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Original Research Paper

Effect of Formaldeyde Induction of Histopathological Features of The Lungs of Wistar Rats *(Rattus Norvegicus)*

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Abstract: Formaldehyde, a known carcinogen prevalent in everyday environments, poses significant health risks, particularly through inhalation exposure. This study investigates the histopathological changes in the lungs of Wistar rats induced by formaldehyde at doses of 20, 30, and 40 parts per million (ppm) over a three-month period. The research aims to elucidate the onset of dysplasia, a cellular defense mechanism characterized by abnormal epithelial proliferation, as a response to carcinogenic exposure. Utilizing a post-test only control group experimental design, we observed that increased formaldehyde exposure correlates with a heightened severity of dysplasia, with a statistically significant result ($p = 0.002$). Our findings indicate that varying doses of formaldehyde lead to differential degrees of dysplasia, underscoring the importance of dose-response relationships in assessing the carcinogenic effects of formaldehyde on lung tissue.

Keywords: Dysplasia, dosage, degree of dysplasia, formaldehyde.

Introduction

Formaldehyde is a universal toxic substance that is easily found in the environment. It can be in the form of motor vehicle emissions and cigarette smoke. Formaldehyde is very commonly used in the production process of several products that are often found in everyday life, such as insulating foam, paint, resin, plastic, synthetic fibers and other products, the main ingredients used in various furniture, carpets, and other household products. This means that formaldehyde is used in the manufacture of objects that are always found where humans carry out activities. (Bernardini et al., 2020). Inhalation of formaldehyde has a definitive effect on cardiovascular systems, it also increases the peroxidation of lipid products and decreases the activity of antioxidant enzymes in the liver (Zhang *et al., 2018)*. The progression of dysplasia to carcinoma in situ and then from carcinoma in situ to invasive carcinoma, results from prolonged exposure to carcinogenic factors, causing genetic and epigenetic alterations. The dominant approach to evaluate potentially malignant head and neck lesions is to perform dysplasia and carcinoma examinations (Ranganath *et al*.,2022).

Daily human interaction with products containing formaldehyde results in daily exposure to this substance. Formaldehyde inhalation has been shown to have negative effects on the cardiovascular system, including decreased heart rate and blood pressure, which can result in sinus bradycardia and atrioventricular arrhythmias. Research shows that exposure to formaldehyde in mice for 4 to 13 weeks causes increased lipid peroxidation and decreased antioxidant enzyme activity in the liver (Zhang et al., 2018). Apart from being

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obtained from external sources, formaldehyde can also be produced internally through normal cellular metabolism. This substance can cause various adverse effects, including tissue damage, impaired energy metabolism, and reduction of the body's antioxidant capacity (Zhang et al., 2018).

Formaldehyde has been recognized as a definitive human carcinogen, particularly associated with lung cancer, since 2004. It is widely used in industry and as a disinfectant. The highest exposures generally occur in the garment, furniture, and floor varnish sectors, as well as in certain occupations in the boardmaking and foundry industries. Formaldehyde-related cancers have been listed as occupational diseases in several countries, including France, Denmark, Taiwan, and Malaysia. Research has also identified a causal relationship between formaldehyde exposure and lung cancer (Kwon et al., 2018). This is important because public understanding of lung cancer including its definition, symptoms, risk factors, and prevention is still limited (Kadriyan et al., 2022). As a result, the risk of exposure to carcinogens and developing lung cancer remains high.

Chromosomal and DNA damage can be caused by the genotoxic and cytotoxic properties of formaldehyde. Increased genomic instability due to exposure to this genotoxic chemical can increase the risk of cancer. Suspicion of the carcinoge Formaldehyde, nic effects of formaldehyde began with the initial findings of lung tumors in mice exposed to this substance. There is also a relationship between increased tumor incidence and cell proliferation that depends on the concentration of formaldehyde. IARC (International Agency for Research on Cancer) concluded that formaldehyde can cause lung cancer based on large studies involving humans and experimental animals (Kang et al., 2021).

Continuous exposure to carcinogenic factors can cause genetic and epigenetic changes that lead to the development of carcinoma in situ, then from carcinoma in situ to invasive carcinoma. Currently, the clinical method for evaluating lesions that show progression to malignant tumors is histopathological examination for dysplasia and carcinoma (Ranganath et al., 2022). Susceptibility to oncogenic events that cause tumor formation is very tissue-specific. The primary novelty of this study lies in its emphasis on the dose-response relationship between the severity of dysplasia and formaldehyde exposure, analyzed in detail using the Kruskal-Wallis statistical method to ensure the precision of results. The objective of this research is to identify and quantify the histological damage to lung tissue caused by graded doses of formaldehyde (20, 30, 40 ppm) and to elucidate the mechanisms of formaldehyde toxicity on lung tissue. This study provides significant benefits by advancing the understanding of formaldehyde's impact, particularly in occupational and environmental settings where exposure is prevalent.

In contrast to other studies, the research by Susilawati et al., (2022) focuses on the protective effects of purple sweet potato ethanol extract against formaldehyde-induced damage to nasopharyngeal mucosa. Similarly, the study by Srividhya et al., (2024) explores histological changes in rat lungs caused by inhaled formaldehyde, emphasizing peribronchiolar fibrosis and alveolar space dilation. Meanwhile, Payani et al. introduce a therapeutic dimension by examining the protective effects of Bronco-T in mitigating oxidative damage to lung tissue.

This study offers a unique perspective by concentrating exclusively on lung tissue, providing quantitative measurements of dysplasia severity and a detailed dose-response analysis without including therapeutic or preventive interventions. The findings contribute significantly to the scientific understanding of formaldehyde-induced toxicity in lung tissue and hold practical implications for developing improved guidelines and regulations to manage formaldehyde exposure in occupational and domestic environments.

Materials & Methods

The instruments used in this experimental study consisted of various tools and materials. The tools used included a medical mask, filter mask, laboratory coat, Minor Surgical Set, scissors, electric solder, cutter, plastic cup, hand attack, clear plastic, personal protective equipment (PPE), PBS, needles, and food and water for the mice. In addition, micropipettes were also used in this research process.

The materials used consisted of a medium-

sized plastic box, iron wire, sieve wire, cotton, formaldehyde at doses of 20, 30, and 40 ppm, rat feed, bedding, and water. The cages for the Wistar rats were specially designed to be able to cause dysplasia economically and effectively. The cage design included the use of buckets, ventilation wires, wire covers, and container covers.

This study was a post-test only experimental study. Sixteen Wistar rats induced by formaldehyde were included in this study. Each rat was divided into 4 groups, namely the control and treatment groups which were further divided into doses of 20, 30, and 40 ppm. Each group used 4 rats. The control group was not given formaldehyde while the treatment group was induced with 20, 30, 40 ppm formaldehyde and given food and distilled water for 12 weeks. The rats were kept in cages specially designed to induce dysplasia effectively and economically (Wedayani et al., 2023), with ventilation on both sides of the cage. This method was designed based on previous research, where a similar design study with a 16-week induction period had successfully produced dysplasia in Wistar rats (Susilawati et al., 2022). At weeks 4, 8, 12, one rat was sacrificed to collect nasopharyngeal and lung tissue. At week 16, 3 rats will be sacrificed. The ethics of this research have been reviewed and have obtained permission from the Ethics Committee of the Faculty of Medicine, University of Mataram (066/UN17.F7/ETIK/2023).

Histological examination was performed at the Anatomical Pathology Laboratory, Mataram University Hospital. The samples were placed in test tubes containing formalin solution for preservation. The samples were then fixed, dried, cut, rehydrated, and stained with Hematoxylin-Eosin staining. Then the tissue preparations were examined to determine the degree of dysplasia. The histopathological data obtained were then analyzed statistically using the Statistical Package for the Social Sciences (SPSS) program running on Microsoft Windows 11. Because the research data is ordinal, which is categorized as mild, moderate, and severe, it is necessary to test the comparison carried out using Kruskal Walis with Post hoc using the Mann Whitney U Test.

Results and Discussion

Histopathological Result of the Lung Tissue

Tissue samples were stained with Hematoxylin-Eosin staining and viewed under the microscope. These are the samples of lung tissues.

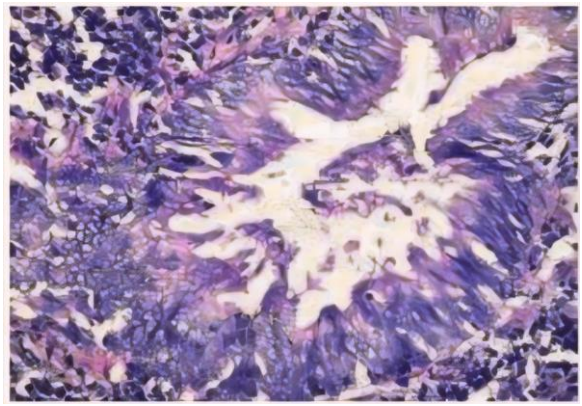

Image 1. Lung Tissue: Glands on Lung with Mild Dysplasia after 20 ppm Formaldehyde Induction on Week 12 (HE 40x)

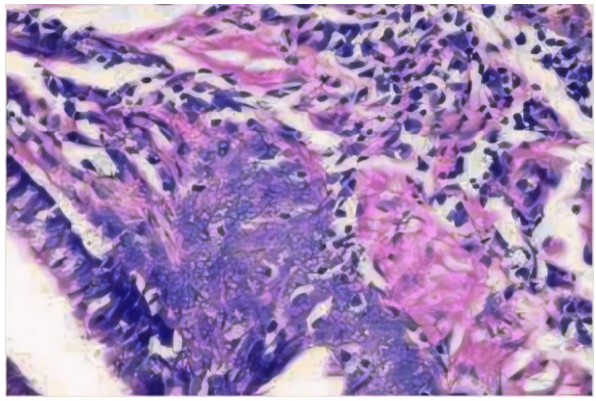

Image 2. Lung Tissue: Glands on Lung with Moderate Dysplasia after 30 ppm Formaldehyde Induction on Week 12 (HE 40x)

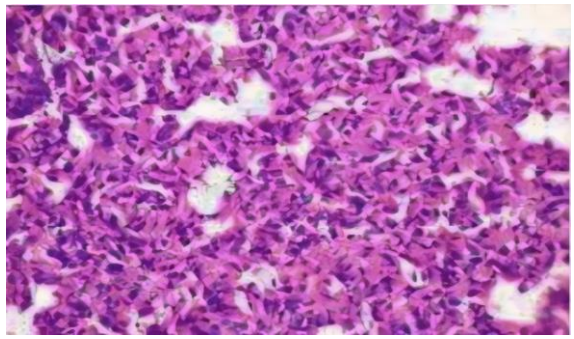

Image 3. Lung Tissue: Glands on Lung with Severe Dysplasia after 40 ppm Formaldehyde Induction on Week 12 (HE 40x)

Table 1. Univariate Analysis

	n	%
Formaldehyde Dosage		
0ppm	4	25
20ppm	4	25
30ppm	4	25
40ppm	4	25
Degree of Dysplasia		
Normal	8	50,0
Mild Dysplasia	2	12,5
Moderate Dysplasia	2	12,5
Severe Dysplasia	4	25,5
Total	16	100,0

Table 1 compiles histopathological data of lung tissue examined from tissue biopsies of Wistar rats terminated at week 12. From this table, it can be seen that 1 group of variable doses of formaldehyde, has 4 total rats where the total of all rats is 16 rats. In the dysplasia degree group, the control group had 8 rats that were not given formaldehyde exposure. While in the treatment group, there were 2 rats that showed mild dysplasia, 2 rats that showed moderate dysplasia, and 3 rats that showed severe dysplasia.

Table 2. Kruskal Walis Test Results

	Degree of Dysplasia								*p*
	Normal		Mild		Moderate		Severe		
	n	%	n	%	n	%	n	%	
0ppm	4	100	0	0	0	0	0	0	**0.002**
20ppm	4	100	0	0	0	0	0	0	
30ppm	0	0	2	50	2	50	0	0	
40ppm	0	0	0	0	0	0	4	100	

Table 2 compiles histopathological data of lung tissue examined from tissue biopsies of Wistar rats terminated at week 12. From this table, it is obtained that in the control group, there are 4 normal rats. While from the treatment group, at a dose of 20 ppm there were 4 normal rats, at a dose of 30 ppm there were 2 rats that showed mild dysplasia results and 2 rats that showed moderate dysplasia results, at a dose of 40 ppm there were 4 rats that showed severe dysplasia results. From the results of this significance test, it can be interpreted that significant results were obtained on the degree of dysplasia. This is evidenced by the result of p at 0.002 ($p<0.05$).

Table 3. Mann-Whitney U Test Results

No.	Formaldehyde Dosage		p
1.	0ppm	20ppm	1
2.	0ppm	30ppm	0,013*
3.	0ppm	40ppm	0,008*
4.	20ppm	30ppm	0,013*
5.	20ppm	40ppm	0,008*
6.	30ppm	40ppm	0,013*

*Notes: Significant ($p<0.05$)

Table 3 summarize the histopathological comparison data of the degree of dysplasia in the lung tissue of Wistar rats after formaldehyde induction with doses of 20, 30, 40 ppm and Wistar rats in the control group that did not receive treatment using the Mann-Whitney test 6 times. Of the 6 Mann-Whitney test results, 1 comparison was not significant and 5 comparisons were significant. At week 12, formaldehyde-induced Wistar rats with a dose of 20 ppm and the control group did not have a significant comparison. This is evidenced by the p results which are above 0.05. Wistar rats induced with formaldehyde at a dose of 30ppm with the control group, 40ppm with the control group, 20ppm with 30ppm, 20ppm with 40ppm, 30ppm with 40ppm have significant comparison results. This is evidenced by the results of p <0.05.

The results of research findings using univariate analysis, in the formaldehyde dose group, a total of 16 rats were divided equally into 4 dose groups. The control group and the treatment dose of 20ppm, 30ppm, 40ppm. In the dysplasia degree group, there were 50 percent of the total rats that were still normal, and the remaining 50 percent showed different levels of dysplasia. There were 2 rats that displayed mild dysplasia, 2 rats moderate dysplasia, and 4 rats severe dysplasia. Because the data of this study is ordinal, which is categorized as mild, moderate, and severe, so it is necessary to test the comparison of bivariate analysis. The analysis performed was using Kruskal Walis with further

analysis using the Mann Whitney U Test. The results of research findings using bivariate analysis with the Kruskal Walis test, in the control group there were 4 rats that displayed normal results. While in the 20ppm dose treatment group there were 4 rats that displayed normal results, the 30ppm dose treatment group had 2 rats that displayed mild dysplasia results and 2 rats that displayed moderate dysplasia, the 40ppm dose treatment group had 4 rats that displayed severe dysplasia results. The findings of the study using bivariate analysis with the mann-whitney u test, researchers conducted 6 comparisons which resulted in 1 comparison showing insignificant results and 5 results showing significant results.

Health Risks Associated with Formaldehyde Exposure

Formaldehyde was chosen because it is often used in the production of various products that we encounter daily, such as insulation foam, paints, resins, plastics, synthetic fibers, and other products that are the main ingredients in various furniture, carpets, and other household products (Bernardini et al., 2020). Formaldehyde exposure is not only experienced by workers who produce it, but also by those who work in pathology and histology, as well as those who handle preserved tissues, such as in anatomy laboratories. Formaldehyde is commonly used as a tissue binder and preservative (Bernardini et al., 2020).

Formaldehyde in high doses can cause respiratory mucosal epithelial dysplasia, which is divided into three levels: mild, moderate, and severe. Formaldehyde, a known carcinogen, can cause nasopharyngeal carcinogenesis in C3H mice. Several studies have shown that inhaled formaldehyde dust particles can cause moderate dysplasia of the respiratory mucosal epithelium. In addition, formaldehyde can react with protein amines, producing methenamine or hexamethylenetramine. Upon entering the body, formaldehyde reacts with DNA, triggering mutations (Sari et al., 2019). Animal studies have shown that formaldehyde in the form of dust particles at 3 ppm can trigger nasopharyngeal carcinogenesis (Sulistyo, 2008).

The Impact of Environmental Carcinogens on Respiratory Health

Continuous exposure to carcinogenic factors can cause genetic and epigenetic changes that lead to progression from carcinoma in situ to invasive carcinoma. Currently, the clinical method to evaluate lesions leading to malignant tumors is histopathological examination to look for dysplasia and carcinoma (Ranganath et al., 2022). Susceptibility to oncogenic events that lead to tumor formation is highly tissue-specific (Ranganath et al., 2022).

Exposure to formaldehyde poses a serious health hazard to the respiratory system. Inhalation of formaldehyde vapor can irritate the respiratory system resulting in symptoms such as wheezing, coughing, and throat irritation. Repeated exposure to formaldehyde has been shown to cause hypersensitivity and allergic responses in the respiratory system. In addition, studies have linked prolonged exposure to the risk of upper respiratory system cancer. The link between formaldehyde exposure and inflammatory lung disease suggests a complex interaction between environmental factors and respiratory system health.

Formaldehyde is an industrial chemical and air contaminant that often causes respiratory tract irritation. Mechanistically, formaldehyde can exacerbate existing inflammation and make people more susceptible to respiratory symptoms by inducing immunological responses, oxidative stress, and airway remodeling. Exposure to formaldehyde can be detrimental to many people, especially in vulnerable groups such as children, the elderly, and those who already have respiratory diseases. Thus, understanding the complex processes behind formaldehyde-induced lung inflammation is crucial.

Dysplasia and Lung Health: The Effects of Formaldehyde Exposure

Based on the degree of severity, dysplasia is divided into 3, namely mild dysplasia, moderate dysplasia, and severe dysplasia. The three types can be differentiated based on the damage to the tissue architecture. Mild dysplasia is identified by the presence of architectural disturbances that only occur in the lower third of the epithelium with cytologic atypia. Moderate dysplasia is identified by architectural disruption that extends to the middle third of the epithelium, with a less severe degree of cytologic atypia. Severe dysplasia is identified by architectural disruption observed in more than two-thirds of

the epithelium, with more severe cytologic atypia (Ranganathan & Kavitha, 2019).

Long-term exposure to formaldehyde can cause histopathologic damage to human lung tissue, similar to the results found in Wistar rats in this study. Histopathologic changes may include dysplasia changes that occur in the lungs. Therefore, workers who are frequently exposed to formaldehyde are at high risk of chronic respiratory distress and other lung diseases. Based on these findings, measures to prevent and control formaldehyde exposure in the workplace are very important. High awareness of the health risks associated with formaldehyde may help many people to take more proactive preventive measures. The results of this study can serve as a basis for the development of stricter policies and regulations regarding the use of formaldehyde in all industries.

Stricter regulations and better supervision can help reduce formaldehyde exposure in the workplace and thus protect human health. During the formaldehyde induction procedure, the researcher needs to open the wire cover of the cage in order to reach the container of cotton wool to be induced with formaldehyde. Sometimes the re-closing of the cage cover wire is inadequate, making it easier for the rats to get out of their own cages. Supervision of the rats was also not carried out continuously within 24 hours so that things like rats running away were only noticed when the formaldehyde induction was about to be carried out again.

Conclusion

This study compared the effects of formaldehyde doses of 20, 30, and 40 ppm on the lung tissue of Wistar rats for 12 weeks. The results of the study showed that there was a significant effect of formaldehyde induction on the condition of the rat lung tissue. The most severe lung tissue damage occurred at a dose of 40 ppm, followed by a dose of 30 ppm and then 20 ppm. Histopathological analysis revealed that significant damage was seen in the groups induced with doses of 30 and 40 ppm, compared to the control group. In addition, formaldehyde induction for 12 weeks with doses of 30 and 40 ppm was shown to cause dysplasia in the lung tissue of rats. These findings highlight the potential health risks posed by long-term exposure to formaldehyde, especially at higher doses.

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