23.6	102	22.8	
Mean age (years) $\pm$ SD	66.04 $\pm$ 10.63		65.37 $\pm$ 10.88		
Median age (min–max)	65.00 (37–98)		66.00 (31–92)		

Characteristic	Case		Control		P value**
	n	%	n	%	
Marital status					0.644
Single	17	7.3	27	6.0	
Married	188	80.7	357	79.9	
Divorced/Separated	28	12.0	63	14.1	
Education completed					0.295
Primary school (Grade 1–6)	217	93.1	402	89.9	
Secondary school (Grade 7–12)	13	5.6	40	8.9	
Undergraduate or higher	3	1.3	5	1.2	
Occupation					0.970
Farmer	131	56.3	252	56.3	
Non-farmer	102	43.7	195	43.7	
Period of residence (years)					0.913
<21	25	10.7	45	10.1	
21–30	32	13.7	66	14.7	
>30	176	75.6	336	75.2	
Distances (m)					0.814
<500	102	43.8	197	44.1	
500–1,000	32	13.7	54	12.1	
>1,000	99	42.5	196	43.8	
Pollution exposure†					0.636
Yes	116	49.8	214	47.9	
No	117	50.2	233	52.1	
Cooking fumes exposure					0.390
Yes	75	32.2	143	32.0	
No	158	7.8	304	68.0	
Cigarette smoking					0.003
Never smoked	144	61.8	298	66.7	
Smoked (current smoker or ex-smoker)					
< 109,500	34	14.6	88	19.7	
≥ 109,500	55	23.6	61	13.6	
Mean (cigarettes) ± SD	175,733±168,868		111,339±107,645		
Median (min-max)	109,500(5,475–876,000)		87,600(5,475–812,500)		
Histology					
Adenocarcinoma	114	48.9			

Characteristic	Case		Control		P value**
	n	%	n	%	
Squamous cell carcinoma	17	7.3			
Small cell carcinoma	21	9.0			
Large cell carcinoma	9	3.9			
Neoplasm, malignant	68	29.2			
Other and unspecified	4	1.7			

*N was 233 for case and 447 for control unless otherwise indicated.

** χ^2 test for categorical data; t-test for continuous data with statistically significant ($p < 0.05$).

†Working in factories with air pollution.

participants to herbicides, insecticides and fungicides (Table 2). The adjusted variables included in the analysis were gender (male, female), age (≤ 54 , 55–64, 65–74, ≥ 75), cigarette smoking (never smoked, smoked $< 109,500$, smoked $\geq 109,500$), occupation (farmer, non-farmer), cooking fumes exposure (yes, no), and exposure to air pollution, i.e., working in factories with air pollution (yes, no). Compared with people in the nonexposed group, those in Q3–Q4 days of using herbicides had an elevated risk of lung cancer with odds ratio (OR) between 2.20 (95% CI 1.27–3.81) for people with Q3 exposure, and 3.99 (95% CI 1.62–7.11) for Q4 exposure ($p < 0.001$). A similar association was also found for days of insecticide use and lung cancer (OR = 2.20 for Q3, and OR = 2.24 for Q4, $p = 0.006$). For individual compounds, lung cancer was statistically associated with a historical use dieldrin (OR = 2.56; 95% CI 1.36–4.81), chlorpyrifos (OR = 3.29; 95% CI 1.93–5.61), and carbofuran (OR = 2.10; 95% CI 1.28–3.42) (Table 3). People in Q3 and Q4 of glyphosate and paraquat exposure also showed an elevated risk of lung cancer (Table 3).

Discussion

The study results showed a positive association between lung cancer and the historical use of herbicides and insecticides (Table 3). Herbicides and insecticides have a stronger association to lung cancer than fungicides. Compared to the nonexposed group, the Q1 group demonstrated lower risks of lung cancer than those in Q2 and Q3, who showed elevated risks, while Q4 had the highest risk, (Q4) (OR = 3.99, 95% CI 1.62–7.11). A similar pattern was also observed among the users of insecticides. The risk of lung cancer exponentially increased due to extended periods of using insecticides, (Q3–Q4) with OR between 2.20 (95% CI 1.24–3.89) and 2.24 (95% CI 1.33–3.72). The highest category of years using herbicides and insecticides also showed a positive association with lung cancer (OR = 1.71; 95% CI 1.33–1.53 and OR = 1.82; 95% CI 1.05–3.16).

These results were consistent with literature indicating the potential carcinogenicity of pesticides²⁹. In an experimental study, exposure to pesticides caused the production of reactive oxygen species (ROS), an oxygen-containing species containing

an unpaired electron, such as superoxide, hydrogen peroxide, and hydroxyl radical, which are highly unstable and may cause DNA damage, protein damage, mutagenicity, necrosis, and apoptosis³⁰. Pesticides may also increase the risk of cancer via other mechanisms including genotoxicity, tumour promotion, epigenetic effects, hormonal action and immunotoxicity³¹. In epidemiological study, evidence linked pesticide exposure to lung cancer are increasing, and the issue will be further discussed in the following section.

For individual pesticides, the study found lung cancer to be statistically associated with dieldrin (OR = 2.56; 95% CI 1.36–4.81), chlorpyrifos (OR = 3.29; 95% CI 1.93–5.61), and carbofuran (OR = 2.10; 95% CI 1.28–3.42) (Table 3). Dieldrin is an extremely persistent organic pollutant linked to many health problems, e.g., Parkinson's disease, breast cancer, affecting the immunity system, the reproductive, and nervous systems³². In the USA, the Agricultural Health Study found seven pesticides including dicamba, metolachlor, pendimethalin, carbofuran, chlorpyrifos, diazinon, and dieldrin to be positively associated with lung cancer¹⁴. Further studies found dieldrin exposure to relate to the highest tertile of days use (RR = 5.30; 95% CI 1.50–18.60)¹⁵. In Thailand, 688 tons of dieldrin was used in 1981–1990, before it was banned on May 16, 1990.

A study among pest control workers in Florida, USA found a long-term exposure to organophosphate and carbamate insecticides to increase mortality risk of lung cancer (OR = 1.4; 95% CI 0.7–3.0) for subjects licensed from 10–19 year; OR = 2.1; 95% CI 0.8–5.5 for those licensed 20 year or more¹¹. In the Agricultural Health Study, a dose response relationship was found between lung cancer and chlorpyrifos (RR = 2.18; 95% CI 1.31–3.64)¹⁷ and diazinon (RR = 3.46; 95% CI 1.57–7.65)¹⁸. Similar results were also replicated in later studies of the Agricultural Health Study cohort for chlorpyrifos (RR = 1.80; 95% CI 1.00–3.23), which are referring to applicators in the lowest category of exposure¹⁷. At this time, chlorpyrifos still not banned by Thai government. On the other hand, chlorpyrifos was the primary insecticide imported to Thailand (1,193,302 kilograms in 2013)³³.

Table 2. Associations between type of pesticides use and lung cancer.

Pesticides use	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
Pesticides (any) (N = 490)						
<i>Herbicides (N = 347)</i>						
Yes	129	54.4	218	48.8	1.30 (0.94-1.79)	1.34 (0.91-1.98)
No	104	44.6	229	51.2		
<i>Number of years using herbicides (N = 347)</i>						
>30	23	9.9	51	11.4	1.69 (1.27-1.71)	1.71 (1.33-1.53)**
11-30	76	32.6	107	23.9	1.56 (1.07-2.27)	1.66 (1.07-2.57)**
1-10	30	12.9	60	13.5	1.10(0.67-1.80)	1.17(0.69-2.00)
Nonexposed	104	44.6	229	51.2	Reference	Reference
P for trend***					0.045	0.047
<i>Number of days using herbicides (N = 347)</i>						
Q4 (>960)	52	22.3	30	6.7	3.59 (2.15-5.98)	3.99 (1.62-7.11)**
Q3 (501-960)	45	18.5	50	10.8	1.88 (1.17-3.02)	2.20 (1.27-3.81)**
Q2 (160-500)	23	10.7	50	11.6	1.03 (0.59-1.78)	1.14 (0.62-2.11)
Q1 (<160)	9	3.9	88	19.7	0.35(0.19-0.64)	0.39(0.20-0.74)
Nonexposed	104	44.6	229	51.2	Reference	Reference
P for trend***					<0.001	<0.001
<i>Insecticides (N = 305)</i>						
Yes	116	49.8	189	42.3	1.35 (0.98-1.86)	1.40 (0.98-2.03)
No	117	50.2	258	57.7		
<i>Number of years using the insecticides (N = 305)</i>						
>30	37	15.9	43	9.6	1.89 (1.16-3.09)	1.82 (1.05-3.16)**
11-30	63	27.0	96	21.5	1.44 (1.03-2.12)	1.62 (1.05-2.49)**
1-10	16	6.9	50	11.2	0.70(0.38-1.29)	0.77(0.41-1.44)
Nonexposed	117	50.2	258	57.7	Reference	Reference
P for trend***					0.009	0.029
<i>Number of days using the insecticides (N = 305)</i>						
Q4 (>1,200)	37	15.9	39	8.7	2.17 (1.29-3.27)	2.24 (1.33-3.72)**
Q3 (481-1,200)	33	14.1	34	7.6	2.13 (1.26-3.61)	2.20 (1.24-3.89)**
Q2 (200-480)	28	12.0	53	11.9	1.16 (0.70-1.93)	1.28 (0.74-2.19)
Q1 (<200)	18	7.8	63	14.1	0.67(0.37-1.18)	0.72(0.40-1.31)
Nonexposed	117	50.2	258	57.7	Reference	Reference
P for trend***					0.001	0.006

Pesticides use	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
<i>Fungicides (N = 116)</i>						
Yes	42	18.0	74	16.6	1.10 (0.73-1.68)	1.05 (0.68-1.64)
No	191	82.0	373	83.4		
<i>Number of years using the fungicides (N = 116)</i>						
>30	7	3.0	10	2.3	1.36 (0.51-3.64)	1.05 (0.37-2.92)
11-30	23	9.9	39	8.7	1.15 (0.66-1.98)	1.13 (0.64-1.99)
1-10	12	5.1	25	5.6	0.93(0.46-1.90)	0.92(0.43-1.92)
Nonexposed	191	82.0	373	83.4	Reference	Reference
P for trend***					0.881	0.355
<i>Number of days using the fungicides (N = 116)</i>						
Q4 (>500)	16	6.8	13	2.9	2.40 (1.13-5.10)	2.00 (0.91-4.40)
Q3 (161-500)	9	3.9	17	3.9	1.03 (0.45-2.36)	1.01 (0.43-2.37)
Q2 (96-160)	9	3.9	22	4.9	0.79 (0.36-1.76)	0.83 (0.36-1.90)
Q1 (<96)	8	3.4	22	4.9	0.71(0.31-1.62)	0.68(0.29-1.590)
Nonexposed	191	82.0	373	83.4	Reference	Reference
P for trend***					0.163	0.189

*Logistic regression adjusted for gender, age (≤ 54 , 55-64, 65-74, and ≥ 75), cigarette smoking (never smoked, smoked $<109,500$, smoked $\geq 109,500$), occupation (farmer and non-farmer), cooking fumes exposure (yes, no), and pollution exposure (working in factories with air pollution) (yes, no).

**Statistically significant ($p < 0.05$).

***P-values for linear trends were derived using a continuous variable with midpoint value of each category.

Table 3. Associations between individual pesticide use and lung cancer.

Pesticide	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
Herbicides						
<i>Glyphosate (N = 281)</i>						
Yes	105	45.1	176	39.4	1.26 (0.91-1.74)	1.29 (0.89-1.88)
No	128	54.9	271	60.6		
<i>Number of days using glyphosate</i>						
Q4 (>1,008)	44	18.9	26	5.8	3.58(2.11-6.07)	3.65(2.05-6.50)**
Q3 (401-828)	36	15.5	33	7.4	2.30(1.37-3.87)	2.52(1.43-4.43)**
Q2 (161-480)	18	7.7	37	8.3	1.02(0.56-1.87)	1.10(0.58-2.09)
Q1 (≤ 160)	7	3.0	80	17.9	0.18(0.08-0.41)	0.20(0.09-0.46)
Nonexposed	128	54.9	271	60.6	Reference	Reference

Pesticide	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
P for trend***					<0.001	<0.001
<i>Paraquat</i> (N = 239)						
Yes	89	38.2	150	33.6	1.22 (0.88–1.70)	1.21 (0.85–1.73)
No	144	61.8	297	66.4		
Number of days using paraquat						
Q4 (>828)	30	12.9	29	6.5	2.11(1.22-3.66)	2.04(1.14-3.67)**
Q3 (401-828)	29	12.4	32	7.2	1.85(1.08-3.18)	1.80(1.02-3.20)**
Q2 (145-400)	21	9.1	35	7.8	1.19(0.67-2.12)	1.26(0.69-2.28)
Q1 (≤144)	9	3.8	54	12.1	0.33(0.16-0.69)	0.35(0.17-0.75)
Nonexposed	144	61.8	297	66.4	Reference	Reference
P for trend***					<0.001	<0.001
<i>2, 4-Dichlorophenoxy acetic acid</i> (N = 117)						
Yes	47	20.2	70	15.7	1.36 (0.90–2.04)	1.42 (0.93–2.18)
No	186	79.8	377	84.3		
Number of days using 2,4-Dichlorophenoxy acetic acid						
Q4 (>480)	9	3.9	20	4.5	0.81(0.40-2.04)	0.88(0.38-2.01)
Q3 (161-480)	11	4.7	12	2.7	1.55(0.82-3.82)	1.58(0.79-3.78)
Q2 (91-160)	10	4.3	14	3.1	1.17(0.67-2.59)	1.19(0.68-2.66)
Q1 (≤90)	17	7.3	24	5.4	0.59(0.25-1.39)	0.65(0.27-1.57)
Nonexposed	186	79.8	377	84.3	Reference	Reference
P for trend***					0.095	0.098
<i>Butachlor</i> (N = 38)						
Yes	14	6.0	24	5.4	1.12 (0.57–2.22)	0.88 (0.42–1.83)
No	219	94.0	423	94.6		
Number of days using butachlor						
Q4 (>220)	6	2.6	4	1.0	2.89(0.80-7.37)	2.02(0.53-7.67)
Q3 (101-220)	3	1.3	5	1.1	1.15(0.27-4.89)	0.95(0.21-4.28)
Q2 (51-100)	4	1.7	5	1.1	1.54(0.41-5.81)	1.47(0.37-5.82)
Q1 (≤50)	1	0.4	10	2.2	0.19(0.02-1.51)	0.19(0.02-1.52)
Nonexposed	219	94.0	423	94.6	Reference	Reference
P for trend***					0.134	0.154
<i>Propanil</i> (N = 32)						
Yes	11	4.7	21	4.7	1.00 (0.47–2.12)	1.06 (0.47–2.41)
No	222	95.3	426	95.3		

Pesticide	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
Number of days using propanil						
T3 (>320)	6	2.6	10	2.2	1.21(0.80-6.30)	1.32(0.61-6.82)
T2 (91-320)	3	1.3	5	1.1	1.15(0.27-4.86)	1.29(0.29-5.60)
T1 (≤90)	2	0.8	6	1.4	0.63(0.12-3.19)	0.68(0.13-3.48)
Nonexposed	222	95.3	426	95.3	Reference	Reference
P for trend***					0.379	0.266
<i>Alachlor</i> (N= 42)						
Yes	14	6.0	28	6.3	0.95 (0.49–1.85)	0.91 (0.45–1.85)
No	219	94.0	419	93.7		
Number of days using alachlor						
Q4 (>885)	6	2.6	5	1.1	2.29(0.69-7.60)	1.87(0.55-6.35)
Q3 (341-885)	5	2.2	5	1.1	1.91(0.54-6.67)	1.85(0.51-6.67)
Q2 (99-340)	2	0.8	8	1.8	0.47(0.10-2.27)	0.52(0.11-2.52)
Q1 (≤98)	1	0.4	10	2.3	0.19(0.02-1.50)	0.17(0.02-1.39)
Nonexposed	219	94.0	419	93.7	Reference	Reference
P for trend***					0.101	0.099
Insecticides						
<i>Organochlorine insecticides</i>						
<i>Endosulfan</i> (N = 79)						
Yes	35	15.0	44	9.8	1.61 (1.00–2.60)	1.60 (0.97–2.63)
No	198	85.0	403	90.2		
Number of days using endosulfan						
Q4 (>850)	10	4.3	10	2.2	2.03(0.83-4.97)	2.01(0.79-5.08)
Q3 (361-850)	8	3.4	10	2.2	1.62(0.63-4.18)	1.38(0.51-3.67)
Q2 (130-360)	8	3.4	13	2.9	1.25(0.51-3.07)	1.31(0.52-3.30)
Q1 (≤129)	9	3.9	11	2.5	1.16(0.67-4.08)	1.18(0.71-4.48)
Nonexposed	198	85.0	403	90.2	Reference	Reference
P for trend***					0.346	0.204
<i>Dieldrin</i> (N = 44)						
Yes	24	10.3	20	4.5	2.45 (1.32–4.53)	2.56 (1.36–4.81)**
No	209	89.7	427	95.5		
Number of days using dieldrin						
T3 (>720)	9	3.9	6	1.3	3.06(1.07-8.72)	3.15(1.08-9.18)**

Pesticide	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
T2 (321-720)	9	3.9	5	1.1	3.04(1.21-7.11)	3.11(1.33-8.68)**
T1 (≤320)	6	2.5	9	2.1	1.36(0.47-3.87)	1.36(0.47-3.95)
Nonexposed	209	89.7	427	95.5	Reference	Reference
P for trend***					0.017	0.022
<i>DDT (N = 50)</i>						
Yes	13	5.6	37	8.3	0.65 (0.34–1.25)	0.67 (0.34–1.31)
No	220	94.4	410	91.7		
Number of days using DDT						
T3 (>250)	7	3.0	10	2.3	1.30(0.48-3.47)	1.28(0.47-.50)
T2 (121-250)	3	1.3	12	2.7	0.46(0.13-1.66)	0.45(0.12-1.66)
T1 (≤120)	3	1.3	15	3.3	0.37(0.10-1.30)	0.41(0.11-1.46)
Nonexposed	220	94.4	410	91.7	Reference	Reference
P for trend***					0.191	0.151
<i>Organophosphate insecticides</i>						
<i>Chlorpyrifos (N = 70)</i>						
Yes	40	17.2	30	6.7	2.88 (1.74–4.76)	3.29 (1.93–5.61)**
No	193	82.8	417	93.3		
Number of days using chlorpyrifos						
T3(>720)	15	6.4	10	2.2	3.42(1.31-6.93)	3.42(1.47-7.96)**
T2 (397-720)	18	7.8	12	2.7	3.02(1.62-7.18)	3.12(1.89-8.97)**
T1 (≤396)	7	3.0	8	1.8	1.89(0.67-5.28)	1.89(0.63-5.61)
Nonexposed	193	82.8	417	93.3	Reference	Reference
P for trend***					<0.001	<0.001
<i>Folidol/parathion (N = 104)</i>						
Yes	40	17.2	64	14.3	1.24 (0.80–1.90)	1.25 (0.78–1.99)
No	193	82.8	383	85.7		
Number of days using folidol/parathion						
Q4 (>720)	12	5.1	11	2.4	2.16(0.93-4.99)	2.10(0.88-5.02)
Q3 (401-1,080)	9	3.9	7	1.6	2.05(0.93-4.15)	2.04(0.88-4.71)
Q2 (140-400)	7	3.0	21	4.7	0.66(0.27-1.58)	0.69(0.28-1.71)
Q1 (≤139)	12	5.2	25	5.6	0.95(0.46-1.93)	0.95(0.85-2.01)
Nonexposed	193	82.8	383	85.7	Reference	Reference
P for trend***					0.105	0.105

Pesticide	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
<i>Mevinphos</i> (N = 38)						
Yes	16	6.9	22	4.9	1.42 (0.73–2.76)	0.89 (0.22–3.65)
No	217	93.1	425	95.1		
Number of days using mevinphos						
T3 (>840)	9	3.9	8	1.8	2.44(0.95-6.29)	2.05(0.77-5.44)
T2 (253-840)	5	2.1	2	0.4	2.89(0.91-5.44)	2.53(0.84-5.53)
T1 (≤252)	2	0.9	12	2.7	0.16(0.22-1.26)	0.16(0.22-1.29)
Nonexposed	217	93.1	425	95.1	Reference	Reference
P for trend***					0.065	0.063
<i>Carbamate insecticides</i>						
<i>Carbaryl/Savin</i> (N = 48)						
Yes	14	6.0	34	7.6	0.77 (0.40–1.47)	0.89 (0.41–1.55)
No	219	94.0	413	92.4		
Number of days using carbaryl/savin						
T3 (>1,050)	7	3.0	8	2.2	1.65(0.59-4.61)	1.71(0.59-4.94)
T2 (321-1,050)	5	2.1	11	2.6	0.85(0.29-2.49)	0.87(0.29-2.63)
T1 (≤320)	2	0.9	15	1.8	0.25(0.15-1.10)	0.25(0.59-4.94)
Nonexposed	219	94.0	413	92.4	Reference	Reference
P for trend***					0.130	0.107
<i>Carbofuran</i> (N = 85)						
Yes	43	18.5	42	9.4	2.18 (1.37–3.45)	2.10 (1.28–3.42)**
No	190	81.5	405	90.6		
Number of days using carbofuran						
Q4 (>1,200)	11	4.7	6	1.4	4.68(1.60-13.68)	4.57(1.53-13.57)**
Q3 (401-1,200)	18	7.7	5	1.1	4.52(1.15-13.06)	4.36(1.99-13.53)**
Q2 (101-400)	8	3.5	14	3.1	1.21(0.50-2.95)	1.11(0.44-2.82)
Q1 (≤100)	6	2.6	17	3.8	0.47(0.15-1.41)	0.44(0.14-1.35)
Nonexposed	190	81.5	405	90.6	Reference	Reference
P for trend***					<0.001	<0.001
<i>Pyrethoid insecticides</i>						
<i>Abamectin</i> (N = 134)						
Yes	44	18.9	90	20.1	0.92 (0.61–1.37)	0.82 (0.53–1.27)
No	189	81.1	357	79.9		

Pesticide	Case		Control		OR (95% CI)	Adjusted OR (95% CI)*
	n	%	n	%		
Total	233	100.0	447	100.0		
Number of days using abamectin						
Q4 (>540)	12	5.2	21	4.7	1.07(0.51-2.24)	0.89(0.41-1.91)
Q3 (361-540)	8	3.4	16	3.6	0.94(0.39-2.24)	0.83(.34-2.02)
Q2 (124-360)	14	6.0	29	6.5	0.91(0.47-1.76)	0.79(0.39-1.58)
Q1 (≤123)	10	4.3	24	5.3	0.78(0.36-1.68)	0.79(0.36-1.74)
Nonexposed	189	81.1	357	79.9	Reference	Reference
P for trend***					0.971	0.391
Fungicides						
<i>Armure/Propiconazole (N = 80)</i>						
Yes	29	12.4	51	11.4	1.10 (0.67–1.79)	1.02 (0.61–1.72)
No	204	87.6	396	88.6		
Number of days using Armure/propiconazole						
Q4 (>480)	10	4.3	9	2.0	2.15(0.86-5.39)	1.95(0.75-5.05)
Q3 (145-480)	8	3.4	12	2.7	1.29(0.52-3.12)	1.01(0.39-2.60)
Q2 (81-144)	6	2.6	13	2.9	0.89(0.33-2.39)	1.02(0.36-2.86)
Q1 (≤80)	5	2.1	17	3.8	0.57(0.20-1.56)	0.53(0.18-1.50)
Nonexposed	204	87.5	396	88.6	Reference	Reference
P for trend***					0.349	0.218
<i>Methyl aldehyde (N = 43)</i>						
Yes	15	6.4	28	6.3	1.02 (0.53–1.96)	1.03 (0.52–2.05)
No	218	93.6	419	93.7		
Number of days using methyl aldehyde						
T3 (>528)	4	1.7	16	3.6	0.48(0.15-1.45)	0.49(0.16-1.53)
T2 (351-528)	4	1.7	4	0.9	1.92(0.47-4.75)	1.77(0.42-4.44)
T1 (≤350)	7	3.0	8	1.8	1.68(0.36-4.69)	1.72(0.59-4.98)
Nonexposed	218	93.6	419	93.7	Reference	Reference
P for trend***					0.284	0.176

*Logistic regression adjusted for gender, age (≤ 54, 55–64, 65–74, and ≥ 75), cigarette smoking (never smoked, smoked <109,500, smoked ≥ 109,500), occupation (farmer and non-farmer), cooking fumes exposure (yes, no) and exposure to air pollution (working in factories with air pollution) (yes, no).

***Statistically significant (p < 0.05).

This study also found three more pesticides, e.g. carbofuran, glyphosate, and paraquat which are significantly associated with lung cancer. To our knowledge, this study is the first to report the association. Carbofuran (2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate) is one of the most toxic broad-spectrum carbamate insecticides. In laboratory studies, although evidence on carcinogenicity is inconclusive, carbofuran has been demonstrated to have mutagenic properties; and there are studies that have linked it to other types of cancer, e.g. lymphoma in mice³. In the Agricultural Health Study, lung cancer risk of carbofuran was extensively studied but no significant association to lung cancer was found^{34,35}. In Thailand, a study reported on 87 different commercial brands of insecticides which were used on 202 rice fields in Suphanburi Province (abamectin 40%, followed by chlorpyrifos 30%, and carbofuran 20%), 93 brands of plant hormones, and 56 brands of chemicals for the control of plant diseases³⁶.

Although, a rough estimation of the use of glyphosate and paraquat were not significantly associated with lung cancer, more detail exposure data showed that people in the higher category of cumulative exposure day, especially those in Q3 and Q4, had an elevated risk of lung cancer (P for trend <0.001) (Table 3). Paraquat (dipyridylum), also known as Gramoxone, is a non-selective herbicide commonly used worldwide^{33,37}. Although, the mechanism of toxicity has not been clearly defined, research found that paraquat can cause damage to the lungs, kidneys, and the liver³⁸. At the cellular level, paraquat can produce reactive oxygen species (ROS), the superoxide free radical, which can initiate or promote carcinogenesis³⁹. In a case study, pulmonary fibrosis was found in the patient with paraquat poisoning⁴⁰. In Thailand, paraquat was banned in May, 2020.

Glyphosate [N-(phosphonomethyl)glycine, also known as roundup] is another broad-spectrum herbicide that has been used widely in Thailand and other countries^{33,37}. In the past decade, cancer potency of glyphosate received much attention and several comprehensive literature reviews are available^{41,42}. In 2015, WHO revised carcinogenicity of glyphosate and classified it as “probable carcinogen”⁴². Laboratory studies found glyphosate to increase incidence of tumour, chromosomal damage, and oxidative stress⁴². Evidence from epidemiological studies were limited. Although it was previously reported to relate to non-Hodgkin lymphoma, glyphosate did not relate to cancer at any sites in the large perspective Agricultural Health Study^{43,44}.

The potential limitations of this type of study were the recall bias where cases and controls can recall past exposure differently. Cases tend to memorize exposure better, particularly when they know or are aware of what caused their illness⁴⁵. However, with limited available information on the issues in Thailand, we did not expect participants to be aware of pesticides as causal factor for lung cancer. It was very likely that the study could have exposure misclassification due to the participants not being able to recall or name the pesticides

they used in the past. In addition, data on pesticide exposure were obtained solely from the interview questionnaire without any exposure measurement. However, this information bias usually occurs evenly across a case and control group, and only has a negative effect on the association⁴⁶. Selection bias might also occur when using non-random sampling or when the study sample did not represent the study population. However, in this study, data from all of the lung cancer patients except those who were severely ill, were collected to minimize the bias.

Conclusion

This study found that the occurrence of lung cancer among people in Nakhon Sawan province, Thailand is associated with pesticide use. Out of 17 individual pesticides investigated, dieldrin, chlorpyrifos, and carbofuran showed significant associations with incidence of lung cancer. These results are consistent with the literature from other parts of the world. This study found that carbofuran, glyphosate, and paraquat to be strongly associated with lung cancer. These issues should receive more attention since these chemicals have been used widely. Further studies should focus on identifying more individual pesticides that could cause lung cancer, as well as other types of cancer.

Data availability

Underlying data

Figshare: Pesticide and lung cancer. <https://doi.org/10.6084/m9.figshare.12356270.v3>²⁹.

This project contains the following underlying data:

- Dataset_pesticide and lung cancer (SAV and CSV). (All underlying data gathered in this study.)
- Data Dictionary (DOCX).

Extended data

Figshare: Questionnaire-pesticide and lung cancer Thailand. <https://doi.org/10.6084/m9.figshare.12356384.v1>²⁷.

This project contains the following extended data:

- Questionnaire-pesticide and lung cancer Thailand (DOCX). (Study questionnaire in English.)

Data are available under the terms of the [Creative Commons Zero “No right reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ? ?

Version 3

Reviewer Report 12 March 2021

<https://doi.org/10.5256/f1000research.54635.r79943>

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Matthew R Bonner

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA

Much of the discussion still relies on older reports from the AHS. Even though reference 35 was added as a citation to the sentence on carbofuran, this AHS report details results for a considerable number of pesticides that overlap with pesticides reported on in this manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cancer epidemiology, pesticides, air pollution, occupational and environmental epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 14 Mar 2021

Chudchawal Juntarawijit

Comment:

Much of the discussion still relies on older reports from the AHS. Even though reference 35 was added as a citation to the sentence on carbofuran, this AHS report details results for a considerable number of pesticides that overlap with pesticides reported on in this manuscript.

Response:

Thank for the suggestion. More information from the latest AHS study (reference 35) has been added to the discussion section.

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 18 January 2021

<https://doi.org/10.5256/f1000research.31201.r76351>

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Matthew R Bonner

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Overall, the revised manuscript is responsive to many of my comments. However, there are several outstanding issues that require additional attention.

1) Response: *Matching of a few variables can be considered loose-matching, therefore, it is more appropriate to analyze using unconditional logistic regression. Kuo and team (2018) said that "There is a presumption that matched data need to be analyzed by matched methods. Conditional logistic regression has become a standard for matched case-control data to tackle the sparse data problem. The sparse data problem, however, may not be a concern for loose-matching data when the matching between cases and controls are not unique, and one case can be matched to other controls without substantially changing the association. Data matched on a few demographic variables are clearly loose-matching data, and we hypothesize that unconditional logistic regression is a proper method to perform." (Kuo, Duan & Grady, 2018)**

The characterization of matching on weak confounding factors as "loose-matching" seems to overlook the bias introduced by matching on confounders. As Neil Pearce states: "In essence, the matching process makes the controls more similar to the cases not only for the matching factor but also for the exposure itself. This introduces a bias that needs to be controlled in the analysis" (Pearce N. Analysis of matched case-control studies. *BMJ* (2016)).¹

This is a well-recognized consequence of matching in case-control studies and mitigating this introduced bias in the analysis is fundamental to conducting a matched case-control study. The sparse data problem that is emphasized in the response is a common problem for most studies regardless of whether matching procedures were used. The use of conditional logistic regression can help with both these issues and should not be ignored because of a presumption of "loose-matching." A comparison between the proportional hazards risk estimates with the unconditional logistic regression risk estimates seems to indicate that little if any bias was introduced by

matching. This is likely due to a weak association between the matching factors and exposure. The methods section should state that conditional and unconditional logistic regression were used, that the results were similar, and results from the unconditional logistics regression are reported.

2) Response: *In this study, we actually collected data from 35 individual pesticides, but 17 of them were excluded due to small sample size (less than 5 in each cell). Therefore, the OR groups may be larger than the individual OR ones.*

This issue is unresolved, and depending on which table or exposure metric, one can render different conclusions about the association between pesticides and lung cancer. In table 2, herbicide days of use has a strong monotonic exposure response gradient, but in table 3, none of the reported herbicides have an association with lung cancer.

Additional Comment:

1) The discussion section on chlorpyrifos and carbofuran describes results from the Agricultural Health Study. However, cited reports are not the most recent reports on these pesticides and lung cancer. A more recent report from 2017, found no association with either chlorpyrifos or carbofuran. The discussion should be updated in light of this more recent report (<https://ehp.niehs.nih.gov/doi/10.1289/EHP456>).²

References

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Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cancer epidemiology, pesticides, air pollution, occupational and environmental epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 10 Feb 2021

Chudchawal Juntarawijit

Comment:

Overall, the revised manuscript is responsive to many of my comments. However, there are several outstanding issues that require additional attention.

1) Response: *Matching of a few variables can be considered loose-matching, therefore, it is more appropriate to analyze using unconditional logistic regression. Kuo and team (2018) said that "There is a presumption that matched data need to be analyzed by matched methods. Conditional logistic regression has become a standard for matched case-control data to tackle the sparse data problem. The sparse data problem, however, may not be a concern for loose-matching data when the matching between cases and controls are not unique, and one case can be matched to other controls without substantially changing the association. Data matched on a few demographic variables are clearly loose-matching data, and we hypothesize that unconditional logistic regression is a proper method to perform."* (Kuo, Duan & Grady, 2018)*

The characterization of matching on weak confounding factors as "loose-matching" seems to overlook the bias introduced by matching on confounders. As Neil Pearce states: "In essence, the matching process makes the controls more similar to the cases not only for the matching factor but also for the exposure itself. This introduces a bias that needs to be controlled in the analysis" (Pearce N. Analysis of matched case-control studies. *BMJ* (2016)).¹ This is a well-recognized consequence of matching in case-control studies and mitigating this introduced bias in the analysis is fundamental to conducting a matched case-control study. The sparse data problem that is emphasized in the response is a common problem for most studies regardless of whether matching procedures were used. The use of conditional logistic regression can help with both these issues and should not be ignored because of a presumption of "loose-matching." A comparison between the proportional hazards risk estimates with the unconditional logistic regression risk estimates seems to indicate that little if any bias was introduced by matching. This is likely due to a weak association between the matching factors and exposure. The methods section should state that conditional and unconditional logistic regression were used, that the results were similar, and results from the unconditional logistics regression are reported.

Response:

The statement that both conditional and unconditional analyses were performed has been added to the method section.

Comment:

2) Response: *In this study, we actually collected data from 35 individual pesticides, but 17 of them were excluded due to small sample size (less than 5 in each cell). Therefore, the OR groups may be larger than the individual OR ones.*

This issue is unresolved, and depending on which table or exposure metric, one can render different conclusions about the association between pesticides and lung cancer. In table 2, herbicide days of use has a strong monotonic exposure response gradient, but in table 3, none of the reported herbicides have an association with lung cancer.

Response:

Taking the suggestion, we decided to recheck the data and found some individual pesticides to have enough sufficient participants to calculate cumulative exposure days. Reanalysis of the data using quartile of exposure days, found good results. Those exposed to glyphosate and paraquat in Q4 and Q3 had a significant association with lung cancer. So, the issue was solved. Thank you very much for your thoughtful suggestions. Without it, we would miss

this important finding.

Also, to make it more consistent, we decided to use 'nonexposed' as a reference instead of Q1, and the reanalysis of the data. This change caused only a minor change in the results.

All parts of the paper (abstract, results, and discussion section) were updated.

Comment:

Additional Comment:

1) The discussion section on chlorpyrifos and carbofuran describes results from the Agricultural Health Study. However, cited reports are not the most recent reports on these pesticides and lung cancer. A more recent report from 2017, found no association with either chlorpyrifos or carbofuran. The discussion should be updated in light of this more recent report (<https://ehp.niehs.nih.gov/doi/10.1289/EHP456>).²

References

1. Marinaccio A, Consonni D, Mensi C, Mirabelli D, et al.: Authors' response: Mezei et al's "Comments on a recent case-control study of malignant mesothelioma of the pericardium and the tunica vaginalis testis". *Scand J Work Environ Health*. 2021; **47** (1): 87-89 [PubMed Abstract](#) | [Publisher Full Text](#)
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Response:

The reference has been updated. Thank you for the information.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 30 October 2020

<https://doi.org/10.5256/f1000research.26600.r73264>

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Matthew R Bonner

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Professions, University at Buffalo, Buffalo, NY, USA

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The manuscript reports the results of a case-control study designed to investigate exposure to pesticides and lung cancer. Cases and controls were recruited between January 1, 2014, and March 31, 2017, from Nakhon Sawan Province, Thailand. Controls were matched to cases on age and sex. Pesticide exposure was assessed with interviews with a structured questionnaire inquiring about days and years of pesticide use. Logistic regression, adjusting for potential confounders, was used to estimate the odds ratio and 95% confidence intervals. Pesticide classes (herbicides and organophosphate) and select specific pesticides were positively associated with lung cancer in this study. The authors conclude that "...lung cancer among Thai people in Nakhon Sawan province is associated with previous pesticide use." Overall, the study seems to be designed well, but crucial information regarding several specific details are missing from the report. These details, and other concerns, are described below.

Comments:

1. Crucial information about the lung cancer cases is missing. Specifically, were the cases comprised of 1st primary lung cancer or were lung cancer cases with a prior history of another cancer, including lung, eligible to participate in the study. Were the lung cancer cases' diagnosis histologically confirmed? What was the stage and grade of these lung cancer cases? On average, how long after their diagnosis were lung cancer cases interviewed?
2. Were potential controls excluded if they had a prior history of cancer?
3. The methods state that two neighbor controls were selected randomly. This implies that there a sampling frame of some sort. That sampling frame for random selection needs to be adequately described.
4. The controls were matched on age and sex to the cases. This necessitates a conditional logistic regression to account for the selection bias introduced by matching. Unconditional logistic regression is inappropriate for a matched case-control study. Breaking the matching and adjusting for the matching factors may not bias the odds ratios, but this should be confirmed by comparing ORs estimated with unconditional logistic regression and conditional logistic regression.
5. In table 2, there is striking qualitative confounding for the pesticide classes (yes vs. no). For instance, the crude OR organophosphates is 0.63 (95% CI = 0.46-0.87) while the adjusted OR is 1.77 (95% CI = 1.22-2.57). The use of unconditional logistic regression might explain this as the crude estimate for such a regression is inappropriate. That notwithstanding, a number of other variables were included in the regressions. Given this qualitative confounding, additional analyses to identify variables or combination of variables is driving this confounding is warranted.
6. Tobacco smoking is a recognized strong risk factor for lung cancer and a known potential confounder in studies of other exposures and lung cancer. As such, substantial efforts to mitigate confounder are often employed. In this study, smoking was a binary (ever vs.

never) variable that may not adequately capture the interrelationship between pesticide use and lung cancer to control confounding. More detailed smoking information, if available, should be explored to determine the potential for residual confounding of the reported associations

7. In table 1, smoking is not associated with lung cancer. This suggests that selection forces in the recruitment of cases and controls are biasing the study results. It seems unusual that 61% of lung cancer cases were never smokers. Is this a typical feature of lung cancer in Thailand?
8. The results reported in tables 2 and 3 seem to be internally inconsistent. For instance, the ORs for organophosphates depicted in table 4 indicate a strong association with lung cancer with days of use (Q4 vs. Q1 OR = 28.43 (95% CI = 11.11-72.76); an extremely large magnitude. However, the ORs for specific organophosphate insecticides are much more modest, although the statistically significant associations with chlorpyfos and dielrin. A similar pattern is evident for herbicide as well. This lack of internal consistency really points to the methodological limitations as a likely explanation for the observed association.
9. Recall bias was discussed as a limitation, but nothing is mentioned about other threats to internal validity. For instance, the potential for selection bias to arise from the recruitment strategies. As mentioned above, the lack of an association with smoking seems to indicate something is awry. In addition, exposure misclassification is undoubtedly present and should be discussed in the Discussion along with the other potential limitations.
10. References 20 and 35 are the same report.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cancer epidemiology, pesticides, air pollution, occupational and

environmental epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 02 Dec 2020

Chudchawal Juntarawijit

Comment:

1. Crucial information about the lung cancer cases is missing. Specifically, were the cases comprised of 1st primary lung cancer or were lung cancer cases with a prior history of another cancer, including lung, eligible to participate in the study. Were the lung cancer cases' diagnosis histologically confirmed? What was the stage and grade of these lung cancer cases? On average, how long after their diagnosis were lung cancer cases interviewed?

Response:

The cases comprised of 1st primary lung cancer. The cases were confirmed by Computerized Tomography scan (CT scan), Magnetic Resonance Imaging (MRI), ultrasound of the whole abdomen, and chest radiography or Chest X-ray (CXR), and histology of primary and metastasis. More information was added to Table 1, and provided in the Table below.

On average, the patients were interviewed approximately 1 year after they had been diagnosed with lung cancer.

Table. More information on morphology and stage of the study cases.

Morphology of lung cancer cases:

Adenocarcinoma	114 (48.9)
Small cell carcinoma	21 (9.0)
squamous cell carcinoma	17 (7.3)
Large cell carcinoma	9 (3.9)
Neoplasm/ malignant	68 (29.2)
Unspecified	4 (1.7)

Stage

IA, IB	14 (6.0)
IIA, IIB	38 (16.3)

IIIA, IIIB	57 (24.5)
IV (Distant metastasis)	0 (0)
Unknown/ unspecified	124 (53.2)

Comment:

2. Were potential controls excluded if they had a prior history of cancer?

Response:

Yes, potential controls were excluded if they had a prior history of cancer.

Comment:

3. The methods state that two neighbor controls were selected randomly. This implies that there a sampling frame of some sort. That sampling frame for random selection needs to be adequately described.

Response:

The control was, in fact, selected using convenience sampling. The information in the manuscript has been revised.

Comment:

4. The controls were matched on age and sex to the cases. This necessitates a conditional logistic regression to account for the selection bias introduced by matching. Unconditional logistic regression is inappropriate for a matched case-control study. Breaking the matching and adjusting for the matching factors may not bias the odds ratios, but this should be confirmed by comparing ORs estimated with unconditional logistic regression and conditional logistic regression.

Response:

Matching of a few variables can be considered loose-matching, therefore, it is more appropriate to analyze using unconditional logistic regression. Kuo and team (2018) said that "There is a presumption that matched data need to be analyzed by matched methods. Conditional logistic regression has become a standard for matched case-control data to tackle the sparse data problem. The sparse data problem, however, may not be a concern for loose-matching data when the matching between cases and controls are not unique, and one case can be matched to other controls without substantially changing the association. Data matched on a few demographic variables are clearly loose-matching data, and we hypothesize that unconditional logistic regression is a proper method to perform." (Kuo, Duan & Grady, 2018)*

We gained interesting information by analyzing some of the data using Cox regression. The comparison between unconditional analysis and the Cox regression, yielded

similar results. (see Table below). Comparing OR between Cox regression and logistic regression).

Table. Comparing OR between Cox regression and logistic regression.

regression	Logistic regression		Cox
Endosulfan (1.12-3.63)	OR (crude)	1.61 (1.00–2.60)	2.01
(0.99-3.33)	OR (adjusted)	1.60 (0.97–2.63)	1.81
Dieldrin (1.57-6.85)	OR (crude)	2.45 (1.32–4.53)	3.28
(1.70-7.68)	OR (adjusted)	2.56 (1.36–4.81)	3.62
Chlorpyrifos (1.91-6.41)	OR (crude)	2.88 (1.74–4.76)	3.50
(2.05-7.22)	OR (adjusted)	3.29 (1.93–5.61)	3.85
Carbofuran (1.43-3.89)	OR (crude)	2.18 (1.37–3.45)	2.36
(1.41-4.01)	OR (adjusted)	2.10 (1.28–3.42)	2.38

*Kuo C-L, Duan Y and Grady J (2018) Unconditional or Conditional Logistic Regression Model for Age-Matched Case–Control Data? *Front. Public Health* 6:57. doi: 10.3389/fpubh.2018.00057

Comment:

5. In table 2, there is striking qualitative confounding for the pesticide classes (yes vs. no). For instance, the crude OR organophosphates is 0.63 (95% CI = 0.46-0.87) while the adjusted OR is 1.77 (95% CI = 1.22-2.57). The use of unconditional logistic regression might explain this as the crude estimate for such a regression is inappropriate. That notwithstanding, a number of other variables were included in the regressions. Given this qualitative confounding, additional analyses to identify variables or combination of variables is driving this confounding is warranted.

Response:

After re-categorizing the smoking variable, and correcting a mistake on the variable coding, the new analysis yielded more consistent results with crude OR at 1.35 (95%CI 0.98-1.86) and adjusted OR at 1.40 (95%CI 0.97-2.02).

6. Tobacco smoking is a recognized strong risk factor for lung cancer and a known potential confounder in studies of other exposures and lung cancer. As such, substantial efforts to mitigate confounder are often employed. In this study, smoking was a binary (ever vs. never) variable that may not adequately capture the interrelationship between pesticide use and lung cancer to control confounding. More detailed smoking information, if available, should be explored to determine the potential for residual confounding of the reported associations

We actually collected data on the amount of cigarettes and smoking duration of the study participants, and then the information was used to compute number of cigarettes smoked by them in their life time. After grouping smoking status into "never smoked", "smoked <109500 cigarettes", and "smoked ≥ 109500 cigarettes", a significant difference between case and control was found. The data was then used for the analysis of the odds ratio.

Comment:

7. In table 1, smoking is not associated with lung cancer. This suggests that selection forces in the recruitment of cases and controls are biasing the study results. It seems unusual that 61% of lung cancer cases were never smokers. Is this a typical feature of lung cancer in Thailand?

Response:

Yes, 61% of the cases never smoked is acceptable. It was reported that smoking prevalence of Thai males decreased from 60% to 39%, and from 5% to 2.1% in females between 1991 and 2014 [1]. While a survey in 2017 reported a smoking prevalence of 20.7% of the total adult population over 15 years old [2].

It was interesting to note that in this study, 49.2% of the cases were adenocarcinoma lung cancer which has a limited relation to cigarette smoking, whereas squamous cell, and small cell lung carcinoma are highly related to smoking [3, 4].

[1] Jeon J, Sriplung H, Yeesoonsang S, Bilheem S, Rozek L, and et al. Temporal Trends and Geographic Patterns of Lung Cancer Incidence by Histology in Thailand, 1990 to 2014. *Journal of Global Oncology* 2018.

[2] *Tobacco Control Research* and Knowledge Management Center (TRC). Annual Report of Thailand Tobacco Survey, 2018. Mahidol University. www.trc.or.th. 2018.

[3] Wu K, Wong E, and Chaudhry S. Lung Cancer; Classification of invasive lung cancer. *Clin*

Chest Med 2002; Mar; 23(1):65-81.

[4] Limsila T, Mitacek EJ, Caplan LS, and Brunneemann KD. Histology and Smoking History of Lung Cancer Cases and Implications for Prevention in Thailand. Preventive Medicine 1994; 23:249-252.

Comment:

8. The results reported in tables 2 and 3 seem to be internally inconsistent. For instance, the ORs for organophosphates depicted in table 4 indicate a strong association with lung cancer with days of use (Q4 vs. Q1 OR = 28.43 (95% CI = 11.11-72.76); an extremely large magnitude. However, the ORs for specific organophosphate insecticides are much more modest, although the statistically significant associations with chlorpyfos and dielrin. A similar pattern is evident for herbicide as well. This lack of internal consistency really points to the methodological limitations as a likely explanation for the observed association.

Response:

In this study, we actually collected data from 35 individual pesticides, but 17 of them were excluded due to small sample size (less than 5 in each cell). Therefore, the OR groups may be larger than the individual OR ones.

Comment:

9. Recall bias was discussed as a limitation, but nothing is mentioned about other threats to internal validity. For instance, the potential for selection bias to arise from the recruitment strategies. As mentioned above, the lack of an association with smoking seems to indicate something is awry. In addition, exposure misclassification is undoubtedly present and should be discussed in the Discussion along with the other potential limitations.

Response:

The problems of selection bias and exposure misclassification has been further discussed in the manuscript as suggested. The problem of lack of association with smoking has already been solved.

Comment:

10. References 20 and 35 are the same report.

Response:

The error has been corrected.

Competing Interests: No competing interests were disclosed.

Reviewer Report 25 June 2020

<https://doi.org/10.5256/f1000research.26600.r65521>

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Ann C Olsson

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Dear authors,

I was pleased to review your paper that describes a case-control study in Thailand including 233 incident lung cancer cases and 458 controls focusing on exposures to pesticides. Please find enclosed my comments for your consideration. In the:

Introduction, first paragraph, I think you mean “**Polycyclic aromatic** hydrocarbons”? I would not call a paper from 1999 “Recent studies.....” because it’s >20 years old.

Methods, first paragraph, it’s a case-control study, not a case-controlled study; it would be good to include a few more details such as any time limit for having resided in the province?; from where did the TCB receive cases?; were the diagnosis confirmed by some diagnostic tool? Please clarify if the 299 were contacted and 229 accepted, or if only 229 were contacted and accepted. I would be surprised if the latter, and wonder why the other were not contacted. We also wish to know the “participation rate” among the control subjects. Neighbours are not a random sample it’s a convenience sample. If you mean that the interviewer randomly selected control subjects among all neighbours you need to explain how this was done, e.g. within a distance from the house or “snowball” technique. Why do you adjust for farming (yes/no)? Please explain your rational. It does not make sense to me.

Questionnaire, the English questionnaire does not indicate that the number of days of pesticide use is per year, so it seems strange that lifetime exposure is calculated by multiplying years with days. Please also clarify if “exposure” refers to “personally mix or apply pesticides” only, or if it also includes working in the fields? Provide more details regarding the data collection e.g. were the interviewers employed for the study full-time, or were they students?, were there any quality control measures implemented, e.g. double interviews of a proportion of subjects, were the interviewers interviewing both cases and controls?

Results, it is very strange that there is not difference between cases and controls regarding smoking, if you have an explanation for this please discuss it later.

Discussion, I don’t think that “the association were **closer** for herbicides and insecticides”, possibly “stronger” or “more pronounced”, and I prefer “more days” rather than “higher days”.

Among the limitations I think there is more to information bias, e.g. it is commonly difficult to assess exposure to specific chemicals because people don’t know the names or don’t recognize exposure. I must admit that I get suspicious that there are no missing in the data and no category for “don’t know” in the questionnaire. I would add potential selection bias to the discussion; although we don’t really know the participation rate among controls or how neighbours were

selected, they are generally not an ideal control population.

Disclaimer:

Where authors/reviewers are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors/reviewers alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Occupational cancer epidemiology, lung cancer, case-control studies, cohort studies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Dec 2020

Chudchawal Juntarawijit

Comment: Introduction, first paragraph, I think you mean “**Polycyclic aromatic hydrocarbons**”? I would not call a paper from 1999 “Recent studies.....” because it’s >20 years old.

Response: The term was changed to polycyclic aromatic hydrocarbons.

Comment: Methods, first paragraph, it’s a case-control study, not a case-controlled study;

it would be good to include a few more details such as any time limit for having resided in the province?; from where did the TCB receive cases?; were the diagnosis confirmed by some diagnostic tool? Please clarify if the 299 were contacted and 229 accepted, or if only 229 were contacted and accepted. I would be surprised if the latter, and wonder why the other were not contacted. We also wish to know the “participation rate” among the control subjects. Neighbours are not a random sample it’s a convenience sample. If you mean that the interviewer randomly selected control subjects among all neighbours you need to explain how this was done, e.g. within a distance from the house or “snowball” technique. Why do you adjust for farming (yes/no)? Please explain your rationale. It does not make sense to me.

Response: The mistake was corrected and more information on residency, TCB, and diagnostic confirmation was added to the Methods. The information of the number of cases was clarified; and information on the participation rate was also provided.

For the question, why did we adjust for farming? Actually, we tried to adjust for occupations since it is very likely that they will be exposed to pesticides differently. At first, there were several types of occupations, but due to the small number of participants in each category, the groups were limited to “farmer” and “none-farmer”. These two groups tended to have different risks of exposure to environmental pesticides, due to the nature of their work and physical health.

Comment:

Questionnaire, the English questionnaire does not indicate that the number of days of pesticide use is per year, so it seems strange that lifetime exposure is calculated by multiplying years with days. Please also clarify if “exposure” refers to “personally mix or apply pesticides” only, or if it also includes working in the fields? Provide more details regarding the data collection e.g. were the interviewers employed for the study full-time, or were they students?, were there any quality control measures implemented, e.g. double interviews of a proportion of subjects, were the interviewers interviewing both cases and controls?

Response:

More information was added and the mistakes were corrected. In this study, “exposure” refers to “personally mixed and/or applied pesticides” only, not working in the field. More information of interviewers was added to the methods. There were no other quality control measures implemented.

Comment: Results, it is very strange that there is not difference between cases and controls regarding smoking, if you have an explanation for this please discuss it later.

Response: Data on cigarette smoke was reanalyzed and the difference was observed using a new category.

Comment:

Discussion, I don’t think that “the association was **closer** for herbicides and insecticides”, possibly “stronger” or “more pronounced”, and I prefer “more days” rather than “higher days”.

Response: The term “closer” was changed to “stronger”

Comment: Among the limitations, I think there is more to information bias, e.g. it is commonly difficult to assess exposure to specific chemicals because people don't know the names or don't recognize exposure. I must admit that I get suspicious that there are no missing in the data and no category for “don't know” in the questionnaire. I would add potential selection bias to the discussion; although we don't really know the participation rate among controls or how neighbours were selected, they are generally not an ideal control population.

Response:

Yes, we agree that it was likely that some of participants could not recall or know the name of the pesticides used. If this type of bias occurs it would be equal between both the case and control groups, and minimize the association between exposure to pesticides and lung cancer. More information regarding bias was added to the Discussion section, and more information about the control group was added to the Methods. Those who could not recall or “don't know” the name of the pesticides were categorized as “not used”.

Competing Interests: No competing interests were disclosed.

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