Meta-Analysis

Pesticide Exposure and Its Correlation with Hemoglobin and Cholinesterase in Farmers Who Used Pesticide

Arum Nuryati¹, Setyo Sri Rahardjo², Bhisma Murti¹

¹)Masters in Public Health, Universitas Sebelas Maret
²)Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: Agriculture is the most important sector in basic human needs. Farmers must improve the quality of agricultural products by using synthetic chemicals, someone who experiences pesticide poisoning will have low cholinesterase levels. This study aims to analyze pesticide exposure to hemoglobin and cholinesterase levels in farmers who use pesticides.

Subjects and Method: This was a systematic review study and meta-analysis conducted with the PRISMA diagram guidelines. The search for articles was carried out taking into account the eligibility criteria defined in the PICO model. Population= farmers using pesticides, Intervention= exposed to pesticides, Comparison= not exposed to pesticides, Outcome= hemoglobin and cholinesterase levels. The article search process was carried out between 2002-2022 from the Pubmed, Science Direct, Google Scholar, Springer Link, Hindawi, and Plose one databases. The keywords used were “hemoglobin”, “exposed pesticide”, “cholinesterase level”, “farmers”, “hemoglobin AND exposed pesticide”, “cholinesterase level AND farmers”, “hemoglobin AND farmers”. The inclusion criteria in this study were the full text of a cross-sectional study, discussing pesticide exposure to hemoglobin and cholinesterase levels in farmers using pesticides, published in English. Final results are presented in the mean SD of the multivariate analysis. Data analysis was performed using RevMan 5.4 software.

Results: A meta-analysis was conducted on 13 articles originating from America, Asia, Africa, and Europe. The results of the meta-analysis showed that farmers exposed to pesticides experienced a decrease in hemoglobin, but it was not statistically significant (SMD= -0.28; 95% CI= -1.10 to 0.54; p=0.500). Pesticide exposure reduced cholinesterase levels in farmers using pesticides, the results were statistically significant (SMD= -2.48; 95% CI= -3.68 to -1.27; p<0.001).

Conclusion: The results of the meta-analysis showed that pesticide exposure decreased hemoglobin and cholinesterase levels in farmers using pesticides.

Keywords: hemoglobin, cholinesterase levels, farmers

Correspondence:
Arum Nuryati. Masters Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: arumnuryati@student.uns.ac.id. Mobile: +6285728792097.

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BACKGROUND

Agriculture is the most important sector in meeting basic human needs, so farmers must improve the quality of their agricultural products by using synthetic chemicals to get optimal agricultural results. As a result of the use of synthetic chemicals, farmers are very vulnerable to exposure to the chemicals used, including pesticides. One of the blood test parameters to measure poisoning due to the use of pesticides in farmers can use the parameter...
of cholinesterase levels in the blood. (Kwanhian et al., 2019).

Pesticides are chemicals that function to control pests and prevent damage to plants. The main active compounds of this material are organophosphates, chlorinated hydrocarbons, and carbamide derivatives (Cuenca et al., 2020). Organophosphate and carbamate pesticides are neurotoxic by inhibiting acetylcholinesterase (AChE), with AChE unable to bind to acetylcholine to stop synaptic transmission. Inhibition of AChE in humans can cause many acute symptoms including dizziness, nausea, difficulty breathing, and even death. In addition, the nonspecific effect produces reactive oxygen species that attack lipids, proteins, and deoxyribonucleic acid (DNA), causing oxidation and membrane damage, enzyme inactivation, DNA damage, and cell death. Several authors have investigated the adverse haematological effects of organophosphates on blood hemoglobin, hematocrit level, red blood cell count, platelet count, and white blood cell count (Araoud et al., 2012).

A person who experiences pesticide poisoning will have low levels of CHE. Some pesticides are anti-CHE which can reduce the activity of CHE enzymes in the body. Decreased enzyme activity can result in nervous system disturbances, poisoning, and even death. Pesticide contamination in humans that enters the body can cause signs and symptoms that can be felt by sufferers and can be observed by others (Talcott, 2017).

People generally think it’s normal for the symptoms that arise in themselves after applying pesticides. They do not check with hospitals or health workers regarding the symptoms that arise which result in undetected cases of pesticide poisoning in the community so that chronic effects cannot be prevented. Symptoms and signs of poisoning vary, including headache, general weakness or fatigue, sweating, vomiting, blurred vision and seizures (BPPSDMK, 2018).

The use of PPE at the time of spraying can affect the number of pesticide particles entering the body of the sprayer. The more complete the PPE used when spraying, the smaller the possibility of abnormal CHE levels (Achmadi, 2016). Worldwide, an estimated three million cases of pesticide poisoning occur each year, resulting in more than 250,000 deaths. It is estimated by the World Health Organization (WHO) that about 18.2 per 100,000 agricultural workers experience work-related pesticide poisoning worldwide. In addition, more than 168,000 people die from pesticide poisoning every year, with most of them coming from developing countries (WHO, 2016 in Ssemugabo, 2017).

Indonesia itself, in 2016 there were 771 cases of pesticide poisoning based on data referenced from the National Poisoning Information Center (Sikernas). Pesticide poisoning in the period April-June 2017 was recorded as many as 180 cases (BPOM, 2017). This research was conducted because research on pesticide poisoning associated with hygiene behavior has several references but research on pesticide poisoning associated with haematological parameters has not been widely studied. The purpose of this study was to analyze the relationship between hemoglobin and pesticide poisoning by measuring cholinesterase levels in farmers using pesticides.

**SUBJECTS AND METHOD**

1. **Study Design**

This study was conducted using a systematic review and meta-analysis. The articles used in this research came from the database, Google Scholar, PubMed, Science
Pesticide exposure: The entry of pesticides into the body through oral, inhalation, and skin. Hemoglobin: Metalloprotein in red blood cells that functions to transport oxygen from the lungs to the rest of the body.

Cholinesterase levels: Enzymes found in cellular fluids that function to stop the action of acetylcoline by hydrolyzing it into choline and acetic acid.

2. Inclusion Criteria
The inclusion criteria in this study were: full text articles with cross-sectional study design, articles with appropriate titles and relating to the effect of pesticides on hemoglobin and cholinesterase levels in pesticide-using farmers, articles published in English and/or Indonesian, Include the results The research consisted of the number of respondents and the Mean SD, and the comparison of the results of hemoglobin and cholinesterase tests on farmers exposed to pesticides with controls.

3. Exclusion Criteria
The exclusion criteria for this study were: a cross-sectional study using hematological examination, cholinesterase levels, pesticide exposure in the research group, articles published before 2002, and non-farmer exposure to pesticides.

4. Operational Definition of Variables
The article search was conducted based on the eligibility criteria used using the PICO model. Population: farmers using pesticides, Intervention: exposure to pesticides, Comparison: not exposed to pesticides, Outcome: hemoglobin and cholinesterase levels.

RESULTS
The article search process was carried out through several journal databases including Google Scholar, PubMed, Science Direct, Springer Link, Hindawi, and PLOS One. The process of searching for related articles can be seen in the PRIMSA diagram in Figure 1.
Figure 1. PRISMA Flowchart

Article identified through database search (n= 1,263) → Deleting duplicate data (n= 325)

Filtered articles (n= 938) → Articles issued (n= 879)

Complete articles deemed eligible (n= 59)

Articles included in the systematic review and meta-analysis (n= 13)

Articles included in the qualitative (n= 13)

Full articles issued with reasons (n= 46)
- Articles that do not include Mean and SD = 31
- Intervention is not exposed to pesticides = 5
- Outcome is not hemoglobin and cholinesterase levels = 10

Figure 2. Map of study area

1 research in Europe
2 research in Africa
2 research in America
8 research in Asia
1. Results of the quality assessment of the cross-sectional study of pesticide exposure to hemoglobin in farmers

Table 1. Assessment of study quality using a cross-sectional study check list published by CEBMa

| No | Indicators                                                                 | Ahmadi et al. (2017) | Aroonvilarat et al. (2015) | Cestonaro et al. (2020) | Lermen et al. (2013) | Garcia et al. (2016) | Nambunmee et al. (2021) |
|----|---------------------------------------------------------------------------|----------------------|---------------------------|------------------------|---------------------|----------------------|------------------------|
| 1  | Do these objectives clearly address the research focus/problem?           | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 2  | Are cross-sectional research methods suitable to answer the research question? | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 3  | Is the research subject selection method clearly written?                 | 1                    | 1                         | 0                      | 1                   | 1                    | 1                      |
| 4  | Does the sampling method not introduce bias (selection)?                  | 1                    | 1                         | 0                      | 1                   | 1                    | 1                      |
| 5  | Does the research sample taken represent the designated population?       | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 6  | Was the sample size based on pre-study considerations?                    | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 7  | Was a satisfactory response achieved?                                     | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 8  | Are the research instruments (exposure to pesticides, Hb levels and cholinesterase levels) valid and reliable? | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 9  | Was statistical significance assessed?                                    | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 10 | Was a confidence interval given for the main outcome?                     | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |
| 11 | Have confounding factors been taken into account?                         | 1                    | 0                         | 1                      | 1                   | 1                    | 1                      |
| 12 | Are the results applicable to your research?                             | 1                    | 1                         | 1                      | 1                   | 1                    | 1                      |

Total: 12 11 11 12 12 12

Note: 1: Yes; 0: No
Nuryati et al./ Pesticide Exposure and Its Correlation with Hemoglobin and Cholinesterase

Table 1. Cont.

| No | Indicators                                                                 | Neupane et al. (2014) | Sine et al. (2021) | Hassanin et al. (2017) | Kori et al. (2019) | Kwanhian et al. (2019) | Sosan et al. (2010) |
|----|----------------------------------------------------------------------------|-----------------------|--------------------|------------------------|---------------------|------------------------|---------------------|
| 1  | Do these objectives clearly address the research focus/problem?            | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 2  | Are cross-sectional research methods suitable to answer the research question? | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 3  | Is the research subject selection method clearly written?                 | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 4  | Does the sampling method not introduce bias (selection)?                  | 1                     | 0                  | 1                      | 1                   | 1                      | 1                   |
| 5  | Does the research sample taken represent the designated population?       | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 6  | Was the sample size based on pre-study considerations?                    | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 7  | Was a satisfactory response achieved?                                     | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 8  | Are the research instruments (exposure to pesticides, Hb levels and cholinesterase levels) valid and reliable? | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 9  | Was statistical significance assessed?                                    | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 10 | Was a confidence interval given for the main outcome?                     | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 11 | Have confounding factors been taken into account?                         | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |
| 12 | Are the results applicable to your research?                              | 1                     | 1                  | 1                      | 1                   | 1                      | 1                   |

**Total** | 12 | 11 | 12 | 12 | 12 | 12 |

**Note:** 1: Yes; 0: No
Table 2. Description of primary studies meta-analysis of pesticide exposure to hemoglobin in farmers

| Author (Year)        | Country | Study Design     | Sample | Population                                      | Intervention                                      | Comparison                                      | Outcome       | Exposed to pesticides | Not exposed to pesticides |
|----------------------|---------|------------------|--------|-------------------------------------------------|--------------------------------------------------|------------------------------------------------|--------------|------------------------|---------------------------|
| Ahmadi et al. (2018) | Iran    | Cross-sectional  | 204    | 100 pesticide spraying farmers working in greenhouse | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 14.80 1.70             | 15.30 1.60                |
| Aroonvilari et al. (2015) | Thailand | Cross-sectional  | 124    | 64 pesticide-using farmers aged 20 to 60         | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 14.64 1.01             | 14.54 1.08                |
| Cestonaro et al. (2020) | Brazil  | Cross-sectional  | 116    | 62 farmers exposed to pesticides aged 23 to 71 years | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 14.30 0.20             | 14.90 0.20                |
| Garcia et al. (2016) | Spain   | Cross-sectional  | 280    | 189 farmers aged 18-66                           | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 14.36 0.10             | 13.85 0.14                |
| Lermen et al. (2018) | Brazil  | Cross-sectional  | 93     | 73 workers in the citrus farming sector aged 13-69 years | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 14.20 1.03             | 14.77 1.06                |
| Nambunmee et al. (2021) | Thailand | Cross-sectional  | 142    | 43 farmers from lowland Thailand                  | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 13.60 1.20             | 14.90 1.50                |
| Neupane et al. (2014) | Nepal   | Cross-sectional  | 180    | 90 vegetable farmers using pesticides             | Exposure to pesticides                           | Not exposed to pesticides                      | Hemoglobin   | 11.32 11.84            | 11.81 12.44               |
## Table 2. Cont.

| Author (Year) | Country    | Study Design   | Sample | Population                                    | Intervention                        | Comparison                        | Outcome   | Exposed to pesticides | Not exposed to pesticides |
|---------------|------------|----------------|--------|-----------------------------------------------|-------------------------------------|-----------------------------------|----------|------------------------|--------------------------|
| Sine et al. (2021) | Morocco     | Cross-sectional | 98     | 49 farmers exposed to pesticides              | Exposure to pesticides              | Not exposed to pesticides         | Hemoglobin | 14.84                  | 15.31                    |
| Sosan et al. (2010) | Nigeria     | Cross-sectional | 72     | 76 farmers from Osun and Ondo areas who use pesticides | Exposure to pesticides              | Not exposed to pesticides         | Hemoglobin | 12.83                  | 14.00                    |
| Hassanin et al. (2017) | Egypt       | Cross-sectional | 200    | 100 pesticide spraying workers                | Exposure to pesticides              | Not exposed to pesticides         | Hemoglobin | 12.64                  | 12.58                    |
| Kori et al. (2019) | India       | Cross-sectional | 105    | 51 agricultural sector workers exposed to pesticides | Exposure to pesticides              | Not exposed to pesticides         | Hemoglobin | 15.05                  | 14.64                    |
| Kewanhian et al. (2019) | Thailand    | Cross-sectional | 100    | 37 rice farmers using pesticides              | Exposure to pesticides              | Not exposed to pesticides         | Hemoglobin | 13.38                  | 12.88                    |
1. Pesticide exposure to hemoglobin in pesticide-using farmers

| Study or Subgroup | Torpapar pestisida | Tidak Torpapar pestisida | Std. Mean Difference | Std. Mean Difference |
|-------------------|--------------------|--------------------------|----------------------|----------------------|
|                    | Mean   | SD     | Total | Mean   | SD     | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| Almasi 2018       | 14.8   | 1.7    | 100   | 15.3   | 1.6    | 194   | -0.30 (0.58, -0.03) |                      |
| Almasi 2015       | 14.54  | 1.61   | 94    | 14.54  | 1.98   | 90    | 0.0% (0.26, 0.45)   |                      |
| Castaneda 2020    | 14.3   | 0.2    | 62    | 14.8   | 0.3    | 54    | 0.2% (0.26, 0.45)   | -2.98 (-3.91, -2.45) |
| Garcia 2016       | 14.36  | 0.1    | 108   | 13.95  | 0.14   | 91    | 0.3% (0.61, -0.05)  | 4.44 (4.09, 4.89)   |
| Hassan 2017       | 12.94  | 2.67   | 100   | 12.36  | 1.52   | 100   | 0.5% (0.24, 0.31)   |                      |
| Koht 2018         | 15.95  | 1.6    | 51    | 14.94  | 1.25   | 54    | 0.4% (0.10, 0.7)    | 0.20 (0.18, 0.22)   |
| Kostova 2019      | 13.38  | 1.73   | 61    | 12.95  | 1.87   | 25    | 0.3% (0.38, 0.02)   | 3.39 (3.08, 0.72)   |
| Lamas 2018        | 14.2   | 1.63   | 73    | 14.27  | 1.96   | 30    | 0.3% (0.55, -0.01)  | -0.54 (0.35, -0.11) |
| Nambooyre 2021    | 13.6   | 1.2    | 43    | 14.19  | 1.6    | 96    | 0.4% (0.29, 0.6)    | -0.91 (-1.29, -0.54) |
| Nejame 2014       | 11.32  | 1.84   | 90    | 11.81  | 1.44   | 80    | 0.4% (0.33, 0.25)   | -0.64 (-0.33, 0.25) |
| Seven 2021        | 14.8   | 1.39   | 49    | 15.33  | 1.92   | 45    | 0.3% (0.78, 0.02)   | -0.30 (0.78, 0.02)   |
| Sora 2010         | 12.83  | 0.75   | 36    | 14     | 0.38   | 36    | 0.0% (0.49, -0.28)  | -3.51 (4.23, -2.78) |

Total (95% CI) 918 796 100.0% -0.28 [-1.10, 0.54]

Heterogeneity Tau^2= 2.05; Chi^2= 822.74; df= 11 (p = 0.00001); P = 58%
Test for overall effect: Z = 0.87 (P = 0.50)

The forest plot showed that farmers exposed to pesticides experienced a decrease in hemoglobin of 0.28 units lower than farmers who were not exposed to pesticides and this result was not statistically significant (SMD=-0.28; 95% CI=-1.10 to 0.54; p=0.500). The heterogeneity in this study showed I^2=98%, so that the distribution of the data was declared heterogeneous (random fixed effect).

**Figure 3. Forest plot of pesticide exposure to hemoglobin in pesticide-using farmers**

The funnel plot in Figure 4 shows the same number of studies with estimates above and below the average estimate, in other words the shape of the funnel plot is more or less symmetrical so it does not indicate publication bias.

**Figure 4. Funnel plot of pesticide exposure to hemoglobin levels in farmers using pesticides**
2. The results of the quality assessment of the cross-sectional study of pesticide exposure on cholinesterase levels in farmers

Table 3. Assessment of study quality using a cross-sectional study check list published by CEBMa

| No | Indicators                                                                 | Ahmadi et al. (2017) | Aroonvi-lariat et al. (2015) | Cestonaro et al. (2020) | Fareed et al. (2013) | Garcia et al. (2016) | Nambunmee et al. (2013) | Neupane et al. (2014) | Sine et al. (2017) |
|----|-----------------------------------------------------------------------------|----------------------|-----------------------------|--------------------------|----------------------|-----------------------|------------------------|----------------------|---------------------|
| 1  | Do these objectives clearly address the research focus/problem?              | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 2  | Are cross-sectional research methods suitable to answer the research question? | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 3  | Is the research subject selection method clearly written?                   | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 0                   |
| 4  | Does the sampling method not introduce bias (selection)?                    | 1                    | 1                           | 0                        | 1                    | 1                     | 1                      | 1                    | 0                   |
| 5  | Does the research sample taken represent the designated population?         | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 6  | Was the sample size based on pre-study considerations?                      | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 7  | Was a satisfactory response achieved?                                       | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 8  | Are the research instruments (Hb levels and cholinesterase levels) valid and reliable? | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 9  | Was statistical significance assessed?                                      | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 10 | Was a confidence interval given for the main outcome?                       | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 11 | Have confounding factors been taken into account?                           | 1                    | 0                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |
| 12 | Are the results applicable to your research?                               | 1                    | 1                           | 1                        | 1                    | 1                     | 1                      | 1                    | 1                   |

| Total                     | 12                   | 11                     | 11                       | 12                     | 12                     | 12                     | 12                     | 12                   | 11                  |

Note: 1: Yes; 0: No
Table 4. Description of the primary study of pesticide exposure to cholinesterase levels in farmers

| Author (year) | Country         | Study Design | Sample | Population | Intervention | Comparison                  | Outcome                     | Exposed to pesticides | Not exposed to pesticides |
|---------------|-----------------|--------------|--------|------------|--------------|-----------------------------|-----------------------------|------------------------|--------------------------|
| Ahmadi et al. (2017) | Iran           | Cross-sectional | 204    | 100 farmers spraying pesticides working in greenhouse | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 23.00 | 30.30 | 10.00 | 7.00 |
| Aroonvilariat et al. (2019) | Thailand | Cross-sectional | 124    | 64 pesticide-using farmers aged 20 to 60 | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 41.11 | 52.91 | 11.53 | 11.92 |
| Cestonaro et al. (2020) | Brazil       | Cross-sectional | 116    | 62 farmers exposed to pesticides aged 23 to 71 years | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 11.35 | 17.04 | 4.07  | 8.28 |
| Fareed et al. (2013) | India         | Cross-sectional | 243    | 166 pesticide sprayers on plantation | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 42.03 | 57.02 | 23.10 | 30.70 |
| Garcia et al. (2016) | Spanish | Cross-sectional | 280    | 189 farmers aged 18-66 | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 19.24 | 29.63 | 0.49  | 0.59 |
| Nambunmee et al. (2019) | Thailand | Cross-sectional | 142    | 43 farmers from lowland Thailand | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 13.83 | 10.73 | 6.00  | 0.83 |
| Sine et al. (2013) | Morocco       | Cross-sectional | 98     | 49 farmers exposed to pesticides | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 7.82  | 10.51 | 2.00  | 2.40 |
| Neupane et al. (2014) | Nepal         | Cross-sectional | 180    | 90 vegetables farmers exposed pesticides | Exposure to pesticides | Not exposed to pesticides | Cholinesterase levels | 32.40 | 35.30 | 34.50 | 37.50 |
2. Pesticide exposure to cholinesterase levels in farmers using pesticides

| Study or Subgroup | Terpapar pestisida Mean | SD | Total | Tidak terpapar Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|-------------------|-------------------------|----|-------|---------------------|----|-------|--------|----------------------------------------|
| Ahmad 2018        | 23                      | 10 | 100   | 30.3                | 7  | 104   | 12.86% | -0.65 [1.13, -0.58]                    |
| Atkinson 2015     | 41.1                    | 11.53 | 64    | 52.91               | 11.92 | 80    | 12.86% | -1.00 [1.37, -0.63]                    |
| Casaleno 2016     | 13.6                    | 4.07 | 62    | 17.04               | 8.28 | 54    | 12.86% | -0.65 [0.62, -0.18]                    |
| Formed 2013       | 42.03                   | 23.1 | 106   | 57.02               | 30.7 | 77    | 12.86% | -0.66 [0.68, 0.31]                     |
| Garcia 2016       | 19.24                   | 0.49 | 109   | 20.53               | 0.59 | 91    | 10.4%  | -19.76 [21.42, -18.09]                 |
| Nambumene 2021    | 13.83                   | 6    | 43    | 10.73               | 0.83 | 95    | 12.86% | 0.32 [0.54, 1.28]                      |
| Nampa 2014        | 32.4                    | 34.5 | 90    | 35.3                | 37.5 | 90    | 12.86% | -0.08 [-0.37, 0.21]                    |
| Sine 2021         | 7.02                    | 2    | 36    | 10.51               | 2.4  | 26    | 12.7%  | -1.20 [-1.71, -0.70]                   |

Total (95% CI) 750 611 100.0% 2.48 [3.68, 1.27]

Heterogeneity: $I^2 = 99\%$, $Q = 84.61, df = 9, p < 0.001$.

Figure 6. Forest plot of pesticide exposure to cholinesterase levels on pesticide-using farmers

The forest plot showed that farmers exposed to pesticides experienced a decrease in cholinesterase levels by 2.48 units lower than farmers who were not exposed to pesticides and this result was statistically significant (SMD= -2.48; 95% CI= -3.68 to -1.27; p<0.001). The heterogeneity in this study showed $I^2 = 99\%$, so that the distribution of the data was declared heterogeneous (random fixed effect).

Figure 5. Forest plot of pesticide exposure to cholinesterase levels on pesticide-using farmers

The funnel plot in Figure 5, shows a tendency for more studies to have a larger estimate than the average estimate, which indicates an underestimate of publication bias.
DISCUSSION

Pesticides are an important source of hazards in agriculture that can cause morbidity and mortality worldwide, especially in developing countries. It is estimated that there are 3 million cases of acute pesticide poisoning that occur every year with 250,000 people dying (Gunnel et al, 2007).

High sulfate content in pesticides can form sulfhemoglobin bonds, which will cause hemoglobin to become abnormal and unable to carry out its function in delivering oxygen. Anemia can occur in patients with organophosphate and carbamate pesticide poisoning because the form of sulfhemoglobin and methemoglobin in red blood cells causes a decrease in hemoglobin levels, resulting in hemolytic anemia. The incidence of hemolytic anemia occurs due to contact with pesticides caused by enzymatic defects in red blood cells and the number of red blood cells and the amount of toxic substances that enter the body.

This meta-analysis investigated pesticide exposure to hemoglobin in pesticide-using farmers with a sample size of 1,714 individuals from 12 cross-sectional studies conducted in America, Africa, Europe, and Asia. The findings of this study explain that exposure to pesticides causes a decrease in hemoglobin. The forest plot results revealed that farmers exposed to pesticides experienced a decrease in hemoglobin compared to farmers who were not exposed to pesticides (SMD= -0.28; 95% CI= -1.10 to 0.54). Consequently, pesticide exposure may be a risk factor for reduced hemoglobin levels in pesticide-using farmers.

Confounding factors were found such as length of exposure to pesticides, duration of spraying, age, gender, use of personal protective equipment, and correct hygiene habits.

Pesticide exposure to hemoglobin in farmers who use pesticides is not statistically significant, it can be caused by pesticide exposure which can be influenced by the duration of pesticide use so that it can cause chronic poisoning. Based on the entrance of pesticides into the human body through the skin, mouth (swallowing), and lungs (inhalation). Chronic poisoning can occur due to exposure to toxic substances in low doses over a long period of time. Some of the factors that can influence it include the use of appropriate PPE, the age of farmers who are still productive, proper nutritional status, and proper hygiene habits in pesticide waste management (Mohammed et al., 2013).

A study involving 200 respondents consisting of 100 farmers using pesticides and 100 healthy people as controls in Egypt, revealed that farmers used excessive amounts of pesticides (not as recommended on the packaging) without knowing the toxicological effects. In this study, it was found that pesticide spraying workers who were often exposed to pesticide mixtures showed abnormalities in several hematological parameters and kidney function (Hassanin et al., 2017).

The cholinesterase enzyme is an enzyme found in cellular fluids whose function is to stop the action of acetylcholine by hydrolyzing it into choline and acetic acid. The use of pesticides to control plant pests carries the risk of accidents to
humans in the form of chronic or acute poisoning and death if the poisoning level is severe and is related to the level of cholinesterase inhibition in the blood (Ramsingh, 2010).

This meta-analysis investigated pesticide exposure to hemoglobin in pesticide-using farmers with a sample size of 1,387 individuals from 8 cross-sectional studies conducted in America, Africa, and Asia. The findings of this study explain that exposure to pesticides causes a decrease in cholinesterase levels. The results of the forest plot revealed that farmers exposed to pesticides experienced a decrease in cholinesterase levels compared to farmers who were not exposed to pesticides (SMD = -2.48; 95% CI = -3.68 to -1.27). Consequently, pesticide exposure may be a risk factor for reduced cholinesterase levels in pesticide-using farmers.

If a person is exposed to organophosphate pesticides, cholinesterase will bind to pesticides that are irreversible. Then a reaction will occur with acetylcholine, so that the examination will show a decrease in cholinesterase activity or an increase in acetylcholine levels. The decrease in cholinesterase activity in erythrocytes can last for 1 to 3 weeks, while the decrease in cholinesterase activity in platelets lasts up to 12 weeks or 3 months (Ramsigh, 2010).

The research of Nambunmee et al. (2021) with the results (p<0.001) showed that farmers who sprayed pesticides experienced a significant decrease in cholinesterase levels compared to the control group who were not exposed to pesticides. Low AChE indicates excessive pesticide exposure can cause health problems. Another finding from a cross-sectional study in the Northern Thailand region, Thailand which included 97 farmers consisting of 70 conventional farmers using pesticides and 27 as controls who had never been exposed to pesticides and were in good health. The results of this study indicate that conventional farmers who use pesticides have lower cholinesterase levels than modern farmers (Forte et al., 2021).

Limitations in this study may occur because the results of the meta-analysis of pesticide exposure to hemoglobin and cholinesterase levels in farmers using pesticides with a cross-sectional study design experienced publication bias, article search bias because it only used 6 databases, and language bias because it only used articles in English. Pesticide exposure can reduce hemoglobin and cholinesterase levels in farmers who use pesticides.

**AUTHORS CONTRIBUTION**
Arum Nuryati is the main researcher who selects the topic, searches for and collects research data. Setyo Sri Rahardjo and Bhisma Murti analyzed the data and review research documents.

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**CONFLICT OF INTEREST**
There is no conflict of interest.
REFERENCES

Achmadi (2016). Kesehatan masyarakat teori dan aplikasi (Public Health Theory and Application). Jakarta: Raja Grafindo Persada.

Ahmadi N, Mandegary A, Jamshidzadeh A, Mohammadi SM, Salari E, Pourgholi L (2018). Hematological abnormality, oxidative stress, and genotoxicity induction in the greenhouse pesticide sprayers; investigating the role of NQO1 gene polymorphism. Toxics, 6(1): 1–15. doi: 10.3390/toxics6010013

Araoud M, Neffeti F, Douki W, Hfaiedh H, Akrout M, Hassine M, Najjar M et al. (2012). Adverse effects of pesticides on biochemical and haematological parameters in Tunisian agricultural workers. J Expo Sci Environ Epidemiol. 22(3): 243–247. doi: 10.1038/jes.2012.11

Aroonvilairat S, Kespichayawattana W, Sornprachum T, Chaisuriya P, Siwadune T, Ratanabanangkoon K (2015). Effect of pesticide exposure on immunological, hematological and biochemical parameters in Thai orchid farmers—A cross-sectional study. Int J Environ Res and Public Health. 12(6): 5846–5861. doi: 10.3390/ijerph120605846.

BPOM (2017). Sistem informasi keracunan (online) (Poisoning Information System (online). Available in http://ik-pom.go.id/v2016/. Access at October 06, 2021

Cuenca BJ, Tirado N, Vikstrom M, Lindh CH, Stenius U, Leander K, Berglund M et al. (2020). Pesticide exposure among Bolivian farmers: associations between worker protection and exposure biomarkers. J Expo Sci Environ Epidemiol. 30(4): 730–742. doi: 10.1038/s41370-019-0128-3

Center for Evidence Based Management (2014). Critical Appraisal Checklist for Cross-sectional Study

Cestonaro LV, Garcia SC, Nascimento S, Gauer B, Sauer E, Goethel G, Peruzzi C et al. (2020). Biochemical, hematological and immunological parameters and relationship with occupational exposure to pesticides and metals. Environ Sci Pollut Res. 27(23): 29291–29302. doi: 10.1007/s11356-020-09203-3.

Fareed M, Pathak MK, Bihari V, Kamal R (2013). Adverse respiratory health and hematological alterations among agricultural workers occupationally exposed to organophosphate pesticides: a cross sectional study in North India. PLoS one Journals.plos.org.

Garcia CR, Parron T, Requena M, Alarcon R, Tsatsakis AM, Hernandez AF (2016). Occupational pesticide exposure and adverse health effects at the clinical, hematological and biochemical level. Life Sci. 145: 274–283. doi: 10.1016/j.lfs.2015.10.013.

Gunnell D, Eddleston, M, Phillips, MR, Konradsen F (2007). The global distribution of fatal pesticide self-poisoning: Systematic review. BMC Public Health. 7(c): 1–15. doi: 10.1186/1471-2458-7-357

Hassanin NM, Awad OM, El-Fiki S, Abou SRAI, Abou SARA, Amer RA (2018). Association between exposure to pesticides and disorder on hematological parameters and kidney function in...
male agricultural workers. Environ Sci Pollut Res. 25(31): 30802–30807. https://doi.org/10.1007/s11356-017-8958-9.

Hundekari IA, Suryakar AN, Rathi DB (2013). Acute organo-phosphorus pesticide poisoning in North Karnataka, India: oxidative damage, haemoglobin level and total leukocyte. Afr Health Sci. 13(1): 129-36. doi: 10.4314/ahs.v13i1.18.

Kori RK, Hasan W, Jain AK, Yadav RS (2019). Cholinesterase inhibition and its association with hematological, biochemical and oxidative stress markers in chronic pesticide exposed agriculture workers. J Biochem Mol Toxicol, 33(9). doi: 10.1002/jbt.20367.

Kwanhian W, Yimthiang S, Jawjit S, Mahaboon J, Thirarattanasunthon P, Vattanasit U (2019). Hematological indices of pesticide exposure on rice farmers in Southern Thailand. Public Health. 14(1): 37–42. doi: 10.21109/kesmas.v14i1.2812.

Mohammed MA, Arafah, A, Afify M, Samy N (2013). Evaluation of Adverse Health Effects of Pesticides Exposure [Biochemical & Hormonal] among Egyptian Farmers. Res J Appl Sci. 9(7): 4404–4409.

Nambunmee K, Kawiya T, Neitzel RL, Seeprasert P (2021). Pesticide Spraying and Reduced Cholinesterase Activity among Hill Tribe Farmers in Thailand. J Health Pollut. 11(31): 1–12. doi: 10.5696/2156-9614-11.31.21-0908.

Neupane D, Jors E, Brandt L (2014). Pesticide use, erythrocyte acetylcholinesterase level and self-reported acute intoxication symptoms among vegetable farmers in Nepal: A cross-sectional study. Environ Health: Glob Access Sci Source. 13(1): 1–7. doi: 10.1186/1476-069X-13-98.

Patil S, Gode N (2019). A cross sectional study of effects of organophosphorus pesticides on cardio respiratory parameters among farm labourers of North Maharashtra. J Appl Physiol. 03 (4): 29-36. https://apad.co.in.

Ramsingh D (2010). The Assessment of the chronic toxicity and carcinogenicity of pesticide toxicology. Hayes Handbook of Pesticide Toxicology, Krieger R, Editor. USA: Elsevier.

Samosir K, Setiani O (2017). Hubungan panganan pestisida dengan gangguan keseimbangan tubuh petani hortikultura di Kecamatan Ngablan Kabupaten Magelang. J Kesehat Lingkung Indonesia. 16(2): 63-69. doi: 10.14710/jkli.16.2.63-69.

Sine H, Achbani A, Filali K (2021). Measuring butyrylcholinesterase activity and hematological parameters in farmers exposed to pesticides: a case and control study from Morocco. Arch Environ Occup Health. 0(0): 1-6. doi: 10.1080/19338244.2021.1886034.

Sosan MB, Akingbohungbe AE, Durosinmi MA, Ojo IAO (2010). Erythrocyte cholinesterase enzyme activity and hemoglobin values in cacao farmers of southwestern Nigeria as related to insecticide exposure. Arch Environ Occup Health. 65(1): 27–33. doi: 10.1080/19338240903390289.
Talcott P (2017). Toxicologic problems in equine internal medicine: Fourth Edition. St Louis Missouri: Elsevier.
Sine H, Achbani A, Filali K (2021). Measuring butyrylcholinesterase activity and hematological parameters in farmers exposed to pesticides: a case and control study from Morocco. Arch Environ Occup Health. 1–6. doi: 10.1080/-19338244.2021.1886034.
Sosan MB, Akingbohungbe AE, Durosinmi MA, Ojo IAO (2010). Erythrocyte cholinesterase enzyme activity and hemoglobin values in cacao farmers of southwestern Nigeria as related to insecticide exposure. Arch Environ Occup Health. 65(1): 27–33. doi: 10.1080/19338240903390289.

Ssemugabo C, Halage AA, Neebye RM, Nabankema V, Kasule MM, Ssekimpi D, Jors E (2017). Prevalence, circumstances, and management of acute pesticide poisoning in hospitals in Kampala City, Uganda. Environ Health Insights. 4(11): 1-8, doi: 10.1177/1178630217728924.
Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, dan Prescott HC (2020). Pathophysiology, transmission, diagnosis, dan treatment of coronavirus disease 2019 (COVID-19): A Review. J. Am. Med. Assoc. 324(8): 782–793. doi: 10.1001/JAMA.2020.12839.