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Humoral Inflammatory Markers of Total Immunoglobulin E (IgE) Exposure on Palm Oil Plantation Pesticide Sprayers

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Abstract

Pesticides are often used in oil palm plantations to prevent disturbing animals and plants. Pesticide sprayers are vulnerable to pesticide exposure which can reduce cholinesterase levels is an indicator of pesticide poisoning. Long-term pesticide exposure and excessive doses cause the production of free radicals in the body, thereby increasing inflammatory markers, one of which is total IgE. This study aimed to describe cholinesterase and total IgE levels in oil palm farmers. This study used the quantitative-descriptive research method. The sampling was conducted at PT. X in Sanggau District of West Kalimantan Province. Examining cholinesterase levels used the Architec c-8000 device with the DGKC butyrylthiocholine 37°C method, while total IgE used the immunochemmiluminescent method with the Immulite 2000 device. The examination was carried out at the Prodia National Reference Lab in Jakarta. Based on the cholinesterase measurement results taken from 133 workers who underwent medical check-ups, 20 data were taken that were close to the threshold value less than normal to examine total IgE levels. The results obtained from the overview of cholinesterase levels showed that 20 pesticide sprayers (100%) had normal cholinesterase levels, and four (20%) had normal total IgE levels. Pesticide exposure will decrease cholinesterase levels, and increase IgE levels

Introduction

The BPS (Statistics Indonesia) states that oil palm plantations in Indonesia are spread across 26 provinces. The 2020 BPS data shows that the island of Kalimantan occupied the second position as the largest oil palm plantation, 5.31 million Ha, followed by the West, Central, and East Kalimantan Provinces, with areas of 2.11, 1.88, and 1.32 million Ha, respectively. This large area of oil palm land has led many residents to work as oil palm farmers (Badan Pusat Statistik, 2017). The use of pesticides is often found in oil palm plantations. Pesticides are toxic substances that potentially cause negative impacts on the environment and biodiversity. Pesticides can cause resistance, resurgence, the emergence of new pests, and health problems for humans and other living things. Indeed, pesticides must be managed with great care. In agriculture, the use of pesticides can have a substantial impact on increasing agricultural yields. In addition, pesticides used sustainably will pollute agricultural land and impact health if they enter the body due to their toxic nature (Kementrian Pertanian Republik Indonesia, 2019).

Measurement of erythrocyte Cholinesterase (EC) and plasma Cholinesterase (PC) activity is recommended for people who use organophosphate pesticides for more than six days in one month. PC is found in the liver and plasma, the function is not known exactly, but it is thought to play a role in lipid metabolism, control choline concentration in plasma, and prevent butyrylcholine accumulation. EC is found within erythrocytes and collagenic synapse located at the junction of neuromuscular neurotransmitter and central nervous system (CNS) connections, peripheral nervous system interneuronal, and neuroglandular

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and neuromuscular connections of the parasympathetic nervous system. Its function is to inactivate the neurotransmitter acetylcholine through biotransformation into choline and acetic acid, which regulate the transmission of nerve impulses (Caro-Gamboa et al., 2020).

The harmful impact of Organophosphates exposure is the inhibition of cholinesterase enzyme activity, this is why these types of pesticides are considered as anticholinesterase substances. Organophosphates and carbamates, which are known to be neurotoxic and responsible for 80% of acute or chronic pesticide poisonings globally, are regularly bio-monitored by cholinesterase enzymes(Benitez & Ramírez-Vargas, 2021; Caro-Gamboa et al., 2020). The lower the level of the cholinesterase enzyme in a person's blood, the more detectable that they are poisoned by pesticides (Kumar et al., 2023). The human body is exposed to pesticides through the skin, mouth, eyes, and respiratory system (Kim et al., 2017).

Pesticide exposure can result in immediate toxic consequences that range in intensity from mild (headache) to severe (diarrhea, pulmonary edema, vomiting, skin rash, respiratory disorders, eye irritation, sneezing, convulsions), or even deadly poisoning (Cuenca et al., 2019; Kalyabina et al., 2021). Long-term exposure may also have chronic health impacts on the nervous system, including aberrant neurodevelopment in children and endocrine disruption leading to precocious puberty (Mostafalou & Abdollahi, 2013). Farmers typically use a variety of pesticide formulations and mixes, some of which have genotoxic effects and may result in the development of cancers such as leukemia, multiple myeloma, malignant lymphomas, brain and prostate cancer (R. M. de Souza et al., 2020; Parrón et al., 2014).

The chronic effects of pesticides include allergic reactions and immune system disorders. Pesticides can also cause abnormal blood profiles since they are suspected of interfering with the organs that form blood cells and the immune system. Pesticide exposure can cause infections and trigger various diseases in the body. Long-term pesticide exposure and excessive doses can cause lipid peroxidation. This chain process will produce free radicals in the body, triggering an inflammatory reaction (inflammation) in response to a foreign object that attacks the body. The immune system will work when detecting foreign objects that can threaten the body's health (Qomariah et al., 2017; Zepeda-Arce et al., 2017). In vivo and in vitro studies have proven that glyphosate has immunotoxic properties and can trigger hypersensitivity due to immune cell dysfunction through mechanisms of oxidative stress and endocrine disruption, triggering increased cytokine production, and has the potential to have acetylcholinesterase (AChE) inhibitor activity. The respiratory tract as one of the main routes of glyphosate to enter the body is at risk of experiencing hypersensitivity due to these mechanisms. Rhinitis and asthma are common respiratory hypersensitivity diseases, and their prevalence is higher in farmers (Maddalon et al., 2021; Molina-Guzmán & Ríos-Osorio, 2020).

Immunoglobulin E (IgE), only found in mammals, is vital in allergic reactions, i.e., type I hypersensitivity reactions. IgE is produced by B lymphocytes which are humoral immunity in specific defense (Qosimah et al., 2020). The research by Aroonvilairat et al. (2105) showed an increase in the IgE concentration in orchid farmers compared to the existing control values (Aroonvilairat et al., 2015). Based on the research by Yaqub (2019), long-term pesticide exposure increases inflammatory markers, one of which is total IgE; the research showed a significant increase in the total IgE level (Yaqub, 2019). In Indonesia, there has not yet been much research on total IgE on pesticide sprayers on oil palm plantations. Consequently, it has attracted the researchers to conduct this study: An Overview of the Total Immunoglobulin E (IgE) Exposure on Oil Palm Plantation Pesticide Sprayers in Sanggau Regency of West Kalimantan Province.

Method

This study used the correlational quantitative research design. It was conducted on 133 oil palm farmers in West Kalimantan Province who underwent medical check-ups for cholinesterase examination. It took 20 farmers using purposive non-random sampling by screening samples of oil palm farmers exposed to pesticides showing cholinesterase examination results below or close to the normal threshold value. This study has obtained the Ethical Clearance Certificate No.KEPK/UMP/100/I/2023 issued by the Health Research Ethics Commission of Universitas Muhammadiyah Purwokerto.

The secondary data were questionnaire results needed as a research control to find out personal data related to research, activities, and medical history of the research samples: the farmers. The examination for cholinesterase and total IgE levels used the serum taken from their blood using 4 mL Vacutainer SST. The serum was obtained by standing the SST tube blood sample for 30 minutes, then centrifuged at 3600 rpm for 10 minutes. The cholinesterase and total IgE levels were examined at the Clinical Laboratories of Prodia in Jakarta and Pontianak. The examination of the cholinesterase level used the Architec c-8000 with the DGKC butyrylthiocholine method at 37°C; the total IgE examination used the Immulite 2000; simultaneously, the total Eosinophil and Basophil used Sysmex XN 350 with Fluorescence Flowcytometry method. The clinical laboratory of Prodia has a standard, i.e., the value for a cholinesterase level is from 5,320 to 12,920 U/L, <87 IU/mL for the total IgE level, eosinophil level = <4%; and basophil reference value = <1%. The data on cholinesterase, total IgE levels, and total Eosinophil and Basophil were analyzed by correlation test using SPSS v26.

Result and Discussion

The study was conducted at Prodia in Pontianak and at Prodia National Reference Lab in Jakarta, and the blood test was collected at PT.X in Sanggau District in West Kalimantan. The medical check-up for cholinesterase examination was carried out on 133 pesticide sprayers. 20 samples were taken, with the cholinesterase value close to the below-normal threshold value, to examine the total IgE level. The reason was that laborers exposed to pesticides would have the cholinesterase level below the normal threshold value. Hence, an overview of total IgE from laborers exposed to pesticides would be well-described. Pesticides used by farmers can enter the body through dermal, inhalation, and digestion processes, this can occur during the transfer, mixing, spraying, washing, and storage of pesticides (Yuantari et al., 2015). The independent variables of pesticide exposure were age, BMI, length of service, frequency of spraying, duration of spraying, and PPE use score (Munfiah et al., 2023). The organophosphate group in the pesticide, which shows the released group (X) or specific, is substituted through nucleophilic replacement by oxonal serine from the active site of the cholinesterase enzyme. The degree of degradation of the cholinesterase enzyme by organophosphates is broadly influenced by the specific compounds, increasing the possibility of the X group being released, and resulting in a high organophosphate affinity for the cholinesterase enzyme. Phosphorus oxone is the structural type of oxygen, the active form linked to cholinesterase. (Figure 1) (Yaqub, 2019).

and the following results were significant with p-value= 0.037.

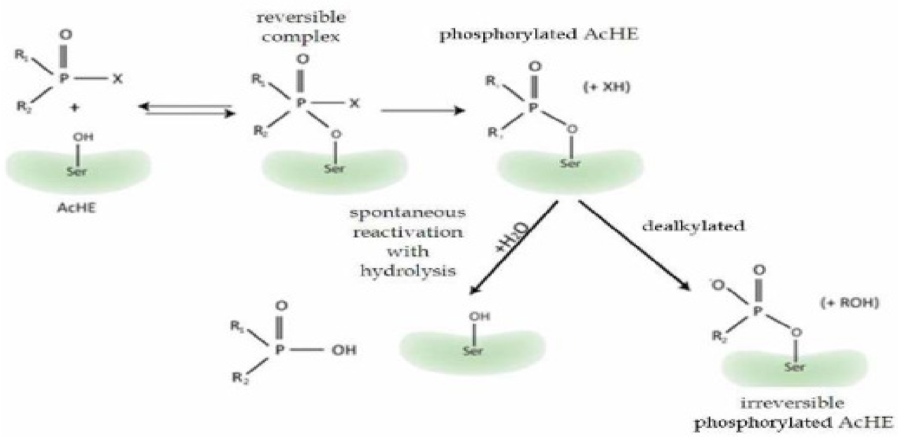

Figure 1. AcEH activation by Organophosphates (Yaqub, 2019)

The Organophosphorus compounds that enter the body will bind serine acetylcholinesterase residues in serum (butyrylcholinesterase, BChE), mainly bound in erythrocyte membranes, (AChE), and the parasympathetic, sympathetic, and central nervous systems. acetylcholine (ACh) represents the central transmitter that is degraded by the enzyme to interrupt the signal (Pope & Brimijoin, 2018; Strelitz et al., 2014; Ramadori, 2023). The toxicity of organophosphorus insecticides is still considered a major global health problem. Malathion is one of the most commonly used organophosphates today due to its relatively low toxicity compared to other organophosphates. However, extensive use can lead to overexposure from multiple sources. The mechanisms of MAL toxicity include inhibition of the acetylcholinesterase enzyme, changes in the balance of oxidants or antioxidants, DNA damage, and facilitation of apoptotic cell damage (Badr, 2020).

Pesticides can accumulate in organisms leading to chronic effects. Numerous studies have found evidence that pesticides can interfere with immunity and have several immunotoxic effects (Mokarizadeh et al., 2015). A common reason for various alterations in immune function brought on by pesticides from the organophosphate and carbamate families is their capacity to block the immune system's essential serine hydrolase and protease enzymes (Joko et al., 2020). Organophosphorus (OP), carbamate, and pyrethroid compounds are proven to inhibit leukocyte survival and growth by inducing apoptosis or cell cycle arrest and interfering with the specific immunological functions of each type of immune cell (Lee & Choi, 2020). The measurement of cholinesterase enzyme activity on pesticide sprayers in oil palm plantations showed normal results for the 20 (100%) respondents. Four (20%) had normal total IgE (<87 IU/mL), and 16 (80%) exceeded the standard value. 12 (60%) had normal total eosinophils, while eight (40%) had more than the normal value. Nine (45%) had normal total basophils, and 11 (55%) exceeded the reference value (Table 2).

Table 2. Frequency distribution of Cholinesterase and IgE enzymes values on Pesticide Sprayers in Oil Palm Plantations

Category*	Frequency	Percentage
Cholinesterase value (U/L)		
Normal	20	100 %
Abnormal	0	0 %
Total IgE value (IU/mL)		
Normal	4	20 %
Abnormal	16	80 %
Eosinophils (%)		
Normal	12	60%
Exceeding normal	8	40%
Basophils		
Normal	9	45%
Exceeding normal	11	55%
Total	**20**	**100 %**

Information: Normal reference value for normal Cholinesterase = 5.320 to 12.920 U/L; normal IgE level = <87 IU/mL; normal eosinophil level = <4%; basophil reference value = <1% ~ (Prodia's Clinical Laboratory)

The average value for the cholinesterase level is 7381.3 ± 142.375 U/L. Subsequently, the farmers' average cholinesterase levels were still within normal since they used personal protective equipment while working, such as head-eye-respiratory-body protection (overall suit/apron) and hand-leg guards (Tallo et al., 2022). The average IgE level and total basophils exceeded the reference value; the IgE level is 582.2 ± 162.729 IU/mL, and the basophils are 1.02 ± 0.117%; while their average total eosinophils were still within safe limits, namely 3.77 ± 0.51758% (Table 3).

Table 3 Descriptive data and correlation analysis between Cholinesterase (CHE) Level on the Total IgE Levels, and total Eosinophil and Basophil

Variable	Mean	Median	SD	Min	Max	Significance
CHE Level (U/L)	7381.3	7447.5	636.7	5602	8084	-
Total IgE Level (IU/mL)	582.2	294	727.7	11.8	2783	0.281
Total Eosinophils (%)	3.77	3.50	2.31	0.20	7.80	0.176
Total Basophils (%)	1.02	1.00	0.52	0.20	2.20	0.756

Source: Primary Data

The correlation analysis showed that the cholinesterase level was not significantly related to IgE level and total eosinophils and basophils. It was due to cholinesterase levels for 20 farmers still within normal limits. However, from the IgE level examination of 20 farmers, it was found that 16 (80%) had an increase in total IgE values, and four (20%) did not. This is based on the research by Aroonvilairat et al. (2015), where there was an increase in IgE concentrations in orchid farmers compared to existing control values (Aroonvilairat et al., 2015). In that study, there was a significant increase in total IgE serum in orchid farmers. Based on research by Yaqub & Sarjudeen A., long-term exposure to pesticides increases inflammatory markers, one of which is total IgE; in the study, there was a significant increase in total IgE levels (Yaqub, 2019). The questionnaire results showed that 14 (70%) farmers complained of itching, dizziness, and nausea after being exposed to pesticides, and the 20 farmers also had no history of asthma or allergies. Thus, such allergies were predicted from the pesticide.

Pesticide exposure in farmers will form ROS causing oxidative stress. Pesticide-induced oxidative stress is caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are associated with several diseases, including cancer, inflammation, and cardiovascular and neurodegenerative diseases (Sule et al., 2022). A high ROS level can cause pathological changes in the nasal and respiratory mucosa, including lipid peroxidation, increased respiratory tract reactivity, increased sensitivity and secretion of the mucosa, production of chemoattractant molecules, and increased vascular permeability. Oxidative stress becomes a trigger from the hypersensitivity reaction, particularly type I hypersensitivity such as asthma or atopic dermatitis, which is a type of allergy mediated by Immunoglobulin E (IgE) (Elshabrawy et al., 2014; Elshabrawy et al., 2014; Liu et al., 2022). Limited in vitro studies have also shown that exogenous antioxidants can reduce or prevent the adverse effects of pesticides (Sule et al., 2022). Research conducted on mice administered by diazinon, the most common organophosphate pesticide used to control pests, has shown that mice induced by diazinon 50 mg/kg + B. vulgaris extract 200 mg/kg, or diazinon 50 mg/kg. After three weeks, cerebrum and cerebellum samples were collected for antioxidant assays. The results indicated that diazinon increased oxidative stress in the brains of mice. The glutathione content and proceedings of antioxidant enzymes, such as glutathione peroxidase, superoxide dismutase, and catalase, were significantly reduced in both the cerebellum and cerebrum of diazinon-treated mice, compared with the control group. In addition, acetylcholinesterase (AChE) activity was inhibited by exposure to this pesticide. Administration of 200 mg/kg B. vulgaris extract with diazinon significantly decreased oxidative stress indices in all experiments (Sonei et al., 2020).

Certain pesticides contribute to mast cell degranulation, and basophils trigger the production of cytokines, such as IL-4, IL-3, and IgE secretion by B cells. After IgE increases to Fc receptors on mast cells/basophils, the bound of IgE receptors with allergens triggers degranulation cells. Allergic mediators will release responses, including histamine, heparin, serotonin, cytokines, proteases, leukotrienes, and prostaglandins. It will contribute to the allergic reaction, including dilation of blood vessels, mucus secretion, and smooth muscle contraction. This process may help explain that the development of IgE antibodies to dichlorodiphenyldichloroethylene (DDE) and pyrethrins in individuals exposed to pesticides is also associated with the risk of developing asthma (R. C. Souza et al., 2020; El-Magd et al., 2011). Research by Yaqub (2019) stated that there was a much higher increase in the number of eosinophils in agricultural laborers exposed to pesticides compared to controls. This study found eight (40%) showing eosinophil levels exceeding the normal threshold value. These findings might indicate allergic sensitization in exposed laborers. Germolec and Luster (1994) in Yaqub (2019) reported that pesticide exposure caused allergic contact dermatitis, an inflammatory response that causes a rash. Health outcomes-related symptoms include eye redness, rash, itching, and chest pain. This is in line with the questionnaire data, where 14 (70%) of respondents complained of itching and redness in the area exposed to pesticides after spraying (Yaqub, 2019).

Eosinophil is vital in the body's defense since it acts as phagocytes and kills microorganisms, especially parasites. Eosinophil cells are also crucial in allergic reactions, which can also be associated with many disorders, such as asthma, tropical pulmonary eosinophilia, Loeffler syndrome, Churg-Strauss syndrome, atopic dermatitis, eosinophilic esophagitis, hyper-eosinophilic syndrome, some malignancies, and adverse drug reactions (Metcalfe et al., 2016; LeMessurier & Samarasinghe, 2019). Oxidative stress triggers hypersensitivity reactions, especially type I, such as asthma or atopic dermatitis (Liu et al., 2022). Hypersensitivity reaction I begins with Th2, which will stimulate the differentiation of B cells into plasma cells, producing IgE. Furthermore, a cross-reaction occurs among basophils, mast cells, and IgE, making basophils release inflammatory mediators chemotactic for eosinophils (Shi et al., 2022).

Basophils are essential in inflammatory and allergic responses, especially hypersensitivity reactions, and fight parasitic infections (Metcalfe et al., 2016). Basophils are critical in IgE-dependent and independent allergic inflammation through migration to sites of inflammation and secretion of various mediators, including cytokines, chemokines, and proteases. Basophils produce large amounts of IL-4 in response to various stimuli. Proteases produced from basophils are also necessary for allergic inflammation. In addition, recent reports have demonstrated the role of basophils in modulating adaptive immune responses, especially in the induction of Th2 differentiation and enhancement of humoral memory responses (Miyake & Karasuyama, 2017). In the case of asthma, the ROS originate from inflammatory cells (such as epithelial cells, macrophages, neutrophils, and eosinophils) and environmental factors (vehicle fumes, UV, chemicals), which activate transcription factors such as NF-κB and AP-1, which increase the release of IL-6, IL-8, and TNF-α, thus activating the T2 inflammatory response and causing the respiratory tract epithelium and capillary endothelial barrier function to be disrupted. ROS can stimulate mast cells and basophils to release histamine, prostaglandin D2, and other pro-inflammatory mediators, as well as increase mucus production by respiratory tract epithelial cells, resulting in airway inflammation. Prostaglandin D2 receptors on the membrane surface of Th2 cells, mast cells, and eosinophils, when they bind to PGD2, increase the transmigration of Th2 cells and activate eosinophils to sites of inflammation, releasing IL-4, IL-5, and IL-13 (Liu et al., 2022).

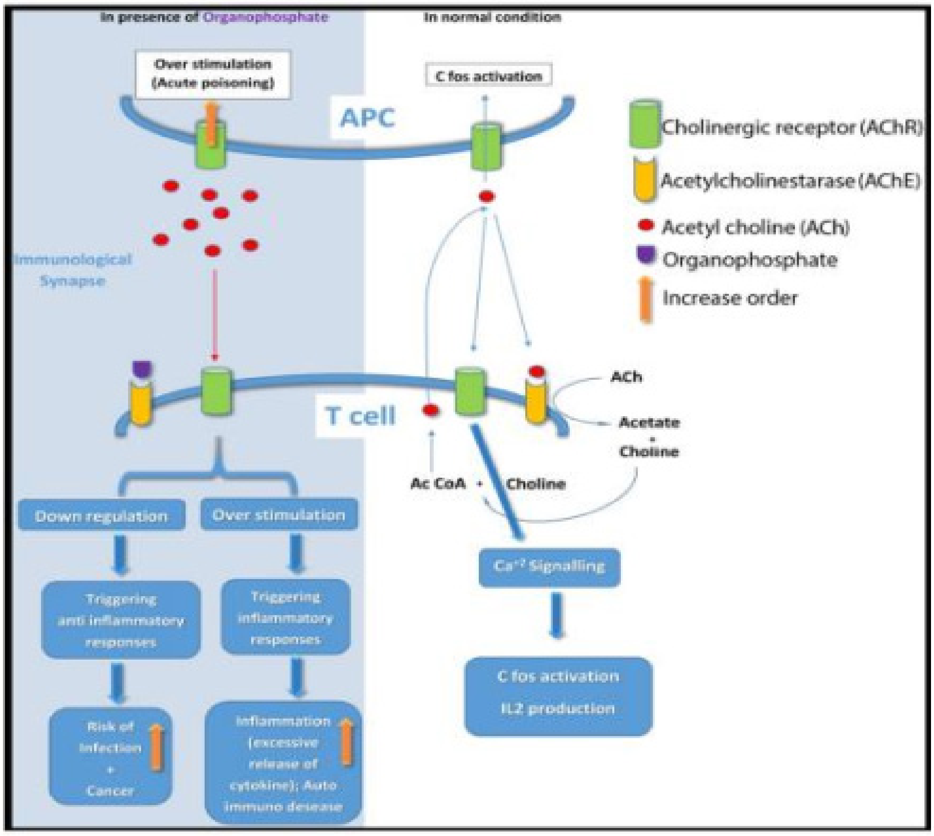

Figure 2. Impaired Cholinergic Response by Organophosphates (Mitra et al., 2019)

The figure above explains the organophosphate-induced cholinergic receptor disturbance in immunological synapses. Overstimulation of cholinergic receptors due to accumulation of ACh in immunological synapses results in intracellular Ca2+ signaling, increased c-fos expression and IL-2-induced signaling in T and B cells, and induction of an inflammatory response in macrophages or antigen-presenting cells (APCs). On the other hand, chronic organophosphate poisoning can trigger anti-inflammatory cholinergic signaling pathways via downregulation of cholinergic receptors, resulting in suppression of T-cell activity and susceptibility to certain cancers and infections, whereas upregulation of receptors results in excess cytokine release leading to autoimmune diseases (Mitra et al., 2019). The journal by E. Corsini (2013) stated that, overall, epidemiological studies raised the possibility that exposure to some pesticides might have been involved in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (Corsini et al., 2013).

Conclusion

This study shows that 20 pesticide sprayers (100%) have normal cholinesterase levels, four (20%) have normal total IgE levels, and 16 (80%) exceed the reference value. Meanwhile, the eosinophil levels of eight (40%) exceed the reference value. The basophil levels of eight (40%), too, exceed the reference value. Pesticide exposure will decrease the cholinesterase level, increase the IgE levels, and affect total basophils and eosinophils.

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