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Research

The Teratogenic Effect of Dimefluthrin-Based Mosquito Coils on Pregnant Mice (*Mus musculus* L.)

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ABSTRACT

Dimefluthrin, a synthetic pyrethroid insecticide, claims to be safe and harmless to mammals. However, the potential risk of mosquito coils containing dimefluthrin to pregnant mice remains uncertain. This study aimed to examine the teratogenic effect of dimefluthrin when inhaled by pregnant mice at different stages of gestation. The study used mosquito coils with 0.031% dimefluthrin as the active ingredient and was exposed to pregnant mice at various pregnancy stages. The results revealed that mosquito coils with dimefluthrin had teratogenic effects, reducing the number of live fetuses and increasing the number of dead fetuses, especially from the seventh to the eighteenth day of pregnancy. Additionally, there was a decrease in fetal weight, length, and volume, particularly during the seventh to eighth day of gestation. Hemorrhages were observed as fetal abnormalities and were highest three hr after exposure every day during pregnancy. The conclusion of this research is pregnant mice exposed to mosquito coil smoke containing dimefluthrin experienced a decrease in the number of live fetuses and an increase in fetal mortality. While there was no significant impact on reabsorption, the fetuses showed reduced weight, and size, and an increased incidence of hemorrhages when exposed for three hr daily during pregnancy.

Key words: Dimefluthrin, fetal abnormalities, mosquito coil, pyrethroid, teratogenic effect

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INTRODUCTION

Indonesia, with its tropical climate, is one of the regions that experiences a high number of diseases caused by mosquitoes. This is because the tropical climate provides a conducive environment for mosquitoes to breed. People from low-income communities are often the most affected by these diseases due to inadequate environmental hygiene. These communities often resort to using mosquito coils to control the mosquito population as they are cheap and easily accessible (Ahmadin *et al*., 2015). A survey by Moore *et al*. (2018) found that out of 17 preferred methods of protecting against mosquito bites, mosquito coils were the fifth most popular.

Insecticides can be both helpful and harmful to human health because they are not only aimed at mosquitoes but also affect humans (Prihati & Nugraheni, 2015). Exposure to mosquito coils can result in insecticide poisoning. These coils are often burned indoors and used overnight in sleeping areas, exposing humans to smoke containing various chemicals for long periods (John & John, 2015). The coils also release microscopic particles (1 lm) of metal fumes, vapors, and free radicals that can irritate the upper respiratory tract when inhaled into the alveolar regions of the lungs (Chang & Lin, 1998; Hogarh *et al*., 2018). Moreover, the components of mosquito coils such as colors, binders, and organic fillers can release large amounts of sub-micrometer particles when burned, which can potentially cause carcinogenesis if they reach the lower respiratory system (John & John, 2015).

Dimefluthrin is an insecticide belonging to the class of

pyrethroids. Pyrethroids are commonly used as active ingredients in mosquito coils that are widely available in markets (Yoo *et al*., 2016). These insecticides are favored due to their fast-acting properties, which result in the paralysis and death of target insects (Sigit *et al*., 2006; Andini *et al*., 2022). Pyrethroids can be absorbed through direct skin contact, inhalation, and consumption of contaminated food or water (Morgan, 2012). Despite claims of low toxicity and safety, there is a growing body of evidence that pyrethroids, even at low levels of exposure, have adverse effects on various aspects of human health, including neurological function, fertility, immune response, and liver and cardiovascular metabolism (Hu *et al*., 2018). Research has shown that the use of pyrethrin-based mosquito coils can significantly increase the number of leukocytes, particularly basophils and lymphocytes (Garba *et al*., 2007; Al-Mamun *et al*., 2017). Long-term exposure to pyrethroids can also affect the biochemical parameters of blood (Narendra *et al*., 2007; Idowu *et al*., 2013), increase the levels of reactive oxygen species (ROS), and lead to over-expression of the gene p53, which is considered the first stage of cellular apoptosis mediated by mitochondria (Madhubabu & Yenugu, 2012).

The pregnancy period is susceptible to environmental influences. According to Sinha *et al*. (2004) and Atta *et al*. (2021), long-term indoor exposure to pyrethroid-based mosquito repellent coils has been linked to chronic neurotoxicity, including failure of the blood-brain barrier and oxidative brain damage. Sinha *et al*. (2006) and Hisada *et al*. (2017) also stated that exposure to pyrethroids during pregnancy can lead to fetal cholinergic dysfunction, resulting in learning and memory deficiencies. Research by Ahmadin *et al*. (2015) showed that exposure to mosquito coils with the active ingredient pyrethroids in pregnant mice caused abnormalities in the fetuses and decreased body weight in the mother mice.

Dimefluthrin is a new generation of pyrethroids that are primarily used in household insecticide products. Despite claims of lower toxicity and relative safety of pyrethroids, the potential risk of dimefluthrin to pregnant mice remains uncertain. Therefore, it is crucial to research to examine the teratogenic potential of dimefluthrin when inhaled by pregnant mice at different stages of gestation.

MATERIAL AND METHODS

Chemicals

Commercial dimefluthrin-based mosquito coils were purchased from a market in West Sumatera, Indonesia. The brand name is BG with an active ingredient 0.031% of dimefluthrin.

Animals

The experiments were conducted using albino mice strain Swiss Webster weighing 25-30 g and 3 months old, obtained from a breeder in West Sumatera. The adult male and female mice were acclimated for seven days in the animal room at the Animal Physiology Laboratory, Department of Biology Andalas University, fed with pellets and water *ad libitum*.

Experimental design

This study used a completely randomized design, consisting of four therapy and six replications. The experimental design is based on a combination of research from Naz *et al*. (2019) and Rahayuningsih (2011). The male mice were introduced to the female mice's cage during estrus with a ratio of 1:4, respectively. The presence of a vaginal plug was examined the following morning to confirm mating and determine the pregnancy days. The pregnant mice were transferred to individual unit plastic cages and randomly divided into four groups, each containing six animals (n=6).

The therapy of this study was divided into four groups, which were the exposure times of a mosquito coil to different stages of pregnancy in mice. The first group was control, with no exposure. The second group involved exposing pregnant mice to the mosquito coil for three hr from days 0 to 18 of pregnancy. The third group involved exposing pregnant mice to the mosquito coil for three hr from days 0 to 7 of pregnancy. The fourth group involved exposing pregnant mice to the mosquito coil for three hr from days 7 to 18 of pregnancy.

The pregnant mice were exposed to the smoke from a dimefluthrin-based mosquito coil through direct inhalation using a gas chamber (Figure 1). After 18 days, the mice were euthanized and a laparotomy was performed to remove the fetuses by dissecting the abdomen upward. The fetuses were then examined to determine their weight, length, volume, and morphological abnormalities.

Viability rate

Observing fetal reabsorption during surgery requires searching for black spots on the uterus. These spots are counted to determine the number of fetuses that have been reabsorbed. The movement and

color of the fetuses are then evaluated to differentiate between live and dead fetuses. Live fetuses generally have a pink color, while dead fetuses tend to be deep red or purplish. Embryos that have not been completely reabsorbed are usually smaller and yellow or orange (Tian *et al*., 2006).

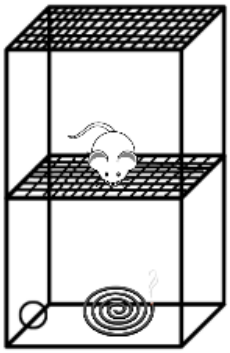

Fig. 1. Gas chamber design. The chamber is made of plywood and has dimensions of 40 cm in length, 40 cm in width, and 50 cm in height. The chamber is divided into two parts, with the bottom containing the mosquito coil and the top housing the mice, both of which are enclosed by wire.

Weight, length, and volume of fetal

The length and weight of live fetuses are measured. The length of the fetus is measured using millimeter paper, and its volume is determined using Archimedes' law. After the fetus has been cleaned of the surrounding amniotic fluid, its weight is measured (Ahmadin *et al*., 2015).

Maternal weight gain and uterine weight

The data collected includes the weight of the uterus and the weight gain of the mother during pregnancy. The weight of the mice will be measured on the first day of pregnancy (day 0) and the last day (day 18) of pregnancy. The weight of the uterus will be measured before and after the fetuses are removed (Setyawati *et al*., 2018).

Fetal malformation

The type and number of malformations and abnormalities are recorded for each therapy. The external morphology of the fetus, including the ears, eyes, feet, and tail is examined. The presence of a cleft palate is determined by inserting a scalpel into the molars, and the head is sliced down the middle, from the left earlobe to the right earlobe (Hayes, 2000).

Data analysis

The viability rate; fetal malformation; maternal weight gain and uterine weight; weight, length, and volume of fetal; were analyzed by using Analysis of Variance (ANOVA). If significant results were obtained, the data were further analyzed using Duncan's New Multiple Range Test (DNMRT) with a significance level of 5%. Data analysis used SPSS 28.0 software for tools analysis.

RESULTS AND DISCUSSION

Viability rate

The percentage of live births among children born to mothers who were exposed and not exposed to smoke from mosquito coils is presented in the following order from largest to smallest: zero hr exposure (T0), three hr exposure during pregnancy (T1), three hr exposure from the first to the seventh day of pregnancy (T2), and three hr exposure from the seventh to eighteenth day of pregnancy (T3) (Table 1). In this study, no fetal resorption was found in any of the groups. In each therapy, it can be seen that the viability rate of the fetus is significantly different, with a corresponding increase in the mean death rate that is significant in the T3 group. When undifferentiated cells are exposed to certain quantities of teratogens, they may become damaged, resulting in cell death and inevitably disrupting embryonic development (Rahayuningsih, 2011).

Table 1. The fetal viability rate from the parent who is exposed to the smoke of mosquito coils

Therapy	Total Fetus ± SD	Live Fetus (%) ± SD	Dead Fetus (%)± SD
T0	10.5 ± 2.34	89.10 ± 0.09^{a}	0.89 ± 0.09^{a}
T1	7.67 ± 4.50	63.54 ± 31.42^{a}	26.45 ± 31.42^{a}
T2	10.5 ± 1.04	51.69 ± 37.43^{ab}	38.33 ± 37.42^{ab}
T3	13.5 ± 2.88	17.53 ± 24.26^{b}	72.42 ± 24.31^{b}

Notation: Different superscripts showed significant differences in the same column (p<0.05)

Pyrethroid is a chemical that enters the body as a xenobiotic (Baratawidjaja, 2004). Dimefluthrin, as a pyrethroid, causes an increase in oxygen consumption, leading to a respiratory burst and the formation of reactive oxygen species (ROS). These ROS initiate chain reactions that form lipid peroxides, damaging the molecular structure of fats and decreasing the percentage of fats such as cholesterol and phospholipids in cell membrane lipid bilayers. This reduced percentage of fat leads to increased cell permeability and swelling, decreased cell membrane integrity, and even lysis. The sensitivity of embryos to pyrethroids varies and is regulated by their developmental stage. Embryos exposed to teratogens during early phases of proliferation may either die or grow normally. Since differentiation has not occurred and injured cells are still in the proliferative stage, they can be overcome by new cell growth. Fetuses can survive and repair damaged cells, while embryos may not and can result in death. Exposure of fetuses to mosquito coils between the seventh and the eighteenth day has been shown to have a higher mortality rate as the fetus no longer can repair tissue damage caused by teratogenic compounds.

The high rate of intrauterine mortality associated with mosquito coil smoke suggests the presence of embryotoxic/fetotoxic components. A fetus that dies has a lower resistance to foreign substances. According to Rahayuningsih (2011), if teratogens impact the embryo during the differentiation or pre-differentiation phase and destroy a significant number of embryonic cells, the embryo will die. This is because the organs involved in metabolic and excretory processes in the embryo are not fully developed, leading to longer-lasting and higher concentrations of substances in the embryo's bloodstream. This can result in embryotoxicity or fetotoxicity and lead to mortality.

Weight, length, and volume of fetal

The weight, length, and volume of the mouse fetuses varied greatly among the different therapies, as shown in Table 2. The fetuses from mothers in the T0 group, who were not exposed to mosquito coil smoke, were significantly heavier, longer, and larger in volume. On the other hand, the fetuses from mothers who were exposed to mosquito coil smoke had reduced weight, length, and volume.

Table 2. The weight, length, and volume of the fetus from the parent who is exposed to the smoke of mosquito coils

Therapy	Weight (g) ± SD	Length (cm) ± SD	Volume (ml) ± SD
T0	1.23 ± 0.11^{a}	1.71 ± 0.06^{a}	1.21 ± 0.09^{a}
T1	1.08 ± 0.20^{a}	1.43 ± 0.33^{ab}	1.09 ± 0.19^{a}
T2	1.03 ± 0.26^{a}	1.30 ± 0.43^{ab}	1.02 ± 0.24^{ab}
T3	0.84 ± 0.19^{a}	0.98 ± 0.39^{b}	0.82 ± 0.16^{b}

Notation: Different superscripts showed significant differences in the same column (p<0.05)

The therapy group in which the mothers were exposed to mosquito coils containing dimefluthrin from the seventh to the eighteenth day of pregnancy (T3) produced smaller fetuses. Exposure to the smoke of mosquito coils significantly impacts the weight, length, and volume of the fetus, especially during the stage of organogenesis and development in the T3 group. The entry of free radicals from the smoke can hinder the optimal growth and development of the fetus. According to Harbinson (2001) and Rahayuningsih (2011), embryonic differentiation begins on the seventh day of pregnancy and continues through the 17th and 18th days of development. Dimefluthrin is a pale yellow liquid with a slight odor and a molecular mass of 374.38 (Mori *et al*., 2014). Although there is a placental barrier that filters and regulates the exchange of nutrients, waste products, and xenobiotics between the mother and fetus, the fetus cannot be fully protected since substances with a molecular mass of less than 1000 can cross the placental barrier with ease. Exposure to pyrethroid-based mosquito coils, such as dimefluthrin, can result in the formation of secondary metabolites that act as free radicals, circulating throughout the body. According to Sundaryono (2011), the presence of free radicals in the bloodstream can affect the body's physiology. Oxygen free radicals, such as superoxide, hydroxyl radicals, and hydrogen peroxide, are the most prevalent in erythrocytes and can destroy cellular components such as DNA,

RNA, carbohydrates, lipids, proteins, and micronutrients (vitamins & minerals).

The free radicals pose a risk to erythrocytes by altering their membrane structure and compromising their flexibility, causing them to break easily (Wijayanthi, 2011). This can result in a decrease in the number of erythrocytes. Lipid peroxidation in the erythrocyte membrane can lead to a loss of membrane fluidity and increase its fragility, causing erythrocytes to easily rupture or undergo hemolysis. This can lead to a low hemoglobin level and a decreased number of erythrocytes, affecting the distribution of nutrients and causing poor nutrition. Poor maternal nutrition can impact the fetus and interfere with its developmental process.

Uterine weight and maternal weight gain

According to the statistical analysis data presented in Table 3, exposure to mosquito coils containing dimefluthrin has a significant impact on increasing the final uterine weight of mice when compared to the control group (T0) and the therapy groups. The entry of dimefluthrin from mosquito coils into the body can produce reactive oxygen species metabolites, leading to the formation of fatty peroxides in a chain reaction. These fatty peroxides can damage the structure of fat molecules in the cell membrane, increasing cell permeability and causing edema. This results from a large-scale influx of molecules from outside the cell, causing the uterus to swell and leading to an increase in weight relative to its normal weight.

Table 3. The weight of the uterus and maternal weight gain in mice exposed to the smoke from mosquito coils.

Therapy	Uterine Weight (gram) ± SD	Maternal Weight Gain (gram) ± SD
T0	1.13 ± 0.03^{a}	2.21 ± 0.06^{a}
T1	1.51 ± 0.05^{b}	1.54 ± 0.04^{b}
T2	1.48 ± 0.05^{b}	1.62 ± 0.02^{b}
T3	1.19 ± 0.05^{a}	1.27 ± 0.10^{c}

Notation: Different superscripts showed significant differences in the same column (p<0.05)

According to Baratawidjaja (2004), the more xenobiotics enter the body, the higher the oxygen demand. This is due to the rapid consumption of oxygen, which creates free radicals or reactive oxygen species (ROS). Which then act as catalysts for the synthesis of fatty peroxides in a chain reaction (OOH). Fatty peroxides in cells and tissues can damage the molecular structure of fats, leading to a decrease in cholesterol and phospholipids in the lipid bilayer of the cell membrane. It increases cell permeability and allows molecules such as Na^{+}, Ca^{2+}, H_2O, and others to enter the cell, causing swelling and possibly reducing cell membrane thickness. However, in this study, the reduction in membrane thickness due to lysis did not occur because the mother's body tried to protect the fetus and the uterus.

Table 3 also showed that exposure to mosquito coils during pregnancy significantly affected maternal weight gain. The group without exposure had the most significant average weight gain, followed by the T1 group, where exposure was carried out for 18 days of pregnancy, and then the T3 group, where the exposure took place from the seventh to the eighteenth day of gestation. During this critical period of organogenesis and development, the fetus needs much nutrition from the mother, so the mother's body optimizes its resources to provide for the growing fetus. As a result, the T3 group had the slightest weight gain, likely due to anemia caused by a disturbed appetite and the reduced number of erythrocytes caused by the entry of xenobiotics from mosquito coils (dimefluthrin). The disrupted delivery of nutrients and the metabolic process of food to energy can cause malnutrition, especially in hypoxic conditions where the body lacks oxygen.

Pyrethroids that enter the body through inhalation can cause lung problems and disrupt the respiratory process. The contents of mosquito coil smoke can cause hypoxia in mice during therapy, as previously reported by Prastiwi (2015). For example, a specific brand of mosquito coils contains 0.1% d-allethrin and 0.25% transfluthrin. In comparison, the same brand's liquid and aerosol products contain 0.4 g/L and 0.10% cypermethrin, which can pollute indoor air and cause hypoxia.

Ramsingh (2010) explains that pyrethroids like dimefluthrin affect erythrocytes by reducing their production or increasing their destruction, which triggers methemoglobin formation in red blood cells. This occurs when iron in the red blood cells is in the oxidized ferric form (Fe^{3+}) instead of the reduced ferrous form (Fe^{2+}), decreasing oxygen availability to tissues. Increased methemoglobin levels lead to functional anemia and can be either congenital or acquired. Most cases of methemoglobinemia are acquired and result from exposure to certain drugs, toxins, or chemicals like insecticides (Do Nascimento *et al*., 2008).

Fetal malformation

According to the data of the statistical analysis in Table 4, exposure to mosquito coils containing dimefluthrin has a significant effect on the percentage of fetal malformations. The type of malformation that appears is caused by exposure to the smoke from mosquito coils with the active ingredient dimefluthrin, which is hemorrhage. Additionally, fetuses exposed to the smoke from mosquito coils in the womb tend to have a smaller body size compared to normal fetuses. The results of the data analysis between normal fetuses and fetuses exposed to mosquito coil smoke showed significant differences. On the other hand, treated fetuses did not show a significant difference from one another. However, based on the average, the highest percentage of defects in the form of hemorrhage in the fetus was found in fetuses exposed to mosquito coil smoke during pregnancy (T1), followed by T3 and then T2.

Table 4. Fetal malformations of mice were exposed to the smoke from mosquito coils.

Therapy	Fetal Malformation (%) ± SD			
	Hemorrhage	Coiled Tail	Incomplete Finger	Palate Cleft
T0	0.89 ± 0.09[a]	0	0	0
T1	21.98 ± 15.10[b]	0	0	0
T2	18.59 ± 9.02[b]	0	0	0
T3	25.12 ± 4.80[b]	0	0	0

Notation: Different superscripts showed significant differences in the same column (p<0.05)

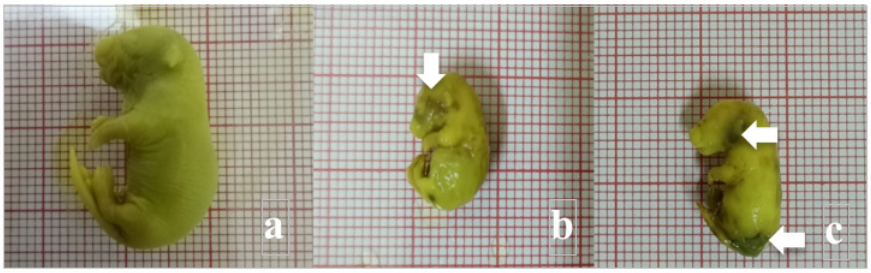

Fig. 2. Fetus Morphology: a. Normal fetus, b. Dwarf hemorrhagic fetus (head), c. Hemorrhagic fetus in some parts of the body (hemorrhagic areas are indicated by arrows).

Hemorrhage is the discharge of blood from the cardiovascular system and the accumulation of blood in spaces or body tissues (Setyawati, 2009). It is a form of external abnormality that often occurs due to a teratogen. Hemorrhage was found in all therapy groups and was present in the head, neck, back, abdomen, legs, and the entire body of the fetuses. Figure 2 shows signs of hemorrhage indicated by arrows. In fetuses, hemorrhage is indicated by a dark color on the head (Figure 2b) and is also found on the abdomen (Figure 2c). Blood spots appearing under the skin are a symptom of this condition. Abnormalities in fetal development can be caused by teratogenic substances entering the body of pregnant women during organogenesis. In the T2 therapy group, where the mice were exposed to the smoke from mosquito coils during the first seven days of pregnancy, the smoke still had an effect even though the fetus had not yet entered the organogenesis stage. This may be due to dimefluthrin (pyrethroid) particles in the mother's body or entering fetal circulation. According to the National Pesticide Information Center (NPIC), in a study with mice, more than 85 percent of the particles left the body in feces or urine within two days. This means that around 15% of the particles are still present in the body, which could affect the fetus.

Several reasons can cause bleeding, one of which is an osmotic imbalance or differences in pressure and viscosity between fluids in the fetal body, such as blood plasma and extra capillary space or extra-embryonic and intra-embryonic fluids. Setyawati (2009) stated that under normal circumstances, the embryo develops in amniotic fluid, which is isotonic to bodily fluids. The presence of foreign chemicals may disrupt osmotic equilibrium. Osmotic imbalances can occur due to changes in fluid pressure and viscosity in different parts of the embryo, between the blood plasma and extra capillary space, or between extra- and intra-embryonic fluids. This difference can cause blood vessels to burst and result in hemorrhage.

Hemorrhage can also occur due to damage to vascular endothelial cells caused by the absence of certain types of hematopoietic cells that are typically required to maintain the blood vessels, or the cells are dysfunctional or fail to produce soluble factors affect vascular integrity (Setyawati & Yulihastuti, 2011). The mechanism by which dimefluthrin induces hemorrhage in the fetus is still unknown. However, it is likely that the composition of smoke and gas particles in mosquito coil smoke, which

varies, influences blood particles. This is in line with Almahdy *et al*. (2013), who suggest that different chemical compositions may cause variations in the composition of gases and smoke particles, resulting in different effects on blood particles. The presence of carbon monoxide in the blood can cause the denaturation of hemoglobin and reduce the supply of oxygen to all body tissues. Carbon monoxide replaces oxygen and accelerates atherosclerosis (the calcification or thickening of blood vessel walls), increasing blood viscosity and making blood clots easier.

CONCLUSION

Inhaling mosquito coil smoke containing dimefluthrin in pregnant mice significantly decreased the percentage of live fetuses and increased the percentage of dead fetuses. There was no significant effect on reabsorption, but fetal weight, length, and volume of fetuses were reduced. The fetal abnormalities in the form of hemorrhage were the highest after three hr of exposure every day during pregnancy.

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ETHICAL STATEMENT

This study was conducted following the Researcher's Guidelines on Code of Practice for the Care and Use of Animals for Scientific Purposes, Andalas University.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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