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Pesticide Exposure and Thyroid Function in Elementary School Children Living in an Agricultural Area, Brebes District, Indonesia

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Abstract

Background: Children living in agricultural areas are at risk of exposure to pesticides due to their involvement in agricultural activities. Pesticides are one of the chemicals classified as endocrine disrupting chemicals.

Objective: To examine the association between exposure to organophosphate pesticides and the occurrence of thyroid dysfunction in children.

Methods: This cross-sectional study was conducted on 66 children in two elementary schools located in an agricultural area in Brebes District, Indonesia, in 2015. To determine the pesticide exposure history, we analyzed urine samples and completed a questionnaire. Meanwhile, thyroid function tests were performed.

Results: Organophosphate pesticide metabolites were detected in urine samples of 15 (23%) of 66 children. Thyroid stimulating hormone (TSH) levels >4.5 μIU/mL were detected in 24 (36%) children. Free thyroxine (FT4) levels of all participants were normal. The mean TSH level in children with positive urinary organophosphate pesticide metabolites (7.74 μIU/mL) was significantly (p=0.005) higher than that in those who were negative (4.34 μIU/mL). The prevalence of hypothyroidism in children with positive urinary organophosphate pesticide metabolites (67%) was significantly higher than that in those who were negative (27%; PR 2.4, 95% CI 1.4 to 4.3).

Conclusion: A history of pesticide exposure could be used as a risk factor for the occurrence of thyroid dysfunction in children living in agricultural areas.

Keywords: Pesticides; Thyroid function test; Child; Agriculture; Indonesia; Organophosphates; Hypothyroidism

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Introduction

Children living in agricultural areas are at risk of exposure to pesticides due to their involvement in agricultural activities. Pesticides are heavily used in Brebes District, one of the agricultural areas in the province of Central Java, Indonesia. Our previous study, conducted in 2014, shows that more than 80% of the elementary school children in these areas are routinely involved in agricultural activities.[1] Pesticides are one of the chemicals classified as endocrine disrupting chemicals (EDCs).[2] Exposure to EDCs interrupts a number of hormonal functions including those of thyroid, insulin, and insulin-like growth factor-1 (IGF-1) hormones.[2,3] Organophosphate, carbamate, and pyrethroid are amongst the most commonly used pesticides in agricultural activities.[4] A study conducted in Mexico shows that exposure to organophosphate pesticides (OPs) induces adverse effects on thyroid functions in farmworkers. More specifically, exposure to OPs increases both thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels and decreases triiodothyronine (T3) levels.[5]

In children, thyroid dysfunction, especially hypothyroidism, can result in disturbed metabolic functions that affect the growth and development; it also leads to metabolic abnormalities similar to those in adults.[6] Our previous study indicates that a history of pesticide exposure is a risk factor for hypothyroidism among women at childbearing age residing in an agricultural area in Brebes District.[7] In addition, data collected from Brebes District Health Office show that the prevalence of goiter among elementary school children living in agricultural area is more than 50% (Health Office of Brebes District, unpublished data 2011).[8] To date, higher rates of goiter are always associated with iodine deficiency.[9] However, our previous study demonstrates that iodine intake among people living in the agricultural areas in Brebes District is normal and sufficient.[7] These findings made us suspicious that the main cause of thyroid disorders in our region may not be iodine deficiency.

The impact of pesticides on an endocrine system is through a multitude of specific mechanisms that can target different levels of the hypothalamic-pituitary-gonad/thyroid/adrenal axes, ranging from effects on hormone receptors to effects on hormone synthesis, secretion or metabolism. Therefore, they can have far-reaching health implications throughout the life course.[2,10] Studies of the impact of pesticide exposure on thyroid function in adults have been previously conducted but there is a paucity of information about the thyroid function in children living in agricultural areas. We conducted this study to investigate the problems related to pesticide exposure and thyroid dysfunction, especially hypothyroidism among elementary school children living in an agricultural area.

Materials and Methods

This was a cross-sectional study. The study population was elementary school-aged children living in agricultural areas. Data were collected over two periods—March to May 2015 and August to October 2015, in accordance with the academic schedule of each selected elementary school.

All students from two elementary schools at subdistrict of Bulakamba in Brebes District were studied. These two schools were located in an agricultural area where goiter was prevalent and pesticide was used ubiquitously (Health Office of Brebes District, unpublished data 2011). The main agricultural commodities in these area were shallots with very frequent and intensive use of pesticides. In addition, the distance between houses,

schools, and farmland are close together, with a total area of approximately 251 000 hectares.

The study was conducted on 75 purposively selected participants from grades 4 and 5. These grades were chosen because in Brebes District children in these grades were generally involved by their parents in agricultural activities. Moreover, children in these grades, mostly aged 8–10 years, were vulnerable to growth and development disorders due to thyroid dysfunction.[11] Sixty-six (89%) of 75 children completed the questionnaires, and gave urine and blood samples. The pesticide exposure was measured by two methods—interviewing about children's involvement in agricultural activities, and analyzing urinary OPs metabolites, dialkyl phosphate (DAP), as OPs were the most widely used pesticides in the studied agricultural areas.

Interview

Interviews with children were conducted during home visits by two trained interviewers using a content validated questionnaire. Questionnaire validation was performed by content validation by experts working at an agricultural office of Brebes District. Each child was asked four questions about pesticide exposure history, specifically the characteristics of children, the habits of children playing on the farms, the involvement of children in agricultural activities, and the types of child engagement in agricultural activities such as looking for caterpillar pests, weeding grass or plant pests, bringing the harvest home, and removing shallots stems.

Assessment of Urinary OPs Metabolites

Morning spot urine specimen was collected and stored at 2–4 °C or kept frozen until they were shipped on dry ice to the laboratory. Six urinary DAP metabolites, resulting from the degradation of at least 28 OPs, were measured in the urine sample as an indicator of the body burden of common OPs.[12] The urinary DAP metabolites consisted of 3-dimethyl alkyl-phosphate (DMAP) molecules, namely dimethyl-phosphate (DMP), dimethyl-thio-phosphate (DMTP), and dimethyl-dithio-phosphate (DMDTP), and 3-diethyl alkyl-phosphate (DEAP) molecules, namely diethyl-phosphate (DEP), diethyl-thio-phosphate (DETP), and diethyl-dithio-phosphate (DEDTP). DMAP metabolites were derived from O, O-dimethyl-substituted OP pesticides such as malathion; DEAP metabolites result from the degradation of O, O-diethyl-substituted OPs such as chlorpyrifos. The measurements were performed by lyophilization and chemical derivatization followed by analysis by isotope-dilution gas chromatography-tandem mass spectrometry.[13] Furthermore, if at least one of the six types of dialkyl-phosphate (DAP) was detected in a urine sample, a history of pesticide exposure was categorized as positive.

Thyroid Function Tests

Serum TSH and FT4 levels were measured. TSH was measured according to the manufacturers instruction of a multiplexing kit from Millipore (The Human Pituitary Panel, Cat no. STTHMAG-21K). Based on their TSH level, the studied children were categorized into three groups—normal/euthyroid (0.07< TSH <4.5 μIU/L), hypothyroid (TSH >4.5 μIU/L), and hyperthyroid (TSH <0.07 μIU/L).[14] FT4 was determined by electrochemiluminescence immunoassay, ECLIA (Elecsys FT_4 reagent kit. Cat No. 11731297-200 test).

Ethics

The study protocol was approved by the Ethics Committee on Health Research, Faculty of Medicine, Diponegoro University/Doctor Kariadi Public Hospital, Semarang, Indonesia (Reg. No. 481/EC/FK-RSDK/2015). All participants or their

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Table 1: Characteristics and the involvement of the studied children in agricultural activities (n=66)

Variable	n (%)
Male sex	34 (52)
The main occupation of household heads	
Unemployed	5 (8)
Farmworker	15 (23)
Landowner	10 (15)
Seller/self-employed	36 (55)
The habit of playing on the farm	52 (79)
Involvements in agricultural activities	48 (73)
Types of child engagement in agricultural activities	
Looking for caterpillar pests	5 (8)
Weeding grass or plant pests	11 (17)
Bringing the harvest home	27 (41)
Removing shallots stems	47 (71)

guardians gave written informed consent.

Statistical Analysis

Statistical analysis was performed by SPSS® for Windows® ver16 (SPSS Inc, Chicago, IL, USA). χ^2 test and prevalence ratio (PR) with 95% CI were used to analyze proportion differences of hypothyroidism based on the involvement of the children in agricultural activities and the results of analysis of OPs metabolites. Mann-Whitney U test was used to compare the differences in TSH and FT4 levels based on the involvement of the children in agricultural activities and the results of analysis of OPs metabolites.

Table 2: Results of urinary pesticide metabolites and thyroid function tests in the studied children (n=66)

Variable	n (%)
Pesticide metabolites in urine	
DETP*	6 (9)
DMDTP†	7 (11)
DETP+DMDTP	2 (3)
Overall (Urinary metabolite positive)	15 (23)
Categories of TSH (μIU/mL)	
<0.7 (hyperthyroid)	1 (2)
0.7–4.5 (euthyroid)	41 (62)
>4.5 (hypothyroid)	24 (36)

*Diethyl-thio-phosphate, †Dimethyl-dithio-phosphate

Results

A total of 66 children (34 boys and 32 girls) participated in this study. They had a mean age of 9.2 (SD 0.67) years. More than half of the household heads of the studied children were sellers/self-employed. Most of the children (73%) were involved in agricultural activities; removing shallots stems was the most common activities undertaken by them (71%) (Table 1).

Two metabolites, DETP and DMDTP, were detected in 8 (12%) and 9 (14%) urine samples, respectively. Two (3%) children had both metabolites (Table 2). Overall, 15 (23%) children had urine samples positive for pesticide metabolites. The mean TSH and FT4 levels were 5.2 (SD 4.8) μIU/L, and 17.6 (2.6) pmol/L, respectively. Based on TSH, hypothyroidism was diagnosed in 24 children (36%) children. However, their FT4 levels were within the normal range of 9.0 to 20.0 pmol/L. This condition was categorized as subclinical hypothyroidism. One child with a TSH of 0.007 μIU/L and a FT4 of 26.6 pmol/L was diagnosed with hyperthyroidism.[14]

The prevalence of positive urinary pesticide metabolite in children who were involved in agricultural activities (29%) was higher than that in those who were not (6%) (PR 5.2, 95% CI 0.7 to 37.1). There was no significant difference in the mean TSH and FT4 levels between these groups (p 0.400 and 0.261, respectively). The mean TSH

level in children whose urine samples were found positive for OPs metabolites was significantly higher than those who were negative (p=0.005) (Table 3).

Types of engagement in agricultural activities did not affect the occurrence of hypothyroidism (Table 4). There was a statistically significant (p=0.014) difference in the prevalence of hypothyroidism between children with positive and negative OPs metabolites (67% *vs* 285%, respectively). Presence of DMDTP metabolite in the urine was significantly (p=0.042) associated with occurrence of hypothyroidism (Table 5).

Table 3: Difference in TSH and FT4 mean levels based on children involvements in agricultural activities and in the results of measuring OPs metabolites in urine

	Mean (SD), median	
Variable	**TSH (μIU/L)**	**FT4 (pmol/L)**
Involvements in agricultural activity		
Yes (n=48)	5.6 (5.5), 3.4	16.9 (3.3), 17.0
No (n=18)	3.8 (2.2), 3.4	18.4 (3.3), 17.9
p value*	0.200*	0.494*
Urinary OPs metabolites		
Positive (n=15)	7.7 (7.2), 5.4	16.7 (1.8), 16.9
Negative (n=51)	4.3 (3.7), 3.1	17.5 (2.8), 17.1
p value*	0.005*	0.371*

**Mann-Whitney U test*

Discussion

The results of thyroid function tests revealed that 24 (36%) of 66 studied children suffered from subclinical hypothyroidism. It was much higher than the prevalence of subclinical hypothyroidism in the community (3%–8%).[15,16] A previous study conducted in Pakistan shows that the prevalence of subclinical hypothyroidism in school children aged 6 to 11 years is 8.4%.[17] The impact of subclinical hypothyroidism on children could not be ignored, because it can adversely affect growth and brain maturation with clinical consequences depending on age and the severity of thyroid impairment.[18] If left untreated, subclinical hypothyroidism will frequently progress to be overt hypothyroidism.[19] In addition, subclinical hypothyroidism in children increases the risk of dyslipidemia and atherosclerosis, as well as mortality due to coronary heart disease later in life.[20,21]

The majority of the participants (73%) were involved in agricultural activities such as looking for caterpillar pests, weeding grass or plant pests, bringing the harvest home, and removing shallots stems. These activities increased the risk of contact between the skin and pesticide residues in the environment (water, soil, and agricultural products). Exposure to toxic substances in human can occur via skin, inhalation and ingestion.[22] Exposure to pesticides occurs from agricultural and household use, use of livestock and pets, and through residues in food and water. A survey of school children in Chile found that 80% of the children had metabolites of chlorpyrifos in their urine, and that this was associated with eating fruits and vegetables.[23] In contrast, in this study, pesticide exposure mainly occurred through children's involvement in agricultural ac-

TAKE-HOME MESSAGE

- The majority (73%) of elementary school children living in agricultural areas were involved in agricultural activities.
- More than 20% of these children had pesticide metabolites in their urine.
- The prevalence of hypothyroidism in children living in agricultural areas was 36%.
- Pesticide exposure is probably the main risk factor for hypothyroidism in these children.

Table 4: Distribution of children with hypothyroidism stratified by their involvement in various agricultural activities

Variable	n (%)	PR (95% CI)
Involvements in agricultural activities		
Yes (n=48)	19 (40)	1.4 (0.6 to 3.2)
No (n=18)	5 (28)	
Looking for caterpillar pests		
Yes (n=5)	2 (40)	1.1 (0.4 to 3.4)
No (n=61)	22 (36)	
Weeding grass or plant pests		
Yes (n=11)	3 (27)	0.7 (0.3 to 2.0)
No (n=55)	21 (38)	
Bringing the harvest home		
Yes (n=27)	13 (48)	1.7 (0.9 to 3.2)
No (n=39)	11 (28)	
Removing shallots stems		
Yes (n=47)	19 (40)	1.5 (0.7 to 3.5)
No (n=19)	5 (26)	

tivities. The results of this study demonstrated that children who were involved in agricultural activity were more likely to have a positive urinary pesticide metabolites compared to those who were not (PR=5.2, 95% CI 0.7 to 37.1).

Table 5: Distribution of children with hypothyroidism stratified by the status of their urinary organophosphate pesticides metabolites

Variables	n (%)	PR (95% CI)
Urinary organophosphate pesticide metabolites		
Positive (n=15)	10 (67)	2.4 (1.4 to 4.3)
Negative (n=51)	14 (28)	
DETP*		
Positive (n=8)	5 (63)	1.9 (1.0 to 3.7)
Negative (n=58)	19 (33)	
DMDTP†		
Positive (n=9)	6 (67)	2.1 (1.2 to 3.8)
Negative (n=57)	18 (32)	

*Diethyl-thio-phosphate, †Dimethyl-dithio-phosphate

We also found that children with OPs metabolites in their urine were 2.4 times more likely to suffer from hypothyroidism compared to those whose urine was found negative for OPs metabolites. This finding was in line with previous studies that reported pesticide exposure results in minor disturbances in thyroid hormone levels among greenhouse worker,[24] and that there was elevated level of TSH and significantly low levels of T3 in a few pesticide formulators in India.[25] Both DETP and DMDTP metabolites in the urine increased the risk of hypothyroidism in children living in agricultural areas (Table 5). DETP is a metabolite of malathion,[13] which is proven to interfere with thyroid function.[26] DMDTP is a metabolite of chlorpyrifos, which has also been proven as a thyroid disruptor.[27] A previous study conducted in Brazil suggested that both cumulative and recent occupational exposure to agricultural pesticides might affect the thyroid function causing hypothyroid-like effects.[28] The mean TSH levels among children who had positive urinary OPs metabolites (7.74 µIU/mL) was significantly (p=0.005) higher than that in those whose urine was found negative for Ops metabolites (4.34 µIU/mL). This result indicated that children with a history of pesticide exposure had a higher possibility of suffering from hypothyroidism. Pesticide can disrupt the synthesis and metabolism of thyroid hormones through several mechanisms: (1) disrupting a TSH receptor (TSH-r) at thyroid gland, inhibiting thyroid hormone synthesis,[29] (2) inhibiting the enzyme deiodinase type I (D1), a catalyst in the transformation of T4 to T3 (an active form of thyroid hormone),[30] (3) competing for binding sites on the thyroid hormone receptor (TH-r) on a target cell due to similarities in chemical structures,[29]

and (4) disrupting the activity of enzyme D3, which functions to transform T4 into reverse-T3 (an inactive form of thyroid hormone), resulting in the lack of the active form of the thyroid hormone (T3) in the body.[29,31]

Our study had several limitations. The cross-sectional nature of the study could only provide evidence for possible association and not for causation. Measurements of a history of pesticide exposure, urinary OPs metabolites, and thyroid function were undertaken at the same time (one-point time approach). Therefore, it is not certain that pesticide exposure occurred prior to the occurrence of hypothyroidism. The number of samples was not large enough.

In conclusion, a history of pesticide exposure could be considered a risk factor for the occurrence of thyroid dysfunction in elementary school children living in agricultural areas. Efforts need to be made to prevent negative effects of pesticide exposure, particularly thyroid dysfunction, in children. Restricting and controlling the use of pesticide should be implemented immediately to prevent the adverse health effects due to pesticide exposure.

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Conflicts of Interest: None declared.

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