PESTICIDE EXPOSURE DURING PREGNANCY INCREASES THE INCIDENCE OF AUTISM

Enggal Hadi Kurniyawan[1], Natasya Dwi Angelina[1], Dilayatul Mukarromah[1], Amalia Dewi Masithoh[1], Darodjadien Naufal Nabawi[1], Alfid Tri Afandi[1], Dicky Endrian Kurniawan[1]
(Faculty of Nursing, Universitas Jember; enggalhadi.psik@unej.ac.id)

Abstract

Pesticides that are often used in the agricultural sector are known as organophosphate, which can affect the functionality of pregnant women and fetal bodies, both acutely and chronically. It can increase the risk of children developing autism spectrum disorders. This literature review aims to identify the type, frequency, dose, and transmission criteria of mothers who are poisoned or exposed to pesticides with the incidence of ASD in children, both pre-birth and early in life. This research uses the study methods of literature review with three online databases, namely Google Scholar, PubMed, and ScienceDirect, with publications between 2017 and 2023. The ten journals explain that Several types of pesticides, such as DDE, pyrethroids, organophosphates, and glyphosate, which are exposed to pregnant women, are associated with the incidence of autism in children in their womb. Usually, children are known to have autism at the age of 3 years or the age of 5 years. Exposure to pesticides during pregnancy can contribute to the risk of developing Autism Spectrum Disorder (ASD) in children. Some pesticides, such as organophosphates, are associated with an increased risk of ASD in children. In addition, acetic acid intake during pregnancy may affect the relationship between pesticide exposure and the risk of developing ASD in children. Health workers can conduct counseling about the dangers of exposure to peptides in fetal development for pregnant women.

Keywords: *Autism; Pesticide; Agricultural; Pregnancy*

Abstrak

Pestisida yang sering digunakan di sektor pertanian dikenal dengan nama organofosfat, yang dapat mempengaruhi fungsi tubuh ibu hamil dan janin, baik secara akut maupun kronis. Hal ini dapat meningkatkan risiko anak terkena gangguan spektrum autisme. Tinjauan literatur ini bertujuan untuk mengidentifikasi jenis, frekuensi, dosis, dan kriteria penularan ibu yang keracunan atau terpapar pestisida dengan kejadian ASD pada anak, baik sebelum melahirkan maupun di awal kehidupan. Penelitian ini menggunakan metode studi literatur review dengan tiga database online yaitu Google Scholar, PubMed, dan ScienceDirect dengan publikasi antara tahun 2017 hingga 2023. Kesepuluh jurnal tersebut menjelaskan bahwa beberapa jenis pestisida seperti DDE, piretroid, organofosfat, dan glifosat , yang terpapar pada ibu hamil, berhubungan dengan kejadian autisme pada anak dalam kandungannya. Biasanya anak diketahui mengidap autisme pada usia 3 tahun atau usia 5 tahun. Paparan pestisida saat hamil dapat berkontribusi terhadap risiko terjadinya Autism Spectrum Disorder (ASD) pada anak. Beberapa pestisida, seperti organofosfat, dikaitkan dengan peningkatan risiko ASD pada anak-anak. Selain itu, asupan asam asetat selama kehamilan dapat mempengaruhi hubungan antara paparan pestisida dan risiko terjadinya ASD pada anak. Tenaga kesehatan dapat melakukan penyuluhan mengenai bahaya paparan peptida pada perkembangan janin bagi ibu hamil.

Kata Kunci : *Autism; pestisida; Pertanian; Kehamilan*

INTRODUCTION

Agronursing is the management of nursing services and care in agriculture, plantations, fisheries, breeding, and agro-industry (Kurniyawan et al., 2023a). Agronursing is a nursing

management system focused on individual, family, and community clients that is comprehensive and holistic in the agricultural environment (Afandi et al., 2023). Agriculture is a production activity based on plant and animal growth, including plantations, forestry, fisheries, and animal husbandry (Kurniyawan et al., 2023b). This agricultural area is an important aspect, especially in improving the quality of life. Most of the places called "Tapal Kuda" have a main livelihood in the agricultural sector.

It is based on the Indonesian Central Bureau of Statistics (BPS), which shows 38.7 million agriculture, forestry, and fisheries workers as of August 2022. This accounts for 28.6% of the total working population of 135.3 million people and is the largest of the other main jobs (BPS, 2022). East Java Province ranks as the twelfth-highest contributor to agricultural sector workers, reaching 92.69 million after Maluku and South Sulawesi, which amount to 93.56 million and 93.33 million, respectively. In addition, agricultural workers in the village are employed by men and highly dominated by women, as much as 46.33% in 2023 (Dinas Kominfo Provinsi Jawa Timur, 2023). This high rate increases the chances of health problems, especially for pregnant women in agricultural areas. This is triggered by job applications requiring the spraying of pesticides.

Pesticides are fertilizers produced with chemicals, microorganisms, and viruses. It is widely applied by farmers to obtain optimal agricultural products to control pests, weeds, insects, and other diseases or animals that damage agricultural products (Saftrina et al., 2018). The type of pesticides that are often used in the agricultural sector are known as Organophosphate Pesticides. This type is considered to have a very high toxic concentration because it inhibits AChE (Acetylcholinesterase Enzyme), which can break down neurotransmitters in the post-synaptic membranes. In addition, organophosphate substances have harmful mechanisms, including pro-inflammation, disruption of GABA signaling, thyroid disorders, oxidative stress induction, and mitochondrial dysregulation gestate (Miani et al., 2021).

Types of ingredients, frequencies, doses exceeding usual limits, and too close use of pesticides can benefit or damage plants and affect the functionality of pregnant women and fetal bodies acutely and chronically (Bertoletti et al., 2023). Reviewing the definition of pregnancy, the condition of a woman carrying a fetus for approximately nine months or 40 weeks due to the conception of spermatozoa and ovum with continued nidation. This pregnancy is divided into three trimesters: the 1st trimester from 1 to 12 weeks, the 2nd trimester from 13 to 28 weeks, and the 3rd trimester from 29 to 40 weeks (Huffman, 2023). This vulnerable trimester is the beginning of exposure to pesticides that affect fetal development.

Although most pregnant women farmers are not directly involved in spraying, they will do their jobs as preparing pesticides until they wash the tools, harvest agricultural products, and

throw away weeds around the spraying area (Saftrina et al., 2018). But their contribution can affect the development of the fetus during conception and pregnancy because high-fat content triggers pesticides to quickly accumulate into body tissues, protein, and bone in the first year of the baby's life, especially those supported by the limitations of the PPE (Personal Protective Equipment) being imposed (Hardiana et al., 2021; Miani et al., 2021). This is due to the ingredients in pesticides that are quickly and perfectly absorbed by the body, either inhalation, ingestion, topical contact, including injured skin, and ingested from food around the pesticide area or agricultural products with improper processing procedures (Widyawati et al., 2018). Health problems acquired after pesticide exposure are complex. One of the authors' concerns is the adverse effects on the functional nervous system, including cognitive, psychomotor, and development of nerve cells that affect development during gestation and early childhood, namely ASD or Autism Spectrum Disorder.

Autism Spectrum Disorder is a heterogeneous neurodevelopmental disorder characterized by atypical socialization characteristics, persistent limitations on interest and behavior, and decreased communication skills (Biosca-Brull et al., 2021). Genetic factors are estimated to account for 38–83%, but environmental factors are also identified as factors that include air pollution, gestational diabetes, autoimmune diseases in the family, and pesticide exposure (Ehrenstein et al., 2019).

Exposure to pesticides such as Organophosphate and Organochlorine increases the risk of children developing spectrum disorders (Lyall et al., 2017). This was supported by research in California (2019) that collected samples of 2,961 children with ASD and obtained a 10:1 ratio that there was a positive correlation between exposure to organophosphate during pregnancy, a radius of 2.000 m from the mother's place and incidence of ASD in the child, especially in the 2nd and 3rd trimesters of pregnancy (Miani et al., 2021). Another study by Kongtip et al. (2017) on Organophosphate exposure to infant development in 5-month-old Thailand was carried out using the Bayley Scales of Infant and Toddler Development-III (Bayley-III) method combined with the metabolic rate of organophosphate in maternal urine in total diethyl phosphate (DEP) and total dimethyl amino phosphate DAP in the 3rd trimester (28 weeks). The results significantly correlate with the decline in PDI and MDI (Mental Development Index) (Kongtip et al., 2017; Saftrina et al., 2018).

The prevalence of autism in children in the world continues to increase. This was explained by the World Health Organization (2018), which stated that an estimated 1 in 160 children worldwide have Autism Spectrum Disorder (ASD). According to data from the Centers for Disease Control and Prevention (CDC) and Developmental Disabilities Monitoring (ADDM) in 2020, approximately 1 in 36 children in the United States were diagnosed with ASD. In addition, about 1 in 6 (17%) children aged 3–17 years were diagnosed with a developmental disability, as reported by parents, during a study period of

2009-2017. These included autism, attention-deficit/hyperactivity disorder, blindness, and cerebral palsy, among others (CDC, 2023).

Currently, based on the Indonesian Central Bureau of Statistics, there are approximately 270.2 million children with autism, a growth of around 3.2 million children (Nurman, 2023). The stagnation or increase in some of the prevalence listed led the author to review the literature on the effects of pesticides on autism so that the types, frequency, dose, and transmission criteria of mothers who are exposed to pesticides can cognitive development can identify the child's mental, psychomotor, and sensory experiences are both pre-post natal and early life.

RESEARCH METHODS

This research uses the study methods of literature review. The secondary data source of the scientific report is contained in the article. Search articles using online databases through Google Scholar, PubMed, and ScienceDirect with publications between 2017-2023. The study results of the three online databases use Indonesian and English keywords. In the Indonesian, using keywords kehamilan AND peptisida OR organofosfat AND autisme AND agrikultural. In English, use keywords prenatal OR infant OR pregnancy AND autism disorder AND pesticides OR organophosphate AND agricultural.

The process of searching the article begins by identifying predetermined keywords. In the identification section, 162 articles that matched the keywords were found. The next stage is screening according to the title and year of the article. At the screening stage, 71 articles matched the search criteria. Furthermore, articles were screened according to the inclusion and exclusion criteria of the research. Thirty-five articles fit the inclusion and exclusion criteria of the study. After that, filter the abstracts that focus on the assessment criteria. At this stage, 18 articles that matched the assessment criteria were found. Then, the articles are re-selected according to the results, language, design, and other criteria. Finally, ten articles that met the research criteria were found and could proceed to the analysis stage.

RESEARCH RESULT

Table 1. The result of the literature review

No	Author and Journal Identity	Journal Title	Objective	Population and Sample	Method	Summary of Result
1.	Author: Ehrenstein et al., Journal Identity: BMJ/2019	Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in	Assessing the impact of early prenatal and infant exposure to pesticides	Population of 2961 individuals diagnosed with ASD in California. Sample of 8 districts	Case study controlled population of ASD cases from California DDS randomly	ASD is predominately male (>80%). Pesticide exposure at conception has a low association. At the same time, during pregnancy and the

	(Ehrenstein et al., 2019)	children: population-based case-control study	with high dose use on ambient and autism spectrum disorders	(San Joaquin, Stanislaus, Merced, Madera, Fresno, Tulare, and Kern).	selected from birth records matched to each case 10:1 based on birth and sex.	first year of life, the baby is at higher risk of ASD, and direction during infancy may also contribute to the risk of severe phenotypic disorders in the form of comorbid ID. There is a slightly to moderately increased risk for prenatal damage to offspring by ten pesticides except myclobutanil compared to offspring born within a 2,000m radius.
2.	Author: Brown et al. Journal Identity: Am J Psychiatry/ 2018	Maternal insecticide levels are associated with autism in offspring from a national birth cohort.	Assess whether there is an increase in maternal POP levels associated with autism in their offspring or their children.	The population of all FMC offspring of 1 million prenatal serum specimen pregnancies (from the 1st to the early 2nd trimester) started in 1983. Sample all members of the 1987–2005 birth cohort who were at risk of autism	Case-control design of the FHDR sample by identifying all records of children (single births) diagnosed with autism since January 1, 1987 - currently 778 of a total of 1,132 cases.	Maternal exposure to p,p'DDE is associated with autism from preterm birth and at a young gestational age due to inhibition of receptor binding, androgen transcriptional activity, and developing androgen action. In addition, the association of maternal p,p'-DDE and autism was isolated for cases with comorbid ID with cognitive, psychomotor, verbal, and memory dysfunction in offspring but did not affect neurocognition. While PCBs do not correlate with autism.
3.	Author: Pu et al. Journal Identity: PNAS/ 2020	Maternal glyphosate exposure causes autism-like behaviors in offspring through	Testing the association of Seh in the pathogenesis of ASD in	The population and samples taken were ten mothers who were	Methods used by accumulating evidence suggest a key role for Seh in the prefrontal	Exposure to high levels of glyphosate (0.098%) during pregnancy and lactation causes ASD-like adolescent offspring behavior. The lower profile of

		increased expression of soluble epoxide hydrolase.	offspring after maternal glyphosate exposure.	exposed to glyphosate.	cortex (PFC) in the development of behavioral disorders such as ASD in adolescent offspring.	Seh protein in PFC, hippocampus, and striatum, significant reduction of glutamate in plasma and brain areas indicating abnormal neurotransmission (NMDAR in pediatric PFC), abnormal gut microbiota resulting in increased acetic acid levels after maternal organophosphate exposure. Thus, Seh is essential in behavioral abnormalities in children after maternal glyphosate exposure and is a promising prophylactic drug for ASD.
4.	Author: Barkoski, et al Journal Identity: Int J Hyg Environ Health /2018	Prenatal phenol and paraben exposures concerning child neurodevelopment, including autism spectrum disorders in the MARBLES study	Assessing exposure to phenols and parabens during pregnancy is associated with an increased risk of clinical ASD or other non-typical (non-TD) developments.	The population and sample in this study were 207 participants with concentrations of exposure to phenol and paraben metabolites during pregnancy and neurodevelopmental assessment of children.	The study included mother-child pairs (N = 207) from the (MARBLES) Cohort Study with urinary phenol and paraben metabolites analyzed using (LC-MS/MS) repeated pregnancy urine samples.	The regression model adjusted for pre-pregnancy body mass index, prenatal vitamin use, homeowner status, year of birth, and sex of the child. Phenol exposure was not significantly associated with the child's diagnosis in a single chemical analysis. Mixed analysis using trinomial WQS regression for significantly increased risk of non-TD compared to TD with a greater overall prenatal mix of phenol and paraben metabolites.
5.	Author: Barkoski, et al Journal Identity: Environ	In utero pyrethroid pesticide exposure concerning autism	tested the association of measured prenatal pyrethroid	This study involved 201 mother-child pairs enrolled in	Mother-child pair participants in the MARBLES longitudinal	MARBLES participants had the highest concentration and the most significant proportion above

	mental Researc h/2021	spectrum disorder (ASD) and other neurodeve lopmental outcomes at three years in the MARBLES longitudina l cohort	exposure with a child's risk for ASD or non-TD, compared with TD.	the MARBLES Study from 2007 – 2014, with a sample of 194 participants who had complete information about exposure.	cohort. With registrars of pregnant women who have a family history of ASD. Multinomial logistic regression was used to obtain the relative risk ratio (RRR) of the mean 3-PBA concentration s.	LOD. Intrauterine exposure to pyrethroid pesticides, having concentrations of 3-PBA from multiple samples collected during the 2nd and 3rd trimesters in the MARBLES Study cohort, was at high risk for developing ASD because of a sibling with ASD. During the 2nd trimester, higher urinary 3-PBA concentrations were associated with a slightly increased risk of ASD in 3-year-olds.
6.	Author: Dries et al. Journal Identity: Environ ment Internati onal/ 2019	Organoph osphate pesticide metabolite concentrati ons in urine during pregnancy and offspring attention-deficit hyperactivi ty disorder and autistic traits	To determine the relationshi p between the concentrat ion of OP exposure in the fetus in the womb to ADH and autism in children.	Nine thousand seven hundred seventy-eight mothers (Rotterdam and the Netherland s who gave birth between April 2002 and January 2006) participated in the study.	Case study measuring DAP concentration in urine samples collected at <18, 18-25, and >25 weeks of gestation using gas chromatograp hy and tandem mass spectrometry.	The median DAP concentration at <18 weeks was 308 nmol/g creatinine; at 18–25 weeks, it was 316 nmol/g creatinine; and at >25 weeks, it was 308 nmol/g creatinine. The concentration of DAP metabolites has no relationship with the properties of ADH. However, other studies state that OP exposure is related to ADH properties but are seen in children aged five years.
7.	Author: Philippat , C. et al. Journal Identity: Int J Hyg Environ Health/ 2019	Prenatal exposure to organopho sphate pesticides and risk of autism spectrum disorders and other non-typical	Know the relationshi p between prenatal biologic markers for OP exposure and the risk of having a child with	The study population was 203 pairs of mothers and children who were at risk for experiencin g autism.	Case study with assays of metabolites in urine samples collected during pregnancy.	After conducting research based on gender, the concentration of dimethylthiophospha te in pregnancy tends to be associated with an increased risk of Autism Spectrum Disorder (ASD) in girls.

		development nt at three years in a high-risk cohort	Autism Spectrum Disorder (ASD).			
8.	Author: Miani, A., et al. Journal Identity: International Journal of Environmental Research and Public Health/ 2021	Autism spectrum disorder and prenatal or early life exposure to pesticides: a short review	It is knowing the relationship between exposure to pesticides with autism and the prenatal period.	Found as many as seven articles that will be reviewed after meeting the criteria.	The literature review method was used by reviewing seven journals regarding pesticide exposure, autism, and prenatal or early life.	Among the different environmental pollutants, pesticides should be considered as an emerging risk factor for ASD. The potential relationship identified between pesticide exposure and ASD needs to be implemented and confirmed by further epidemiological studies based on individual assessments in both outdoor and indoor conditions, including any confounding factors, and using statistical models that account for single and multiple pesticide residues.
9.	Author: Bennett, D. H., et al. Journal Identity: Environment International/ 2022	Environmental Exposures to Pesticides, Phthalates, Phenols and Trace Elements are Associated with Neurodevelopment in the CHARGE Study	Determine whether higher childhood exposures to environmental phenols, phthalates, pesticides, and trace elements are associated with an increased likelihood of a diagnosis of ASD, DD, or OEC compared	This study involved 627 children aged 2–5 years who participated in the CHARGE study.	As a result, adjusted multinomial regression models of each chemical with a diagnosis were performed.	Many urine chemistries are associated with an increased likelihood of ASD, DD, or OEC compared with TD; however, most did not remain significant after adjustment for the false discovery rate. In analyses that adjusted for confounders and other exposures, the results showed an association between the effects of the pesticide mix and the increased risk of ASD.

				to TD.		
10.	Author: Schmid et al. Journal Identity: Environmental Health Perspectives/ 2017	Combined Prenatal Pesticide Exposure and Folic Acid Intake concerning Autism Spectrum Disorder	Examining combined exposure to maternal FA and pesticides concerning ASD.	Participants were Californian children born from 2000–2007 who were enrolled in the CHARGE case-control study at age 2–5 years, had clinically confirmed ASD (n = 296) or developmentally typical (n = 220), and had information about maternal additional FA and pesticide exposure.	Additional FA of mothers and use of household pesticide products were collected retrospectively in telephone interviews from 2003-2011. High daily FA intake vs. Low dichotomized at 800 lg (median). The mother's address is linked to a statewide database of commercial applications for estimating exposure to agricultural pesticides.	In the present study population, the association between pesticide exposure and ASD was attenuated between those with high versus low FA intake during the first month of pregnancy. Confirmatory and mechanistic studies are needed.

DISCUSSION

This study investigated the relationship between pesticide exposure and autism spectrum disorders and considered these disorders with comorbid intellectual disabilities. This study also showed a small to moderate increased risk for disorders in offspring with prenatal exposure to several types of pesticides such as organophosphate chlorpyrifos, diazinon, malathion, permethrin, and bifenthrin pyrethroids, as well as glyphosate, avermectin, and methyl bromide compared to female offspring without long-distance exposure, 2000 meters from their residence. The risk was more pronounced for autism spectrum disorder with comorbid intellectual disability associated with exposure to pesticides during the first year of life. The pesticides considered for analysis were chosen based on experimental evidence demonstrating neurodevelopmental toxicity. These findings support the hypothesis that prenatal and infant exposure to pesticides to these substances increases the risk of autism spectrum disorders and that exposure in infancy may contribute to the risk

of more severe phenotypic disorders with comorbid intellectual disability. Several previous studies have also shown that exposure to pesticides during pregnancy can cause nervous system disorders, including cognitive and psychomotor impairments, neurodegeneration, and developmental disorders, which can contribute to the risk of developmental disorders in children, including ASD (Ehrenstein et al., 2019).

Maternal exposure to DDT/DDE is associated with premature birth and small gestational age status and is associated with the risk of Autism Spectrum Disorder (ASD). Maternal PCB exposure was not associated with prematurity or small-for-gestational-age status. P,p'-DDE inhibits androgen receptor binding, androgen-induced transcriptional activity, and androgen action in developing mice. Offspring of mice injected with valproic acid (VPA), an in-utero risk factor for autism, showed reduced androgen receptor expression in most cerebellar lobules in boys and girls. Cerebellar abnormalities, including Purkinje cell numbers, have been demonstrated in the brains of autism and mice exposed to prenatal VPA, and conversely, PCBs increase androgen receptor transcription (Brown et al., 2018).

Many urine chemistries are associated with an increased likelihood of ASD, DD, or OEC compared with TD. In analyses that adjusted for confounders and other exposures, the results showed an association between the effects of the pesticide mix and the increased risk of ASD (Bennett et al., 2022).

The association between pesticide exposure and ASD was attenuated among those with high versus low FA intake during the first month of pregnancy. Confirmatory and mechanistic studies are needed to confirm the relationship between pesticide exposure and the risk of developing ASD in children and to understand the mechanisms underlying this relationship. This indicates that further research is needed to understand the relationship between pesticide exposure and the risk of ASD in children and to determine the factors that may influence this relationship (Schmidt et al., 2017).

CONCLUSIONS AND SUGGESTIONS

There is a relationship between exposure to pesticides such as DDE, pyrethroids, organophosphates, and glyphosates during pregnancy in the third trimester and the incidence of autism in children born. Even though women are not directly involved in spraying pesticides, preparing pesticide ingredients, washing tools, and pulling weeds around the spraying area can trigger autism in children. Therefore, it is necessary to educate farmers about the importance of personal protective equipment to avoid excessive exposure to pesticides while working; also, pregnant women can reduce their activities in agricultural areas to prevent unwanted events or the risk of autism in their babies.

BIBLIOGRAPHY

Afandi, A. T., Kurniyawan, E. H., Cahyani, S. D., Fajriati, W. N., Oktaviana, A. . D., Nur, K. R. M., & Kurniawan, D. E. (2023). The Effect of STH Worm Infection on the Nutritional Status of Farmers in the Agronursing Area: Literature Review. Health and Technology Journal (HTechJ), 1(4), 427–436. https://doi.org/10.53713/htechj.v1i4.90

Barkoski, J. M., Philippat, C., Tancredi, D., Schmidt, R. J., Ozonoff, S., Barr, D. B., Elms, W., Bennett, D. H., & Hertz-Picciotto, I. (2021). In utero pyrethroid pesticide exposure in relation to autism spectrum disorder (ASD) and other neurodevelopmental outcomes at 3 years in the MARBLES longitudinal cohort. *Environmental Research*, *194.* https://doi.org/10.1016/j.envres.2020.110495

Barkoski, J., Tancredi, D. J., Elms, B., Barr, D. B., Ozonoff, S., Bennett, D. H., & Hertz-Picciotto, I. (2018). Prenatal exposure to organophosphate pesticides and risk of autism spectrum disorders and other non-typical development at 3 years in a high-risk cohort. *International Journal of Hygiene and Environmental Health*, *221*(3), 548–555. https://doi.org/10.1016/j.ijheh.2018.02.004

Bennett, D. H., Busgang, S. A., Kannan, K., Parsons, P. J., Takazawa, M., Palmer, C. D., Schmidt, R. J., Doucette, J. T., Schweitzer, J. B., Gennings, C., & Hertz-Picciotto, I. (2022). Environmental Exposures to Pesticides, Phthalates, Phenols and Trace Elements are Associated with Neurodevelopment in the CHARGE Study. *Environment International*, *161*, 1–11. https://doi.org/10.1016/j.envint.2021.107075

Bertoletti, A. C. C., Peres, K. K., Faccioli, L. S., Vacci, M. C., da Mata, I. R., Kuyven, C. J., & Dal Bosco, S. M. (2023). Early exposure to agricultural pesticides and the occurrence of autism spectrum disorder: a systematic review. *Revista Paulista de Pediatria*, *41*, 1–9. https://doi.org/10.1590/1984-0462/2023/41/2021360

Biosca-Brull, J., Pérez-Fernández, C., Mora, S., Carrillo, B., Pinos, H., Conejo, N. M., Collado, P., Arias, J. L., Martín-Sánchez, F., Sánchez-Santed, F., & Colomina, M. T. (2021). Relationship between Autism Spectrum Disorder and Pesticides: A Systematic Review of Human and Preclinical Models. *International Journal of Environmental Research and Public Health*, *18*(10), 1–30. https://doi.org/10.3390/ijerph18105190

BPS. (2022). *Persentase Tenaga Kerja Informal Sektor Pertanian (Persen), 2020-2022.* Https://Www.Bps.Go.Id/.

Brown, A. S., Cheslack-Postava, K., Rantakokko, P., Kiviranta, H., Hinkka-Yli-Salomäki, S., McKeague, I. W., Surcel, H. M., & Sourander, A. (2018). Association of Maternal Insecticide Levels with Autism in Offspring from a National Birth Cohort. *American Journal of Psychiatry*, *175*(11), 1094–1101. https://doi.org/10.1176/appi.ajp.2018.17101129

CDC. (2023). *Data and Statistics on ASD.* Https://Www.Cdc.Gov/.

Dinas Kominfo Provinsi Jawa Timur. (2023). *Angkatan Kerja Perempuan Perdesaan Didominasi Sektor Pertanian.* Https://Kominfo.Jatimprov.Go.Id/.

Dries, M. A. V. D., M. Guxens, et al. (2019). Organophosphate Pesticide Metabolite Concentrations in Urine During Pregnancy and Offspring Attention-Deficit Hyperactivity Disorder and Autistic Traits. Enviromental International. 131(102002): 1-12. https://doi.org/10.1016/j.envint.2019.105002

Ehrenstein, O. S. V, Ling, C., Cui, X., Cockburn, M., Park, A. S., Yu, F., Wu, J., & Ritz, B. (2019). Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: Population based case-control study. *The BMJ*, *364*, 1–10. https://doi.org/10.1136/bmj.l962

Hardiana, A. H., Setiani, O., & Darundiati, Y. H. (2021). Faktor Penentu Paparan Pestisida pada Petani Wanita terhadap Kejadian BBLR. *Jurnal Riset Kesehatan Poltekkes Depkes Bandung*, *13*(1), 102–110. https://doi.org/10.34011/juriskesbdg.v13i1.1839

Huffman, J. W. (2023). *Pregnancy*. Https://Www.Britannica.Com/.

Kongtip, P., Techasaensiri, B., Nankongnab, N., Adams, J., Phamonphon, A., Surach, A., Sangprasert, S., Thongsuksai, A., Srikumpol, P., & Woskie, S. (2017). The Impact of Prenatal Organophosphate Pesticide Exposures on Thai Infant Neurodevelopment. *International Journal of Environmental Research and Public Health*, *14*(6), 1–12. https://doi.org/10.3390/ijerph14060570

Kurniyawan, E. H., Afandi, TA., Shindy Gentsia Rahardika, FikaPutri Kharisa, Septiani Eka Lestari, Aril Alifia Salsabila, and Ahmad Zainuri. (2023a). Overview of the Occurrence of Green Tobacco Sickness (GTS) in Tobacco Farming Areas: A Literature Review. Journal of Local Therapy, 2(2), 73-83.

Kurniyawan, E. H., Cahyani, P. S. R., Khoiriyah, A. A., Purnomo, F. K. A., Afandi, A. T., Kurniawan, D. E., & Nur, K. R. M. (2023b). Coping Mechanisms Used by Farmers to Encounter Psychosocial Problems: Literature Review. Health and Technology Journal (HTechJ), 1(4), 445–454. https://doi.org/10.53713/htechj.v1i4.84

Lyall, K., Croen, L. A., Sjödin, A., Yoshida, C. K., Zerbo, O., Kharrazi, M., & Windham, G. C. (2017). Polychlorinated Biphenyl and Organochlorine Pesticide Concentrations in Maternal Mid-Pregnancy Serum Samples: Association with Autism Spectrum Disorder and Intellectual Disability. *Environmental Health Perspectives*, *125*(3), 474–480. https://doi.org/10.1289/EHP277

Miani, A., Imbriani, G., De Filippis, G., De Giorgi, D., Peccarisi, L., Colangelo, M., Pulimeno, M., Castellone, M. D., Nicolardi, G., Logroscino, G., & Piscitelli, P. (2021). Autism Spectrum Disorder and Prenatal or Early Life Exposure to Pesticides: A Short Review. *International Journal of Environmental Research and Public Health*, *18*(20), 1–15. https://doi.org/10.3390/ijerph182010991

Nurman, I. (2023). *3,2 Juta Anak Indonesia Menderita Autism Spectrum Disorder*. Https://Inisumedang.Com/.

Philippat, C., J. Barkoski, et al. (2019). Prenatal Exposure to Organophosphate Pesticides and Risk of Autism Spectrum Diorders and Other Non-Typical Development at 3 Years an A High-Risk Cohort. Int J Hyg Environ Health. 221(3): 548-555. https://doi.org/10.1016/j.ijheh.2018.02.004.

Pu, Y., Yang, J., Chang, L., Qu, Y., Wang, S., Zhang, K., Xiong, Z., Zhang, J., Tan, Y., Wang, X., Fujita, Y., Ishima, T., Wan, D., Hee Hwang, S., Hammock, B. D., Hashimoto, K., Staci Bilbo, by D., & Pletnikov, M. M. (2020). Maternal glyphosate exposure causes autism-like behaviors in offspring through increased expression of soluble epoxide hydrolase. *PNAS*, *177*(21), 11753–11759. https://doi.org/10.1073/pnas.1922287117/-/DCSupplemental

Saftrina, F., Permata Sari, R., & Sutarto. (2018). Pengaruh Paparan Pestisida pada Masa Kehamilan terhadap Perkembangan Anak. *JK Unila*, *2*(1), 63–67.

Schmidt, R. J., Kogan, V., Shelton, J. F., Delwiche, L., Hansen, R. L., Ozonoff, S., Ma, C. C., McCanlies, E. C., Bennett, D. H., Hertz-Picciotto, I., Tancredi, D. J., & Volk, H. E. (2017). Combined Prenatal Pesticide Exposure and Folic Acid Intake in Relation to Autism Spectrum Disorder. *Environmental Health Perspectives*, *125*(9), 1–12. https://doi.org/10.1289/EHP604

Widyawati, S. A., Siswanto, Y., & Pranowowati, P. (2018). Potensi Paparan Pestisida dan Dampak pada Kesehatan Reproduksi Wanita Tani Studi Di Kabupaten Brebes. *Jurnal Ilmu Keperawatan Maternitas*, *1*(1), 31–38. https://journal.ppnijateng.org/index.php/jikm