

## PESTICIDES EXPOSURE AND THYROID HORMONE LEVELS AMONG AGRICULTURAL WORKERS AND PESTICIDE APPLICATORS: A SYSTEMATIC REVIEW

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### Article Info

Submitted : 22 May 2022  
In reviewed : 27 June 2022  
Accepted : 13 July 2022  
Available Online : 31 July 2022

**Keywords :** Pesticides exposure, Thyroid disruption, Thyroid stimulating hormone, Thyroxine, Triiodothyronine

**Published by** Faculty of Public Health  
Universitas Airlangga

### Abstract

**Introduction:** Presently, the global consumption of pesticides including insecticides, herbicides, and fungicides to protect crops is increasing. Pesticides' role as Endocrine-Disrupting Chemicals (EDCs) has gained great concern in the field of thyroid hormones. Therefore, this systematic review aimed to determine the link of pesticide exposure with thyroid hormone levels among male agricultural workers and pesticide applicators. **Discussion:** It was discovered that the majority of reviewed articles have similar results concerning the effects of pesticide exposure on the serum levels of thyroid hormones among either farmworkers or pesticide applicators. Commonly, insecticides, herbicides, and fungicides are known as one of the EDCs. The results showed the elevation of TSH and T<sub>4</sub> serum levels mostly occurred among groups exposed to insecticide application only rather than those exposed to various pesticide types. Moreover, the hormonal change differed based on each class of pesticide. **Conclusion:** This review suggests that some types of pesticides extensively used in agriculture might be involved in the increase and decrease in thyroid hormone levels among exposed individuals. Further studies should assess specific types of pesticides and the adverse health effects which involve confounding factors to yield robust analysis.

## INTRODUCTION

Agrochemicals are various types of chemical substances applied extensively in agriculture for many purposes, namely to control different insects using insecticides, destroy weeds and unwanted plants with herbicides, prevent fungal growth through fungicide application, control rodents such as mice and rats using rodenticides, and to increase agricultural productivity (1-2). All human populations in the world are not completely free from exposure to pesticides that lead to the occurrence of either acute or chronic diseases (3). Currently, the consumption of pesticides to protect crops is rising particularly in developing countries even though some kinds have been banned due to the toxicological effects generated (4-5). Many of these chemicals have long half-lives, meaning they persist in the environment for a long period after being applied (5). Legacy pesticides are chemicals that have been used for a long

time, and they can be harmful to the environment (5). Of the 287 pesticides evaluated by the European Food Safety Authority (EFSA), over 100 showed signals of thyroid dysfunction (5). In terms of insecticides, there are five classifications used in the agricultural sector based on their modes of action and chemical structures, namely organochlorines, organophosphates, carbamates, pyrethroids, and neonicotinoids (6). Organochlorines are one of the pesticides commonly used in eradicating disease vectors and pests in the agricultural sector and households, as well as for public health (7). Even though developed countries have started to forbid the application of organochlorine compounds for agricultural purposes due to their ecotoxicity, adverse health effects, and environmental persistence, they are still used by some countries (8). The organophosphates are also employed extensively to control pests and protect crops, thereby causing broad exposure to low levels of the chemical

### Cite this as :

Suratman S, Suhartono S. Pesticides Exposure and Thyroid Hormone Levels Among Agricultural Workers and Pesticide Applicators: A Systematic Review. *Jurnal Kesehatan Lingkungan*. 2022;14(3):178–192. <https://doi.org/10.20473/jkl.v14i3.2022.178-192>

among general populations (9). In the past, carbamate insecticides were greatly applied in the farming sector and households but they were banned due to the adverse health effects produced (10). Meanwhile, since the application of organophosphates has been restricted, pyrethroids as synthetic insecticides are largely used by farmers or different households (10). Furthermore, neonicotinoid insecticides, known as neonics, are the newest types employed in agriculture, particularly for fruits, vegetables, and grains, as well as in industries, homes, and veterinary settings since the 1980s (11-12). Presently, seven active constituents of the neonicotinoid are available in the market namely imidacloprid, dinotefuran, acetamiprid, thiamethoxam, nitenpyram, clothianidin, and thiacloprid (12). Even though the toxicity level of this insecticide in humans and mammals is lower than the other types, they are suspected to accumulate in foods or in the environment which in the long-term can produce harmful effects (13).

A study in Indonesia reported that pesticide sprayers applied various types of insecticides such as organophosphate, carbamate, and pyrethroid with different active constituents including mancozeb, heptachlor, aldicarb, chlorpyrifos, cypermethrin, and dichlorvos (14). This condition leads to an increase in the number of people specifically farmworkers and their families exposed to pesticides either during agricultural activities or at home even though proper personal protective equipment is worn (4). Some studies demonstrated a significant relationship between pesticide exposure and cancer risks (15-17), which include diseases persisting for a long time, such as insulin-dependent (6, 18-20), cardiac (21-22), and neurological disorders (23-24). Thyroid hormone disruption can cause organ disorders that are linked with many diseases (25). Besides, environmental chemicals, for example, heavy metals including mercury, lead, arsenic, and fluoride are available in the form of pesticides or synthetic organic chemicals and can act as Endocrine-Disrupting Chemicals (EDCs) (26). They can disrupt the hypothalamus–pituitary–thyroid axis, in combination or individually (5). EDCs are known as chemical substances that tend to distort some receptors like Thyroid Hormone (TR), Peroxisome Proliferator-Activated Receptors (PPARs), and estrogen (27). Thyroid hormones including triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) play a crucial role in cell homeostasis by regulating various physiological processes such as organ development, and cellular and body metabolism (25).

Currently, pesticides' role as EDCs has gained great concern in the field of thyroid hormones (28). EDCs

are interpreted as substances originating externally and capable of changing the endocrine system function and causing harmful effects on the exposed population (29-30). These chemicals interfere with hormone action and can change endocrine function which causes harmful effects on human and wildlife health (29). Some kinds of pesticides that are suspected to disrupt the endocrine include insecticides namely organophosphate, pyrethroids, and neonicotinoids, and fungicides such as triazoles, bifonazole, imazalil, and flusilazole (30). The other type of insecticides such as Organochlorine Pesticides (OCPs) has a similar structure to  $T_3$  and  $T_4$ . Therefore, it may act as a thyroid hormone by binding the receptors, leading to thyroid disorders (28).

Compared to other environmental chemicals such as Polychlorinated Biphenyls (PCBs) and Polybrominated Diphenyl Ethers (PBDEs), generally, the degree of pesticides' structural similarity to thyroid hormones is not high, hence there is less investigation of pesticides as TR binders (31). Occupational exposure to EDCs is one of the major causes of thyroid hormone disorders among male farmworkers and pesticide applicators who are included in the population at risk of exposure to pesticides in their working area. Agricultural workers and pesticide applicators have the greatest exposure to Highly Hazardous Pesticides during handling, dilution, mixing, and application (32). These agrochemicals enter the human body through various routes including Inhalation, ingestion, or dermal penetration (33). Occupational exposure to pesticides particularly organochlorine, organophosphate, and pyrethroids demonstrate an association with adverse health effects among male workers such as type 2 diabetes, prostate cancer, a decrease in semen quality, and reduced testosterone production (27). Therefore, this systematic review aimed to determine the link of pesticide exposure with thyroid hormone levels among male agricultural workers and pesticide applicators. The novelty of this systematic review is an identification of the alteration in thyroid hormone levels among the high-risk groups exposed to pesticides particularly male agricultural workers and applicators based on previous studies.

## DISCUSSION

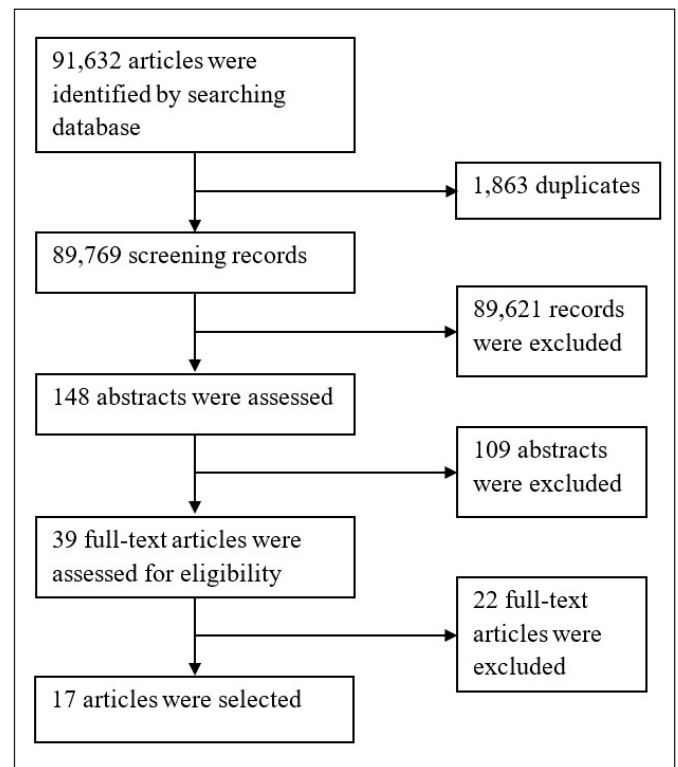
The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (34) were applied for observational studies to determine the association between exposure to pesticides, including insecticide, rodenticide, herbicide, and fungicide, and the

changes in thyroid hormones levels among agricultural employees (farmers or farmworkers) and pesticide applicators or formulators.

A systematic search of original articles was performed from Science Direct (86,946 articles), PubMed (4,478), BMJ (1), BMC (3), and Proquest (204) using the following keywords: “pesticide” OR “pesticide exposure” AND “endocrine” OR “thyroid hormones” AND “male farmer” OR “male farmworker” OR “male pesticide formulators” OR “male pesticide applicators” during the periods of 2010-2021. Some criteria were considered for this purpose namely a) original articles with cross-sectional, case-control, or cohort designs and b) studies focusing on all types of pesticides used in agriculture. Others were c) well-defined pesticide exposure and d) studies focusing on exposure among male groups of farmers, farmworkers, and formulators or applicators.

The articles’ quality was determined by assessing the methodological quality, particularly for observational studies on up to 17 of 27 items arranged by Downs and Black (35) including the following parameters, namely clear descriptions of hypotheses or aim or objective, key results, and participants’ attributes. Others are crucial confounders’ distributions, major discoveries, approximations of the random variability, the attributes of participants difficult to find, values of absolute likelihood, sample representativeness, participants recruitment over the same period and from the same population, and appropriateness of statistical analyses. A score of zero was provided when a study did not fulfill certain determined parameters. Specifically for crucial confounders, a score of two was assigned while it was in accordance with a required parameter, and one when partially fulfilled, and the maximum score was 18 points.

Based on titles and abstracts of 91,632 articles identified, there were 1,863 duplicates, 89,621 were not related to the study subject which included qualitative study, populations such as prenatal groups, neonates, children, women, and animals, or outcomes different from thyroid hormone levels, and 109 review articles were excluded. After continuing to read the remaining 39 articles, another 22 were excluded due to being a non-representative sample and outside the topics, while 17 manuscripts were selected (Figure 1).



**Figure 1. Preference of Papers with the Topics of Pesticide Exposure and Thyroid Hormone Levels on Male Groups of Farmers, Farmworkers, and Pesticide Formulators or Applicators.**

Article scores based on quality assessment of D&B ranged from 15 to 17 points. Five articles had D&B scores below 16 (36-40) mainly due to no description of follow-up losses and the p-value was not reported (37-40) as demonstrated in Table 1.

Of the 17 selected articles, four were cross-sectional, five were case-control, seven were longitudinal studies including cohort, and one was experimental. Four studies were conducted in Thailand, three each in the United States of America and Brazil, two in Pakistan, and the others from Mexico, Algeria, Iran, Romania, and Palestine. Sixteen studies were related to exposure to various types of pesticides (insecticides, fungicides, and herbicides), and one was based on just one type (insecticide) as presented in Table 1.

According to Table 1, 11 articles evaluated pesticide exposure among male farmers or farmworkers (37-47) and six studies were conducted with either pesticide applicators or sprayers (36, 48-51).

**Table 1. The Association of Pesticide Exposure with Thyroid Hormone Levels**

Author/year Country	Study Design/ Downs and Black	Sample	Thyroid Hormones Outcome/ Exposure	Measurement (95% CI)	Results of Effects	Adjusted Factors	Conclusion
Lacasana M, Lopez-Flores I, Rodriguez-Barranco M, Aguilar-Garduno C, Blanco-Munoz J, Perez-Mendez O, et al. (2010) (41) Mexico	Longitudinal study/ D&B – 16 (no description of following up drop-out participants)	136 male floriculture workers in the rainy season and another 84 in the dry season	<b>Outcome:</b> Serum levels of Thyroid Stimulating Hormone (TSH), Total Triiodothyronine (T <sub>3</sub> ), and Total Thyroxine (T <sub>4</sub> ) <b>Exposure:</b> Insecticide (organophosphate)	TSH (mIU/ml) T <sub>3</sub> (ng/dl) T <sub>4</sub> (µg/dl)	<b>Geometric Mean ± SD</b> Rainy season: 4.4 ± 1.9 Dry season: 2.8 ± 1.4 p-value: <0.001 Rainy season: 78.0 ± 15.2 Dry season: 77.5 ± 14.8 p-value: 0.57 Rainy season: 9.0 ± 3.2 Dry season: 5.8 ± 6.6 p-value: <0.001	-	TSH and T <sub>4</sub> geometric mean levels during the rainy season were significantly higher than during the dry season. In contrast, T <sub>3</sub> levels did not statistically differ between both periods.
Khan DA, Ahad K, Ansari WM, Khan H (2011) (36) Pakistan	Case-Control/ D&B – 15 (no description of following up drop-out participants; the population of participants was not homogenous)	42 male spray applicators 46 control group (cotton pickers)	<b>Outcome:</b> Serum levels of TSH, Total Triiodothyronine (TT <sub>3</sub> ), and Free Thyroxine (FT <sub>4</sub> ) <b>Exposure:</b> Insecticides (organophosphate, organochlorine, pyrethroid)	TSH (mIU/L) TT <sub>3</sub> (nmol/L) FT <sub>4</sub> (pmol/L)	<b>Mean (Range)</b> Case : 1.35 (0.9-1.85) Control : 1.05 (0.58-1.70) p-value : 0.167 Case : 2.0 (1.8-2.3) Control : 1.9 (1.7-2.0) p-value : 0.113 Case : 10.1 (9.4-11.0) Control: 10.3 (9.1-11.4) p-value : 0.648	▪ Age ▪ Sex	The levels of thyroid hormone among exposed participants to insecticides were statistically relatively the same as the unexposed group.
Slimani S, Boulakoud MS, Abdennour C (2011) (37) Algeria	Case-Control/ D&B – 15 (no reported p-value; no description of following up drop-out participants)	20 male free-air field workers 20 male greenhouse workers 20 male unexposed workers	<b>Outcome:</b> Serum levels of TSH, TT <sub>3</sub> , and FT <sub>4</sub> <b>Exposure:</b> Pesticides	TSH (mIU/mL) TT <sub>3</sub> (pmol/L) FT <sub>4</sub> (pmol/L)	<b>Mean</b> Free-Air workers: 1.5 Greenhouse workers: 2.5 Control: 1.0 p-value: - Free-Air workers: 5.3 Greenhouse workers: 5.3 Control: 5.4 p-value: - Free-Air workers: 13.5 Greenhouse workers: 13.4 Control: 13.9 p-value: -	▪ Age	The levels of FT <sub>3</sub> among all exposed groups were relatively the same as those in the other group. Notwithstanding, FT <sub>4</sub> levels among the exposed groups slightly declined in contrast with the unexposed. Serum TSH levels significantly rose in the greenhouse male workers compared to the other groups.
Goldner WS, Sandler DP, Yu F, Shostrom V, Hoppin JA, Kamel F, et al. (2013) (52) The United States of America	Prospective Study/ D&B – 16 (no description of following up drop-out participants)	22,246 male pesticide Applicators	<b>Outcome:</b> Hypothyroidism Hyperthyroidism 'Other' thyroid disease <b>Exposure:</b> 50 Specific Pesticides (Fumigants, Fungicides, Herbicides, and Insecticides)	<b>Hypothyroid</b> Herbicides: 2,4-D 2,4,5-T 2,4,5-TP Alachlor Dicamba Petroleum oil <b>Insecticides:</b> <b>Organochlorine</b> Chlordane DDT Heptachlor Lindane Toxaphene <b>Organophosphate</b> Diazinon Malathion <b>Carbamate</b> Carbofuran	<b>OR 95%CI</b> 1.35 (1.04-1.76) 1.38 (1.12-1.69) 1.39 (1.06-1.82) 1.24 (1.02-1.5) 1.37 (1.13-1.66) 1.23 (1.02-1.48) 1.36 (1.12-1.66) 1.25 (1.00-1.56) 1.30 (1.04-1.62) 1.35 (1.10-1.66) 1.35 (1.07-1.70) 1.24 (1.02-1.50) 1.29 (1.03-1.62) 1.31 (1.08-1.59)	▪ Age ▪ Education ▪ BMI	The herbicides 2,4-D, 2,4,5-T, 2,4,5-TP, alachlor, dicamba, and petroleum oil and eight insecticides had association with the increase of hypothyroidism. However, the herbicides 2,4,5-TP (OR = 0.46, 95% CI = 0.23, 0.90), butylate (OR = 0.69, 95% CI = 0.49, 0.98), and the insecticide carbofuran (OR = 0.69, 95% CI = 0.49, 0.98) were associated with the decrease of hyperthyroidism.



Author/year Country	Study Design/ Downs and Black	Sample	Thyroid Hormones Outcome/ Exposure	Measurement (95% CI)	Results of Effects	Adjusted Factors	Conclusion
Farokhi F, Taravati A. (2014) (48) Iran	Case-Control/ D&B – 16 (no description of following up drop-out participants)	40 adult male pesticide sprayers 20 controls	<b>Outcome:</b> Serum levels of TSH, T <sub>3</sub> , and T <sub>4</sub>  <b>Exposure:</b> Insecticides (organophosphate and organochlorine)	TSH (mIU/l)  T <sub>3</sub> (nmol/l)  T <sub>4</sub> (µg/dl)	<b>Mean ± SD</b> Sprayers: 2.64 ± 1.51 Control: 1.33 ± 0.83 p-value : 0.007  Sprayers: 1.12 ± 0.52 Control : 1.55 ± 0.57 p-value : 0.018  Sprayers: 9.29 ± 2.12 Control: 10.85 ± 2.82 p-value: 0.091	<ul style="list-style-type: none"> <li>Age</li> <li>Sex</li> </ul>	Exposure to both types of insecticides affected the elevation of TSH levels and the T <sub>3</sub> and T <sub>4</sub> reduction. These types of pesticides generated the occurrence of hypothyroidism among pesticide sprayers.
Simescu M, Igna CP, Nicolaescu E, Ion I, Ion AC, Caragheorghopol A, et al (2014) (38) Romania	Case-Control/ D&B – 15 (no reported p-value; no description of following up drop-out participants)	108 (19 males and 89 females) Greenhouse Workers (GHWs) 27 controls	<b>Outcome:</b> Serum levels of TSH, FT <sub>4</sub>  <b>Exposure:</b> Insecticides (chlorpyrifos, trichloropyridinol (TCP), dimethoate, cypermethrin, carbofuran)	TSH (µIU/mL)  FT <sub>4</sub> (pmol/L)	<b>Mean ± SD</b> GWHs : 2.58 ± 2.71 Control: 1.53 ± 0.86 p-value: -  GWHs : 16.13 ± 3.32 Control: 17.64 ± 2.93 p-value: -	<ul style="list-style-type: none"> <li>Age (18-78 years old)</li> <li>Normal iodine intake</li> <li>Plain village</li> </ul>	Organophosphate and carbamate pesticides could interfere with the thyroid (leading to histopathological damage and functional involvement).
Quraishi R (2015) (42) Pakistan	Experimental/ D&B – 16 (no description of following up drop-out participants)	30 male agricultural workers 30 university students (controls)	<b>Outcome:</b> Serum levels of TSH, T <sub>3</sub>  <b>Exposure:</b> Pesticides	TSH (ng/dl)  T <sub>3</sub> (nmol/l)	<b>Mean ± SD</b>  workers: 1.13 ± 1.02 students: 2.14 ± 0.60 p-value : 0.000  workers: 1.35 ± 0.38 students: 1.22 ± 0.25 p-value : 0.05	<ul style="list-style-type: none"> <li>Age (20-40 years old)</li> </ul>	There was a decrease in TSH levels and an increase in T <sub>3</sub> hormone levels among farming employees. The level of thyroid hormone in farmers working with pesticides was significantly affected.
Piccoli C, Cremonese C, Koifman RJ, Koifman S, Freire C (2016) (39) Brazil	A cross-sectional study/ D&B - 15 (no reported p-value; no description of following up drop-out participants)	Adult agricultural workers (n=275)	<b>Outcome:</b> Serum levels of FT <sub>4</sub> , TT <sub>3</sub> , and TSH  <b>Exposure:</b> Pesticides	Free T <sub>4</sub> (ng/dL)  Total T <sub>3</sub> (ng/dL)  TSH (µIU/mL)	Adjusted regression coefficients (95%CI) for % change in hormone levels  Farmer (ref= non-farmer)  Male : 1.04 (0.96-1.13) Women : 0.94 (0.87-1.02)  Male : 1.06 (1.01-1.12) Women : 0.95 (0.91-1.00)  Male : 0.67 (0.49-0.92) Women : 0.90 (0.69-1.18)	<ul style="list-style-type: none"> <li>Age</li> <li>BMI</li> <li>Current smoking status</li> <li>Alcohol intake</li> <li>Years of education</li> </ul>	A significant reduction of 33% of TSH occurred among male farmers compared to non-farmers. Employees working in an intensive season of pesticide application have a significant relationship with their increased TSH levels.
Al-Shanti TA, Yassin MM (2017) (40) Palestine	Observational study/ D&B - 15 (no reported p-value; no description of following up drop-out participants)	96 male farmworkers exposed to pesticides and another 96 non-exposed controls from different Governorates of Gaza Strip (their ages matched)	<b>Outcome:</b> Serum levels of T <sub>4</sub> , T <sub>3</sub> , and TSH  <b>Exposure:</b> Pesticides	T <sub>4</sub> (µg/dl)  T <sub>3</sub> (ng/dl)  TSH (µIU/ml)	<b>Mean Level</b> Farmworkers : 8.2 Controls : 9.3  Farmworkers : 101.0 Controls : 115.9  Farmworkers : 2.4 Controls : 2.0	-	The mean level of serum TSH in pesticide-exposed farmworkers was significantly higher than that of controls. However, the control groups significantly had higher mean levels of serum T <sub>3</sub> and T <sub>4</sub> than the farmworkers.

Author/year Country	Study Design/ Downs and Black	Sample	Thyroid Hormones Outcome/ Exposure	Measurement (95% CI)	Results of Effects	Adjusted Factors	Conclusion
Lerro CC, Freeman LEB, DellaValle CT, Kibriya MG, Aschebrook- Kilfoy B, Jasmine F, et al. (2017) (49) The United States of America	Cohort study/ D&B - 16 (no description of following up drop- out participants)	679 male pesticide applicators enrolled in a substudy of the Agricultural Health Study	<b>Outcome:</b> Serum levels of TSH, T <sub>4</sub> , T <sub>3</sub> , and antithyroid Peroxidase (anti- TPO)  <b>Exposure:</b> Insecticides (organochlorine, organophosphate, carbamate, pyrethroid)	Extensive use of the insecticide aldrin (third and fourth quartiles of intensity- weighted days vs no exposure) significantly related to subclinical hypothyroidism (OR <sub>Q3</sub> =4.15, 95% CI: 1.56 - 11.01; OR <sub>Q4</sub> =4.76, 95% CI: 1.53 - 14.82, ptrend <0.01), higher TSH (p <sub>trend</sub> =0.01) and lower T <sub>4</sub> (p <sub>trend</sub> =0.04).  Extensive use of the herbicide pendimethalin is also significantly related to subclinical hypothyroidism (fourth quartile vs no exposure where OR <sub>Q4</sub> =2.78, 95% CI: 1.30 - 5.95, p <sub>trend</sub> =0.02), higher TSH (p <sub>trend</sub> =0.04) and anti-TPO positivity (p <sub>trend</sub> =0.01).  The fumigant methyl bromide was inversely related to TSH (p <sub>trend</sub> =0.02) and positively linked with T <sub>4</sub> (p <sub>trend</sub> =0.01).	<ul style="list-style-type: none"> <li>▪ Age</li> <li>▪ State</li> <li>▪ Body mass index</li> <li>▪ Smoking</li> </ul> Correlated pesticides	<ul style="list-style-type: none"> <li>▪ Thyroid dysfunction occurred among male pesticide applicators after experiencing a long period of exposure to some pesticide types such as aldrin, pendimethalin, and methyl bromide.</li> </ul>	
Bernieri T, Rodrigues D, Barbosa IR, Ardenghi PG, Silva LBd (2018) (43) Brazil	Case-Control study/ D&B - 16 (no description of following up drop- out participants)	46 rural workers exposed to pesticides and 27 non-exposed subjects as a control group	<b>Outcome:</b> Serum levels of FT <sub>4</sub> , TT <sub>3</sub> , and TSH  <b>Exposure:</b> Pesticides	FT <sub>4</sub> (ng/dL)  TT <sub>3</sub> (ng/dL)  TSH (μUI/mL)	<b>Median ± SD</b> Exposed : 0.78 ± 0.15 Control : 0.66 ± 0.09 p-value : <0.001  Exposed : 139.0 ± 28.6 Control : 104.5 ± 20.0 p-value : <0.001  Exposed : 2.15 ± 1.09 Control : 2.91 ± 1.35 p-value : 0.007	-	There was a significant decrease in TSH and an increase in TT <sub>3</sub> and FT <sub>4</sub> among rural workers compared to the control group.

Author/year Country	Study Design/ Downs and Black	Sample	Thyroid Hormones Outcome/ Exposure	Measurement (95% CI)	Results of Effects	Adjusted Factors	Conclusion
Shrestha S, G.Parks C, S.Goldner W, Kamel F, M.Umbach D, H.Ward M, et al. (2018) (50) The United States of America	Prospective Cohort study/ D&B - 17	829 pesticide applicators with hypothyroidism	<b>Outcome:</b> Hypothyroidism <b>Exposure:</b> Insecticides (organochlorine and organophosphate), Herbicides	Organochlorine Insecticides Aldrin: Heptachlor: Lindane: Chlordane Organophosphate Insecticides Coumaphos: Diazinon Dichlorvos Malathion Herbicides Dicamba: Glyphosate 2,4-D	HR (95%CI); p-value 1.28 (1.02-1.60); 0.03 1.35 (1.07-1.70); 0.01 1.54 (1.23-1.94); <0.01 1.21 (1.04-1.41); 0.02 1.44 (1.06-1.95); 0.02 1.27 (1.10-1.48); <0.01 1.42 (1.17-1.72); <0.01 1.23 (1.04-1.46); 0.02 1.27 (1.08-1.50); <0.01 1.28 (1.07-1.52); 0.01 1.30 (1.07-1.58); 0.01	<ul style="list-style-type: none"> <li>▪ Sex</li> <li>▪ Education</li> <li>▪ State</li> <li>▪ Smoking</li> </ul>	Hypothyroidism risk significantly increased among pesticide applicators aged > 62 years old who have ever used four types of organochlorine (aldrin, heptachlor, and lindane), specifically, it occurred among all involved participants exposed to chlordane. Also, people that used four types of organophosphate insecticides had a similar experience (e.g. those >62 years old using coumaphos. However, the risk among all participants increased due to exposure to diazinon, dichlorvos, and malathion) as well as three types of herbicides namely dicamba, glyphosate, and 2,4-D.
Kongtip P, Nankongnab N, Kallayanatham N, Pundee R, Choochouy N, Yimsabai J, et al. (2019) (44) Thailand	Cross-Sectional study/ D&B - 16 (no description of following up drop-out participants)	195 conventional farmers (CF) and 222 organic farmers (OF)	<b>Outcome:</b> Serum levels of TSH, FT <sub>3</sub> , FT <sub>4</sub> , T <sub>4</sub> , and T <sub>3</sub> <b>Exposure:</b> Insecticide Fungicide Herbicide	TSH (μIU/ml) FT <sub>3</sub> (ng/dL) FT <sub>4</sub> (ng/dL) T <sub>3</sub> (μg/dL) T <sub>4</sub> (μg/dL)	<b>Geometric Mean (Min-Max)</b> CF: 1.26 (0.06-7.07) OF: 0.89 (0.02-8.51) p-value: <0.001 CF: 0.34 (0.25-0.64) OF: 0.31 (0.16-0.90) p-value: <0.001 CF: 0.82 (0.55-1.63) OF: 0.82 (0.52-1.21) p-value: 0.810 CF: 1.03 (0.55-1.92) OF: 0.87 (0.30-2.50) p-value: <0.001 CF: 8.37 (4.10-14.05) OF: 8.07 (3.05-16.31) p-value: 0.128	-	Conventional farmers had higher levels of TSH, FT <sub>3</sub> , T <sub>3</sub> , and T <sub>4</sub> compared to the organic.
Santos R, Piccoli C, Cremonese C, Freire C (2019) (45) Brazil	Cross-Sectional study/ D&B - 17	50 males with experience in agricultural work for at least one year and their family members aged 18 years or older living in the farm area during the low and high pesticide application season. A total of 122 participants.	<b>Outcome:</b> Serum levels of TSH, FT <sub>4</sub> , TT <sub>4</sub> , FT <sub>3</sub> , and TT <sub>3</sub> <b>Exposure:</b> Insecticide Fungicide Herbicide	TSH (mIU/L) FT <sub>4</sub> (ng/dL) TT <sub>4</sub> (mg/dL) FT <sub>3</sub> (pg/mL) TT <sub>3</sub> (ng/mL)	<b>Mean (SD)</b> Low: 3.31 (1.86) High: 3.23 (1.83) p-value: 0.38 Low: 1.22 (0.42) High: 1.20 (0.16) p-value: 0.02 Low: 9.63 (2.04) High: 8.92 (1.82) p-value: <0.01 Low: 3.56 (0.65) High: 3.47 (0.47) p-value: 0.07 Low: 1.06 (0.26) High: 1.04 (0.23) p-value: 0.65	-	Lifetime years of agricultural work are significantly related to the decrease of TT <sub>4</sub> and could slightly change the levels of FT <sub>4</sub> or TT <sub>4</sub> and/or T <sub>3</sub> . Thyroid disruptions might occur after exposure to agricultural pesticides during either a brief or long period.

Author/year Country	Study Design/ Downs and Black	Sample	Thyroid Hormones Outcome/ Exposure	Measurement (95% CI)	Results of Effects	Adjusted Factors	Conclusion
Nankongnab N, Kongtip P, Kallayanatham N, Pundee R, Yimsabai J, Woskie S (2020) (46) Thailand	Longitudinal study/ D&B - 16 (no description of following up drop-out participants)	213 conventional farmers (CF) and 225 OF	<b>Outcome:</b> Serum levels of TSH, FT <sub>3</sub> , FT <sub>4</sub> , T <sub>4</sub> , and T <sub>3</sub> <b>Exposure:</b> Insecticide Fungicide Herbicide	TSH (μIU/mL) FT <sub>3</sub> (ng/dL) FT <sub>4</sub> (ng/dL) T <sub>3</sub> (ng/mL) T <sub>4</sub> (μg/dL)	<b>Estimated Marginal Geometric Mean for four rounds of measurement</b> CF: 1.37 (1.27-1.48) OF: 1.03 (0.96-1.11) p-value: <0.001 CF: 0.34 (0.34-0.35) OF: 0.32 (0.32-0.33) p-value:<0.001 CF: 0.85 (0.83-0.86) OF: 0.87 (0.85-0.88) p-value: 0.095 CF: 0.97 (0.94-1.00) OF: 0.87 (0.85-0.89) p-value: <0.001 CF: 7.99 (7.76-8.23) OF: 7.56 (7.36-7.77) p-value: 0.008	<ul style="list-style-type: none"> <li>▪ BMI</li> <li>▪ Gender</li> <li>▪ Baseline age</li> </ul>	Conventional farmers had higher levels of TSH, FT <sub>3</sub> , T <sub>3</sub> , and T <sub>4</sub> contrasted to the OF.
Kongtip P, Nankongnab N, Pundee R, Kallayanatham N, Pengpumkiat S, Chungcharoen J, et al. (2021)(51) Thailand	Longitudinal study/ D&B - 16 (no description of following up drop-out participants)	51 sugarcane farmers (pesticide sprayers)	<b>Outcome:</b> Serum levels of TSH, FT <sub>3</sub> , FT <sub>4</sub> , T <sub>4</sub> , and T <sub>3</sub> before and after spraying <b>Exposure:</b> Insecticide (chlopyrifos and/or cypermethrin) Herbicide (paraquat and/or glyphosate)	TSH (μIU/mL) FT <sub>3</sub> (ng/dL) FT <sub>4</sub> (ng/dL) T <sub>3</sub> (μg/mL) T <sub>4</sub> (μg/dL)	<b>Geometric Mean (GSD)</b> before: 1.44 (1.99) after: 1.51 (1.76) p-value: 0.551 before: 0.29 (1.18) after: 0.30 (1.18) p-value: 0.056 before: 0.92 (1.17) after: 0.97 (1.17) p-value: 0.002 before: 0.96 (1.23) after: 0.86 (1.24) p-value: 0.073 before: 8.14 (1.22) after: 7.94 (1.24) p-value: 0.265	<ul style="list-style-type: none"> <li>▪ Gender</li> </ul>	The farmers investigated one day after applying chlopyrifos had higher levels of FT <sub>4</sub> than before spraying. Conversely, the application of cypermethrin, paraquat, or glyphosate for spraying crops did not produce a difference in terms of serum levels of TSH, FT <sub>3</sub> , FT <sub>4</sub> , T <sub>4</sub> , and T <sub>3</sub> .
Sirivarasai J, Chanprasertyothin S, Kongtip P, Woskie S. (2021) (47) Thailand	Longitudinal study/ D&B - 16 (no description of following up drop-out participants)	Chemical worker (CW) group (n=216) and Organic Workers (OW) (n=229)	<b>Outcome:</b> Serum levels of TSH, FT <sub>3</sub> , and FT <sub>4</sub> <b>Exposure:</b> Herbicides Insecticides Fungicides	TSH (μIU/mL) FT <sub>3</sub> (ng/dL) FT <sub>4</sub> (ng/dL)	<b>Geometric Mean (Range)</b> CW: 1.58 (0.056-10.13) OW: 1.12 (0.019-8.51) p-value: <0.001 CW: 0.34 (0.25-1.47) OW: 0.31 (0.16-0.60) p-value: 0.001 CW: 0.83 (0.55-1.63) OW: 0.82 (0.52-1.21) p-value: 0.531	-	The TSH and FT <sub>3</sub> levels among chemical workers were slightly higher than those in OW and were statistically significant. In contrast, the FT <sub>4</sub> levels were not significant between both groups.

Fifteen studies measured serum levels of thyroid hormones including Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT<sub>3</sub>), Free Thyroxine (FT<sub>4</sub>), Triiodothyronine (T<sub>3</sub>), Thyroxine (T<sub>4</sub>), and Total Triiodothyronine (T<sub>3</sub>). Meanwhile, one evaluated the occurrence of hypothyroidism, hyperthyroidism, and other thyroid diseases (52) and the remaining one only assessed hypothyroidism (50) as demonstrated in Table 1.

Ten of eleven studies conducted with either farmers or farmworkers showed that exposure to various types of pesticides application significantly affected the level of thyroid hormone compared to unexposed groups

(38-47). However, the remaining one indicated that the difference in thyroid hormone levels among both exposed and unexposed groups was statistically insignificant (37) as presented in Table 1.

Three of the six articles (50%) evaluating exposure to only insecticide application demonstrated its tendency to significantly increase the geometric mean of TSH serum levels among exposed groups compared to the unexposed, namely 4.4 mUI/ml: 2.8 mUI/ml (41), 2.64 mUI/l:1.33 mUI/l (48), and 2.58 μIU/mL:1.53 μIU/mL (38) respectively with a p-value < 0.05. Meanwhile, the other three stated this condition to be insignificant as presented in Table 1.



Similarly, four of the eleven articles (36%) evaluating exposure to the application of various pesticide types indicated the combination of insecticide, fungicide, and herbicide while spraying crops could elevate the geometric mean of TSH serum levels among exposed groups, namely 2.5 mIU/mL:1.5 mIU/mL (37), 1.26  $\mu$ IU/ml:0.89  $\mu$ IU/ml (44), 1.37  $\mu$ IU/mL:1.03  $\mu$ IU/mL (46), and 1.58  $\mu$ IU/mL:1.12  $\mu$ IU/mL (47) respectively with a p-value < 0.05. In contrast, the remaining seven articles stated this condition as insignificant as presented in Table 1.

Concerning T<sub>4</sub> serum levels, the geometric mean among groups exposed to only insecticide application (9.0  $\mu$ g/dl) was significantly higher than that of the unexposed (5.8  $\mu$ g/dl) as shown by only one article (41). Also, the geometric mean of T<sub>4</sub> serum levels among groups exposed to various pesticide types, namely 7.99  $\mu$ g/dL was significantly higher compared to the unexposed i.e. 7.56  $\mu$ g/dL (46) as presented in Table 1.

The geometric mean of FT<sub>4</sub> serum levels among groups exposed to only insecticide application was slightly higher compared to the unexposed (36, 38). These results were similar to that of the groups exposed to various pesticide types (39, 43, 47, 51) as demonstrated in Table 1.

In terms of T<sub>3</sub> serum levels, one of the two articles assessing only insecticide application as an exposure source indicated significant differences in the geometric mean between exposed and unexposed groups (48). T<sub>3</sub> serum levels among exposed groups (1.12 nmol/l) were significantly lower compared to the unexposed (1.55 nmol/l) with a p-value =0.018 (48) as presented in Table 1. Different results were obtained through studies evaluating T<sub>3</sub> and exposure to various types of pesticides. Two articles showed that T<sub>3</sub> serum levels among exposed groups were significantly higher compared to the unexposed (44, 46), but three demonstrated the opposite results (40, 42, 51).

FT<sub>3</sub> serum levels were also investigated by five articles among either farmworkers or pesticide applicators exposed to various pesticide types (44-47, 51). Furthermore, three showed that FT<sub>3</sub> serum levels among exposed groups were significantly higher than in the unexposed (44, 46- 47). In contrast, the remaining two indicated that FT<sub>3</sub> serum levels were not different between both groups (45, 51). Thyroid hormone concentrations may change due to the effects of some pesticide types such as insecticides, herbicides, and/or fungicides on the hypothalamus–pituitary–thyroid axis. This involves disrupting central regulation, iodine uptake, thyroid hormone synthesis, and the hormone receptors' production ability (47).

Exposures to six kinds of herbicides namely 2,4-D; 2,4,5-T; 2,4,5-TP; Alachlor; Dicamba; and Petroleum oil as well as eight insecticides types including organochlorine (chlordane, DDT, heptachlor, lindane, and toxaphene), organophosphate (diazinon and malathion), and carbamate (carbofuran) were associated with elevated hypothyroidism odds (52). Similarly, hypothyroidism risk significantly increased among pesticide applicators aged > 62 years old who have ever used four types of organochlorine including aldrin, heptachlor, and lindane, specifically, all participants exposed to chlordane encountered this condition. The risk also increased in those >62 years old exposed to four types of organophosphate insecticides such as coumaphos, however, this experience occurred among all involved participants that applied diazinon, dichlorvos, and malathion, as well as three herbicides types namely dicamba, glyphosate, and 2,4-D (50).

It was discovered that the majority of reviewed articles had similar results concerning pesticide exposure effects on the serum levels of thyroid hormones among farmworkers or pesticide applicators. Pesticides such as insecticides, herbicides, and fungicides are known as one of the EDCs (28). Organophosphate groups, particularly chlorpyrifos, widely used insecticides, and other kinds of pesticides namely pyrethroids, phenylpyrazoles, or neonicotinoids play important role in terms of thyroid disruptions (53). Additionally, exposure to Persistent Organic Pollutants including organochlorine pesticides e.g. dichlorodiphenyltrichloroethane, hexachlorobenzene, and chlordane, is significantly associated with an increase in thyroid disease incidence (54).

Action mechanisms of EDCs comprise estrogenicity, androgenicity, thyroid change, hormone receptors' transformation, retinoic acid alteration, change of target tissues, pancreatic beta-cell disorder, inhibition of hormone metabolism, and modifying effects of hormones (55). EDCs tend to regulate the levels of endogenous hormones by disrupting synthesis, secretion, transport, action, and degradation through mechanisms concerning the identical hormone receptors and signaling pathways (2). These chemicals can bind to receptors to imitate endogenous hormones, and they act by changing hormone signaling through different means (56). EDCs may also engage as agonists with more than one receptor, including non-nuclear receptors, to facilitate genomic interactions, or as antagonists, wherein they serve as a conformational alternative to the receptor for the hindrance of normal activities. They may additionally cause non-genomic signaling that is free of nuclear receptors (56). EDCs disturb endogenous

hormone synthesis and degradation to change hormonal levels (56). TR is included as a class of ligand-dependent transcription factors (56). There are four active isoforms of TR namely TR $\alpha$ 1, TR $\beta$ 1, TR $\beta$ 2, and TR $\beta$ 3 which bind T<sub>3</sub> and thyroxine T<sub>4</sub> (56).

Thyroid gland hormones play an important role in the common progress of the body. Furthermore, their synthesis is regulated by the Hypothalamus–pituitary–thyroid (HPT) axis. Lessened thyroid hormonal levels stimulate the hypothalamic thyrotropin to release a hormone (TRH) that can improve TSH secretion from the anterior pituitary. Thyrocytes stimulate the quantity of thyroid human hormones (57). Active iodide is required during the synthesis process performed through sodium or iodide symporter, thyroglobulin production, and iodination of thyroglobulin by thyroid peroxidase enzyme (57). The thyroid gland has an important role to generate T<sub>4</sub> which is converted to T<sub>3</sub>. The pituitary gland makes TSH which informs the thyroid gland about the quantity of T<sub>4</sub> and T<sub>3</sub> needed to be produced. TSH level in the bloodstream indicates the quantity of T<sub>4</sub> that the pituitary gland asks the thyroid gland to produce. Once this level is quite high, it means the thyroid gland is underactive or presence of hypothyroidism. The pituitary produces much TSH enough to stimulate the thyroid gland for secretion (12). Endocrine glands produce hormones that are carried into the bloodstream to regulate physiological systems (30). One of the main endocrine axes is the thyroid axis. It has an important role in controlling thyroid hormones needed for growth, brain, and energy metabolism (30). Pesticides are included as thyroid disruptors that affect the hypothalamus/ pituitary/thyroid axis (12). The identification of EDCs in a human body can be performed by collecting serum, urine, and breast milk for analysis at a laboratory even though quantifying the results is not easy (2).

Thyroid hormones have an important role in normal brain development, metabolism control, and other aspects of normal physiology in adults (55). Under- or over secretion of thyroid hormones due to exposure to chemical substances such as pesticides can lead to metabolic disturbances, as well as physical and neurobiological changes (55). Lower levels of thyroid hormones in a community tend to be a sign of increased risk of harmful health effects (28). The levels of thyroid hormones particularly TSH, T<sub>3</sub>, and T<sub>4</sub> are still the commonest outcome to evaluate the effect of pesticide exposure on thyroid disruption (12). Presently, the most sensitive biomarker to identify thyroid status is TSH (12).

The hypothalamus controls the endocrine system which is associated with the nervous system. Then, the

pituitary gland that has a pair of lobes (a rear/posterior and an antecedent lobe that secrete different hormones) accepts signals from the hypothalamus (55). Endocrine glands consist of the pituitary, thyroid, and adrenal glands, plus gonads and specific parts of the pancreas (55). Furthermore, serum levels of thyroid hormones are investigated by the mechanism of negative feedback interceded by the effects of circulating thyroid hormones at the pituitary level (55). The hypothalamus secretes the thyrotropin hormone that stimulates the anterior pituitary to produce TSH (12). Once thyroid hormone levels are low in the blood, the anterior pituitary automatically secretes TSH. Afterward, TSH stimulates the fusion and secretion of T<sub>3</sub> and T<sub>4</sub>. These hormones are carried in the serum by thyroid-binding globulin (TBG) to the tissues to deliver proteins. TBG plays an important role to transport proteins in humans. Moreover, iodothyronine deiodinases convert T<sub>4</sub> to T<sub>3</sub> as the active hormone in the liver or local tissues (12).

Based on serum levels of thyroid hormones, thyroid disorders are divided into four criteria, namely clinical and subclinical stadium hyperthyroidism plus clinical and subclinical stadium hypothyroidism (48). People with a level of T<sub>4</sub>>12.4  $\mu$ g/dl or T<sub>3</sub>>2.8 nmol/l and TSH $\leq$ 0.1 mIU/l are suffering from clinical hyperthyroidism. Supposing they have TSH $\leq$ 0.5 mIU/l with normal levels of T<sub>3</sub> and T<sub>4</sub>, the condition is considered subclinical hyperthyroidism. Meanwhile, people with a level of T<sub>4</sub><4.5  $\mu$ g/dl and TSH $\geq$ 10 mIU/l are categorized under clinical hypothyroidism. Furthermore, subclinical hypothyroidism occurs once the TSH level is between 5 and 10 mIU/l and T<sub>4</sub> is normal (48). Various levels of TSH and thyroid hormones demonstrate that there is possible thyroid dysfunction (57).

Many chemical substances including pesticides have similarities in structure with T<sub>3</sub> and T<sub>4</sub>. Therefore, they interfere with the binding of thyroid hormones to their receptors or transfer proteins which leads to subclinical hypothyroidism (48). Some insecticides and fungicides are known to inhibit the role of thyroid peroxidase and thyroid hormones (53).

Interestingly, the increase of TSH and T<sub>4</sub> serum levels mostly occurs among groups exposed to only insecticide application rather than those exposed to various pesticide types as presented in Table 1. Notwithstanding, TSH and T<sub>4</sub> serum levels among these groups exposed to the different types are still within the normal level range and no article has considered thyroid disorders among either farmworkers or pesticide applicators. In contrast, a study in China demonstrated the negative relationship between Persistent Organic Pollutants and T<sub>3</sub>, T<sub>4</sub>, FT<sub>3</sub>, and FT<sub>4</sub> among male participants (54). Some kinds of

pesticides like organophosphate, organochlorine, and carbamates are more often linked to thyroid axis disruption (12). The thyroid hormonal change differ based on each class of pesticide (12). Pesticides are divided into four classes namely extremely hazardous or class Ia, highly hazardous or Ib, moderately hazardous or II, and slightly hazardous or III (58). A research conducted in Batu City showed that long-period of exposure to organophosphate (OP) could elevate TSH levels and reduce the amount of  $T_3$  and  $T_4$  among pesticide sprayers contrasted with those unexposed (14). Organophosphate pesticides act as EDCs by disrupting hormone levels and binding to the receptors of estrogen, androgen, mineralocorticoid, glucocorticoid, and thyroid hormone (59). Malathion and chlorpyrifos are extensively used to protect crops, and influence the production of thyrotrope, leading to thyroid hormone decrease (12). Organophosphate pesticides have shown adverse results for thyroid, gonad, and adrenal glands. Hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-gonadal communication, and functions overlap. The adrenal hormone is capable of inducing the availability of gonadotropin-releasing hormone (GnRH) released from the hypothalamus and the thyroid hormone could hinder GnRH production (59). Moreover, organophosphate pesticides may have an effect on the hypothalamus and pituitary in the human brain (59). Brief and everlasting exposure to organophosphate insecticides tends to cause poisoning and disruption of pituitary functions (60). Furthermore, modes of action of organochlorine pesticides in reducing or increasing TSH levels in the human body are through mechanisms including the occupation of distributor proteins, the elevation of hepatic metabolism, and circumstantial effect on thyroid function (12). The levels of organochlorine particularly endosulfan are positively related to uric acid, creatinine, and TSH, but negatively linked to free thyroxine (61). The most persistent artificial chemicals including aldrin and dieldrin in a group of organochlorine pesticides and as persistent organic pollutants are still found in agricultural areas with various health effects on the human body's physiological systems (62). These pesticides act as EDCs by mimicking or blocking the hormonal receptors (62). Carbamate serves as EDCs by inhibiting the iodinating activity of thyroid peroxidase (TPO) (12). One Spanish study demonstrated that the metabolite of a kind of carbamate insecticide (carvaryl), namely 1-naphthol (1N), had a significant association with the changes in thyroid hormone levels (10). Pyrethroid insecticides disrupt thyroid signaling pathway, while the structure of pyrethrins resembles thyroid hormones, hence they could interfere with the hormone homeostatis

(12). Additionally, the most commonly used metabolite to identify many pyrethroid types, namely 3-phenoxybenzoic acid (3-PBA), had significant relationship with the changes in thyroid hormone levels (10). Pyrethroids act as EDCs through various mechanisms on some receptors such as steroid receptors by functioning as natural hormones to bind the steroid nuclear receptors, then switch on voltage-gated sodium channels that play a crucial role in neuroendocrine cells, voltage-sensitive calcium channels, and signaling molecules (63). They also have EDCs trait and potentially link to the hypothalamic-pituitary-gonadal axis (63). In terms of herbicides, particularly glyphosate, short or long-term exposure to glyphosate could modify microbiome status (12).

The significant results associated with the occurrence of hypothyroidism among pesticide applicators are shown in two articles (50, 52). The previous use of some herbicide types like 2,4-D, 2,4,5-T, 2,4,5-TP, alachlor, dicamba, and petroleum oil is significantly associated with the increased risk of hypothyroidism among male pesticide applicators (52). Additionally, experience in applying eight insecticide types such as organochlorines consisting of chlordane, DDT, heptachlor, lindane, and toxaphene, organophosphates including diazinon and malathion, and carbamate which comprised of carbofuran had a potential risk to elevate hypothyroidism occurrence (52). Increasing risk of hypothyroidism also occurred with a rising level of exposure among male pesticide applicators for herbicides such as alachlor and 2,4-D, and insecticides e.g. aldrin, chlordane, DDT, lindane, and parathion (52). According to another study conducted in the US, the hypothyroidism risk significantly increased among pesticide applicators aged > 62 years old who have ever used four types of organochlorine including aldrin, heptachlor, and lindane, specifically, all participants exposed to chlordane encountered this condition. The risk also increased in those >62 years old exposed to four types of organophosphate insecticides such as coumaphos, however, the experience occurred among all involved participants that applied diazinon, dichlorvos, and malathion, as well as three herbicides types namely dicamba, glyphosate, and 2,4-D (50). Organochlorine pesticides are included in a group of chlorinated hydrocarbon derivatives that are harmful, persistent, and concentrated inside the bodies of living things (64).

Most of the reviewed manuscripts had adequate scores following the criteria of D&B. Certain articles got low grades because no p-value was reported and follow-up losses were not described (36-40). Some studies did not assess the confounding factors for serum levels of thyroid hormones that may affect their associations, for

example, lifestyle factors such as smoking, body mass index (BMI), and the intake of iodine, a minor element obtained from foods (40, 41, 43-45, 47, 57). These factors revealed the most beneficial relationship with both TSH and thyroid hormones. BMI levels were positively linked to TSH and free  $T_3$  levels while smoking mainly led to a rise in the amount of  $T_3$  and  $T_4$ . Iodine increased the amount of TSH, and thyroid hormone decreased (57). Additionally, some other factors including age, work duration, the use of proper personal protective equipment, adjustment of sprayer's body position to wind direction during spraying, and organophosphate pesticides' application have a significant association with the TSH elevation and decrease of  $T_3$  and  $T_4$  levels (14). Conversely, high-intensity days of applying fumigants such as methyl bromide were linked to the declined TSH amount, significant rise in  $T_4$ , and non-significant  $T_3$  elevation (49). Also, intensive application of the fungicide captan was related to increased TSH (49).

There are some limitations to the evidence that may exist in the reviewed articles, particularly concerning the relation of pesticide exposure to thyroid hormone levels. First, most of the reviewed articles used observational studies such as cross-sectional or case-control approaches. A prevalence study has some weaknesses, specifically in terms of association strength. Pesticide exposure must be experienced before the occurrence of thyroid disruptions. Therefore, there were many difficulties to ensure the increase or decrease of thyroid hormone levels among the participants occurred due to pesticide exposure or other EDCs available in the environment. Meanwhile, a case-control study used in the reviewed articles has limitations in terms of recall bias and sample size. Most of the articles particularly the ones that applied a case-control study had a small number of samples for each group (case and control) ranging from 20 to 46 participants. Differences in study designs, setting, pesticide exposure timing, number of involved participants, kinds of thyroid-related outcome assessment, adjustment of confounding variables in data analysis, and the statistical analysis types used might lead to various results of thyroid hormone levels (65).

#### ACKNOWLEDGMENTS

The writing of this article has no conflict of interest and no funding assistance was received.

#### CONCLUSIONS

This review suggests that some types of pesticides such as insecticides, herbicides, and fungicides extensively used in agriculture might be

involved in the increase and decrease in thyroid hormone levels among exposed individuals.

It was evidenced that occupational or environmental exposure to pesticides can affect serum levels of thyroid hormones. This might relate to the occurrence of serious health events in the future. Further studies need to assess specific types of pesticides and the adverse health effects which involve confounding factors to yield robust analysis including a large number of participants for both exposed and unexposed groups using an experimental design.

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