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Research article

The determinants of thyroid function among vegetable farmers with primary exposure to chlorpyrifos: A cross-sectional study in Central Java, Indonesia

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ABSTRACT

Objectives: Occupational pesticide exposure, chlorpyrifos (CPF) in particular, may adversely affect the thyroid. The purpose of this study was to evaluate the determinants of thyroid function as indicated by the serum concentration of thyroid-stimulating hormone (TSH) among Indonesian vegetable farmers with primary exposure to CPF.

Methods: A total of 151 vegetable farmers participated in this study. The sociodemographic and occupational characteristics of the participants were obtained using a structured interviewer-administered questionnaire. A validated quantitative method was used to estimate the cumulative exposure level (CEL). Serum TSH, thyroglobulin (Tg), free thyroxine (FT4), and urinary iodine excretion (UIE) were measured in the laboratory. The difference in TSH concentrations according to CEL and other characteristics were analysed using the Mann-Whitney *U* test. A multiple linear regression model was used to evaluate the potential determinants of TSH.

Results: The mean age was 50 (SD 9.4) years. The median concentrations of TSH, FT4, and Tg/FT4 ratio were 1.46 mIU/L, 1.17 ng/dL, and 6.23×10^2, respectively. We observed that higher TSH concentrations were found among those with a higher Tg/FT4 ratio, were classified as high CEL, and had lower UIE or FT4.

Conclusions: Our findings show that Tg/FT4 ratio, CEL, FT4, UIE concentrations, and post-spraying days were determinants of TSH concentrations among farmers with primary exposure to CPF. These results indicate that farmers are exposed to agents with thyroid-disrupting

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properties, thus supporting previous evidence showing the potential for thyroid disorders in agricultural populations exposed to pesticides.

1. Introduction

One of the most important occupational health risks for small-scale farmers is exposure to multiple pesticides and inappropriate pesticide handling [1]. Organophosphate (OP) pesticides are the most widely used insecticides, which accounted for almost 60% of the total amount of insecticides in 2015, and of this, 40% was chlorpyrifos (CPF) [2]. Previous studies reported poor pesticide handling practices, high frequency of use of multiple pesticides, and low utilization of personal protective equipment (PPE) in small-scale agricultural settings [3–6]. Several agricultural tasks including mixing, loading, spraying pesticides, cleaning used equipment, re-entering the sprayed area, and also manipulating or harvesting pesticide-contaminated crops have the potential to expose farmers to pesticides [7,8]. Those risks are real in Indonesia, where agriculture is one of the main economic sectors. Many Indonesian farmers are in small-scale farming that uses pesticides extensively. In addition, the cumulative CPF exposure among Indonesian farmers was high [9]. Thus, although the severity of the health problems was determined by several factors, including the type of pesticide, concentrations, intensity, exposure duration, the proper use of personal protective equipment (PPE), and individual susceptibility [10–12], the dependence on pesticides raises concerns about the potential health impacts of these activities.

Occupational and environmental OP exposure, CPF in particular, may cause a range of health problems including neurological symptoms, endocrine disruption, and hormonal imbalance [13,14], The thyroid gland that produces thyroid hormones has a significant role in the human body, as it is involved in many physiological activities and acts on almost all body tissues including a major role in the metabolism, growth, and development [15,16]. Approximately 11% of the adult population is affected by subclinical thyroid dysfunction, making it a significant global public health problem [17,18]. Concerning the potential for endocrine disruption of CPF on thyroid function, although the exact association is controversial, previous epidemiological studies have reported some evidence of the potential impact of OP exposure on thyroid function [19–22].

Epidemiological studies addressing the effects of CPF exposure on the thyroid, particularly thyroid-stimulating hormone (TSH), free thyroxine (FT4), and thyroglobulin, are limited and inconclusive. The objective of our study was to evaluate the determinants of thyroid function as represented by the serum concentration of thyroid-stimulating hormone (TSH) among Indonesian vegetable farmers with primary exposure to CPF in Central Java, Indonesia. We hope our results will provide valuable information about the impact of CPF exposure on thyroid function so that it might be useful for further exposure management and pesticide-related disease prevention strategy.

2. Materials and methods

2.1. Study population

We conducted a cross-sectional study from July to October 2020 in two villages: Pancot, Tawangmangu District, and Adipuro, Kaliangkrik District, both known as centers of vegetable and garlic production in Central Java, Indonesia. The minimum sample size requirement for our study was 146, which was calculated using the sample size formula to compare the mean of two independent populations with a 95% confidence interval and 10% precision error. A consecutive sampling method was applied in this study and we decided to take all eligible participants. There were 195 vegetable farmers aged 18–65 years who were actively using CPF for at least one year and gave written consent to participate in the study as the sample frame of the study. A small remuneration was given to the participants in each phase for their participation in this study.

In the first phase, the participants were interviewed for sociodemographic and occupational (i.e., agricultural work-related) characteristics and underwent a health examination. During the health examination, height and weight were measured, and at the same time, a spot urine sample was taken to test for urinary iodine excretion (UIE). Participants were requested to take part in the second phase at the appointed time.

175 participants took part in the second phase and received an explanation of the results of their respective screening tests. Twenty (20) participants who did not come during the second phase were considered to have withdrawn from the study. Among those who attended the second phase, 24 participants had UIE <50 μg/L, or did not complete the confirmation of their medical and occupational history, or decided not to continue as participants were excluded from the study. Therefore, 151 eligible participants underwent blood sampling and completed all examinations. We also collected the information of the last spraying date to be deducted against the second phase attendance date of each participant to calculate the post-spraying days, i.e., blood collection for thyroid test after the number of days from the last spraying days.

2.2. Individual characteristics

Weight and height were measured during the first visit and subsequently used to calculate the body mass index (BMI) expressed in kg/m^2. The information regarding the sociodemographic characteristics of the study population was obtained through an interview using a questionnaire. Participants were also asked about their smoking habits and personal medical history.

2.3. Cumulative exposure level and occupational characteristics

The occupational characteristics of the study population were obtained using a structured interviewer-administered questionnaire. During the interview session, participants were asked about their farming activities including daily work duration, lifetime years of pesticide use, number of spraying days in a year, PPE utilization, personal hygiene habits, spill management practices, and several agricultural work-related characteristics. The cumulative exposure level (CEL) of chlorpyrifos was estimated using a validated quantitative method from Dosemeci et al. [23], as a function of pesticide exposure intensity level (IL), the lifetime years of pesticide use and the number of days spraying per year. The IL was estimated from several agricultural- and pesticide-related activities mentioned above where a score was given for each parameter. According to this estimation, the participants were then classified into two groups based on the median value of CEL [9]. The questionnaire and IL scoring matrix were available in a supplementary file (**Suppl.1**).

2.4. Urinary iodine excretion, TSH, FT4, thyroglobulin tests

Spot urine samples and venous blood samples of study participants were collected. Urine and blood samples were placed in separate boxes with ice and transported to the laboratory where they were stored at −20 °C before analysis. Urinary iodine excretion was analysed in Prodia Industrial Toxicology Laboratory, Cikarang, Indonesia using the Agilent ICP-MS 7700× system according to the Centers for Disease Control and Prevention method (CDC 3002.1) [24]. The limit of detection for this test was 1 ppb. The thyroid parameters i.e., serum TSH, FT4, and thyroglobulin were analysed using the Roche Cobas e−411 platform by manufacturer protocols and standard clinical laboratory methods. The detection limit for each assay was as follows: Elecsys TSH 0.005–100 mIU/L; Elecsys FT4 III 0,04–7.77 ng/dL; and Elecsys Tg II measuring range 0.04–500 ng/mL. The normal reference ranges according to the manufacturer were 0.270–4.20 mIU/L; 0.93–1.7 ng/dL; and 3.5–77 ng/mL for TSH, FT4, and thyroglobulin, respectively. All of the test procedures were conducted by Prodia Occupational Health Center, Cikarang, Indonesia. The ratio of thyroglobulin to FT4 is the result of a direct calculation of the thyroglobulin value multiplied by 100, as a unit conversion, divided by the FT4 value.

2.5. Statistical analysis

The analysis was performed using SPSS 20 for Windows. The characteristics of the study population were described using mean (SD) or median (minimum-maximum). The Mann-Whitney *U* test was used to measure the difference in the TSH concentrations of the study population according to individual and occupational characteristics. All p-values were two-sided, with significance considered at $p < 0.05$ for these tests. Multiple linear regression analysis was used to examine the association between TSH and its potential determinants, including Tg/FT4 ratio, FT4, age, sex, smoking habits, CEL, and occupational characteristics. Age, sex, and smoking habits which are known as the factors that may affect TSH concentrations [25,26] were included in the multivariate model together with the variables associated with TSH at a significance level of $p \leq 0.20$ in the simple regression analysis. Following the stepwise procedure, all contributing variables associated with TSH at a significance level of 0.05 were retained in the final model as the determinants of TSH. Since the tolerance score was well above 0.2 and the variance inflation factor scores were below 10, we suggest no multicollinearity in our data. The residual values in our model were independent because the obtained Durbin-Watson statistics value was very close to 2.

2.6. Ethics approval

The Ethical Committee of the Faculty of Medicine Universitas Indonesia approved the study protocol on March 23, 2020 (No. KET-339/UN2.F1/ETIK/PPM.00.02/2020). Informed consent was confirmed by the Ethical Committee. Written informed consent was obtained from all participants.

Table 1
Characteristics of the study population.

Characteristics (n = 151)	Description
Body mass index (kg/m^2)	22.9 (2.9)
Urinary iodine excretion (μg/L)	173.5 (118.5–254.2)
TSH (mIU/L)	1.46 (0.87–2.03)
Thyroglobulin (ng/mL)	7.87 (3.94–13.32)
FT4 (ng/dL)	1.17 (1.07–1.31)
Thyroglobulin (Tg)/FT4 ratio (x 10^2)	6.23 (3.86–10.92)
Lifetime years of pesticide use (year)	25 (18–30)
Number of days spraying per year (day)	104 (61–146)
Cumulative exposure level (x 10^3)	25.95 (15.65–43.13)
Post-spraying days (day)	1 (1–3)
Arable land area (acres)	0.20 (0.11–0.25)
Daily work duration (hours)	6 (6–7)
Duration of spraying pesticide (hours/day)	0.43 (0.29–0.80)
Volume of the mixture applied (litre/day)	19.2 (12.0–32.0)

Values are presented as mean (standard deviation) or median (1st quartile–3rd quartile).

3. Results

A total of 151 vegetable farmers were included in this study. The mean (standard deviation; SD) age was 50 (SD 9.4) years. Among them, 137 (91%) were male; 143 (95%) were married; 131 (87%) had a low educational level; 73 (48%) were smokers, 71 (47%) were classified as high CEL group and only 9 (6%) used CPF as the sole pesticide. Regarding the use of PPE during pesticide handling, the most frequently used PPE was boots worn by 58% of the participants, whereas 15% of our study participants reported never using PPE.

The characteristics of the study population were shown in Table 1.

The median concentration of urinary iodine excretion among our study population was adequate. Our study population has been using pesticides for about 25 years and the number of days spraying per year is considered high since they were regularly exposed to pesticides about 2 days per week throughout the year.

Significantly higher median TSH concentrations were observed in the high CEL group and among those who used ≤2 additional pesticides to CPF as described in Table 2. In addition, the description of the FT4 and Tg/FT4 ratio according to participant characteristics were presented in Table S1. Using simple linear regression (Table S2), we found several variables to be associated with TSH at a significance level of $p \leq 0.20$ and therefore were included in the multivariate model. Following the stepwise procedure, Tg/FT4 ratio, CEL, FT4, post-spraying days, and UIE were retained in the final model as the determinants of TSH. The results were shown in Table 3.

4. Discussion

The mean age, the median lifetime years of pesticide use, and the number of days spraying per year suggest that the farmers in our study have lived most of their lives in this profession and the agricultural methods as well as all their work practices have been implemented over many years.

Our findings show that Tg/FT4 ratio, CEL, FT4, UIE concentrations, and post-spraying days were determinants of serum TSH concentrations among our study participants, indicating a potential effect of pesticide exposure on the thyroid. The majority of epidemiological studies published so far that address the thyroid impacts on pesticide-exposed farmers reported decreased circulating thyroid hormones and increased TSH concentrations. A decrease in total T3 accompanied by an increase in TSH concentrations was reported to be associated with total OP metabolites, suggesting that exposure to OP may play an important role in thyroid disruption [27]. Another study reported an association between the TCPy, a specific metabolite of CPF, and increased TSH levels and also a suggestive inverse association to FT4 in their study population [28]. Among the adult male sprayer, exposure to OP and organochlorine pesticides may be responsible for increasing TSH levels and decreasing T3 and T4 serum hormone levels [20]. Similar conditions were found in another study showing thyroid function, particularly in men, was found to be affected by both cumulative and recent occupational exposure to agricultural pesticides, resulting in an increase in TSH accompanied by a decrease in FT4 [21]. The lifetime use of several pesticides among male pesticide applicators in the Agricultural Health Study was also found to be associated with increased TSH levels [29]. Additionally, the evidence of structural damage to thyroid follicles due to CPF exposure has also been previously reported [30,31]. Animal studies suggest that chlorpyrifos is associated with thyroid disruption. *In vivo*, a mouse study reported that CPF could induce thyroid alterations with decreased T4 levels and increased cell height in dams [32]. Another rat study showed a similar result with a decreased serum T3 and T4 and an increase of TSH that was postulated to be attributed to structural damage of CPF to thyroid tissue [33].

Thyroid hormone synthesis starts with the anterior pituitary secretes TSH in response to feedback from circulating thyroid hormone which stimulates the thyroid gland to produce thyroid hormone. The TSH regulates iodide uptake so that the iodination of selected

Table 2
Comparison of serum TSH in study participants grouped according to the pesticide-exposed activities.

Variable	n	TSH[a]	p-value[b]
Type of knapsack sprayer			
Manual pressurized	35	1.69 (1.15–1.99)	0.189
Motorized	116	1.36 (0.83–2.17)	
Spraying time			
Other than morning	60	1.36 (0.77–1.87)	0.076
Morning time	91	1.53 (0.97–2.23)	
Additional pesticides to CPF			
> 2 pesticides	44	1.18 (0.75–1.84)	0.023
≤ 2 pesticides	107	1.51 (0.97–2.28)	
Re-enter the treated farm area			
Frequent	33	1.16 (0.91–1.75)	0.349
Rare/never	118	1.49 (0.85–2.18)	
Direct contact with pesticides			
Frequent	110	1.45 (0.87–2.01)	0.576
Rare/never	41	1.48 (0.86–2.34)	
Cumulative exposure level			
High	71	1.79 (1.02–2.57)	0.001
Low	80	1.19 (0.80–1.75)	

[a] Median (1st quartile–3rd quartile) in mIU/L.
[b] From Mann-Whitney *U* test.

Table 3
Multiple linear regression analysis of the association between TSH and potential determinants.[1].

Variables[2]	B	SE (B)	Beta	95% CI for B (LL; UL)	*p*-value
Constant	1.95	0.34		1.28; 2.61	<0.001
Tg/FT4 ratio (x 10^2)	0.07	0.01	0.45	0.05; 0.09	<0.001
Cumulative exposure level	−0.58	0.18	−0.22	−0.94; −0.23	0.002
Post-spraying days (day)	0.16	0.05	0.20	0.06; 0.26	0.003
UIE (μg/L)	−0.002	0.001	−0.15	−0.003; < −0.001	0.026
FT4 (ng/dL)	−0.39	0.18	−0.14	−0.74; −0.03	0.033

TSH, Thyroid stimulating hormone; B, parameter estimate; SE (B), standard error for B; CI, confidence interval; LL, lower limit; UL, upper limit; Tg, thyroglobulin; UIE, urinary iodine excretion; FT4, free thyroxine.
[1] $R^2 = 0.38$; Adjusted $R^2 = 0.36$.
[2] Tg/FT4 ratio, post-spraying days, UIE, FT4 (continuous variable); cumulative exposure level: high (reference) or low.

tyrosine from thyroglobulin, a large glycoprotein that functions as an iodide store and plays an important role in thyroid hormonogenesis, can be initiated and followed by a series of steps of thyroid hormone synthesis [34–36]. Since most steps involved in thyroglobulin biosynthesis and secretion are TSH-dependent, thus thyroglobulin concentrations will increase following the TSH stimulation during the synthesis of TH [26].

We observed in our study that higher CEL was associated with higher median TSH concentrations. The median Tg/FT4 ratio in the high CEL group was also significantly higher compared to those in the low CEL group indicating more hormonal imbalance with higher exposure. Therefore, we discussed the possibility that the farmers were exposed to the potential thyroid-disrupting substance. The FT4 concentrations were negatively associated with TSH, while Tg/FT4 ratio was positively associated with TSH. This situation raises the opinion that thyroid follicular damage due to CPF exposure has a more significant adverse effect on thyroid hormone synthesis than the thyroglobulin synthesis pathway. Using the argument that CPF causes damage to the thyroid follicular epithelium, it was thought that the thyroid hormone and thyroglobulin synthesis process runs under non-optimal conditions. The disruption in thyroid hormone synthesis leads to a relatively low thyroid hormone production and low circulating thyroid hormone, thus, a feedback mechanism to the anterior pituitary has occurred that results in increased TSH secretion. Therefore, increased TSH levels and Tg/FT4 ratio are considered potential factors indicating thyroid disruption due to CPF exposure. This phenomenon was observed in this study and also explains that the Tg/FT4 ratio is the main factor contributing to TSH levels in multiple linear regression analysis.

The post-spraying days were positively associated with TSH concentrations, the longer post-spraying days lead to higher TSH. We considered these findings to suggest that farmers were exposed to certain levels of pesticide exposure that have the potential to cause chronic or cumulative effects rather than acute effects on the thyroid. We also found that UIE was negatively associated with TSH concentration. UIE is a useful assay for assessing iodine intake since in adults most dietary iodine is eventually excreted in the urine. Thus, the median concentration of UIE reflects the optimal iodine intake among our study population. Iodine deficiency, indicated with UIE below 100 μg/L in the population, is associated with serum TSH concentration. Conversely, excess iodine will subsequently be associated with decreased TSH [37–39].

Our study population used CPF during their agricultural activities, and 94% of participants reported using two or more pesticides. A similar condition for farmers using multiple pesticides was also found in other countries [5,40]. Although additional pesticides were not found to be significant in the final regression model, we observed in the present study that farmers who applied ≤2 additional pesticides had higher TSH concentrations. This result leads to the assumption that fewer additional pesticides used by farmers may be followed by an increase in the amount of CPF used as the primary pest control agent. Furthermore, the tendency to use complex mixtures of pesticides in agricultural practice should remain a concern because of the potential interaction of the mixtures used, the possibility of acute toxicity associated with the unsafe use, and also makes it almost impossible to determine a single pesticide or class as the causative agent of thyroid disruption. This is due to the multiple modes of action involved and the fact that each chemical can interfere with one another resulting in complex dose-response interactions [41].

Smoking is associated with several health problems. Although we found no difference in TSH concentrations according to smoking status, previous studies have reported the relationship between smoking and thyroid function. Cigarette smoking is associated with decreased thyroid peroxidase antibody (TPOAb) which may lead to disruption in thyroid hormone synthesis [42]. However, the exact mechanism remains unclear that requires further study. As smoking during pesticide spraying is a common practice in agricultural settings [43,44], the potential of oral exposure to pesticides can also occur if contaminated hands are not washed properly before such activity, making it an important risk factor.

The measurement of multiple thyroid parameters i.e., TSH, FT4, and thyroglobulin to characterize the altered thyroid function was a strength of our study as it represents an important marker in thyroid hormone synthesis. However, we realize that autoimmune thyroiditis is one of the most important causes of hypothyroidism and one of the markers of autoimmune thyroid disease is the detection of TPO antibodies that affect the inhibition of TPO in thyroid hormone synthesis [45]. In this study, TPO antibodies were not tested to analyse the possibility of the participants suffering from autoimmune thyroiditis, thus, the role of TPO antibodies in thyroid disorders among CPF pesticide sprayers cannot be ruled out. The use of validated quantitative methods for CEL estimation supported by detailed information on occupational characteristics of pesticide exposure was also the strength of our work. However, we recognize the possibility of misclassification of exposure estimates due to the self-reported participants' information persists. We did not observe the exact quantity of CPF or other pesticides as well as the composition of the mixture used by the farmers. Occupationally exposed farmers may also be exposed to pesticides by consuming contaminated food and drink, however, the information on daily food consumption was not collected. In addition, it is known that certain foods may affect iodine levels which is important in thyroid biosynthesis. We acknowledge these as the limitations of our study. Apart from the potential interactions of a complex mixture of pesticides used by the farmers, another limitation regarding our cross-sectional study design made it difficult for us to establish a causal relationship between CPF exposure and thyroid disruption. Nevertheless, the limitations inherent in our study warrant further studies to confirm our findings by emphasizing the causal relationship between CPF exposure and thyroid disruption.

This study evaluated the TSH, FT4, and thyroglobulin concentrations among Indonesian vegetable farmers with primary exposure to CPF. The Tg/FT4 ratio, CEL, FT4, UIE concentrations, and post-spraying days were determinants of TSH concentrations among our study participants. Our findings show that those with higher CEL were associated with higher TSH concentrations. These results indicate that farmers were exposed to agents with thyroid-disrupting properties, thus supporting previous evidence showing the potential for thyroid disorders in agricultural populations exposed to pesticides. We recommend that pesticide exposure management will benefit farmers' health conditions, especially their thyroid health. Exposure control through training and assistance in the selection of pesticides, comprehensive pesticide management accompanied by continuous assistance, and encouraging the use of PPE and adequate work clothes for farmers and pesticide sprayers in particular will result in reduced exposure. Reducing the exposure levels would allow a significant benefit to the potential health effects of pesticide exposure, particularly on thyroid function. Furthermore, a periodic medical examination that emphasizes thyroid parameters, i.e., TSH and Tg/FT4 ratio may be considered for early detection of thyroid disorders.

Author contribution statement

Jen Fuk Liem; Imam Subekti: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Muchtaruddin Mansyur, Dewi S. Soemarko, Aria Kekalih: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Franciscus D. Suyatna; Dwi A. Suryandari; Safarina G. Malik; Bertha Pangaribuan: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16435.

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