*INTERNATIONAL JOURNAL OF SCIENCE, TECHNOLOGY AND DESIGN*

**ULUSLARARASI**
**BİLİM, TEKNOLOJİ VE TASARIM DERGİSİ**

ISSN: 2757-8127, https://dergipark.org.tr/tr/pub/istd

# Fenarimol'e Maruz Kalan Sıçanların Çeşitli Dokularında LDH Aktivitesindeki Değişiklikler

Egemen DERE

*B.U.Ü., Fen Edebiyat Fakültesi Biyoloji Bölümü, Moleküler Biyoloji Anabilim Dalı, Bursa, TÜRKİYE, ORCID ID 0000 0001 9572 1051*

*Corresponding Author: Egemen DERE,* edere@uludag.edu.tr

## Özet

*Fenarimol, özellikle üzüm bağlarında mantar hastalıklarıyla mücadelede kullanılan, meyve ve sebze yetiştiriciliğinde yaygın şekilde tercih edilen bir fungisittir. Hem östrojenik hem de antiandrojenik aktivite gösteren bu bileşik, gama-glutamiltransferaz, glikoz-6-fosfataz ve alkalin fosfataz gibi önemli enzimler üzerinde etkili olabilmektedir. Bu çalışmada ise laktat dehidrogenaz (LDH) enzimi ele alınmıştır.*

*Fenarimol, $LD_{50}$ dozu olan 200mg $kg^{-1}$ düzeyinde, erkek ve dişi sıçanlara intraperitoneal olarak uygulanmıştır. Uygulamayı takiben 2, 4, 8, 16, 32, 64. ve 72. saatlerde sıçanların karaciğer, böbrek, beyin ve ince bağırsak dokularından alınan örneklerde LDH enzim aktivitesindeki değişimler belirlenmiştir.*

*Elde edilen bulgular, Fenarimol uygulamasının incelenen tüm dokularda LDH aktivitesini artırdığını göstermiştir. Bu artış, her iki cinsiyette de 72. saate doğru azalma eğilimi göstermiştir. LDH aktivitesindeki bu artışların, ilgili dokularda hücresel hasar meydana geldiğine işaret ettiği düşünülmektedir.*

***Article Info***

*Research Article*
*Received:01/05/2025*
*Accepted: 20/05/2025*

***Anahtar Kelimeler***

*fenarimol, karaciğer, böbrek, beyin, ince bağırsak, laktat dehidrogenaz*

***Öne Çıkanlar***

*1-Fenarimol uygulaması hem erkek ve dişi sıçanların LDH aktivisinde artışlara neden olmuştur.*

*2-Sıçanların karaciğer, böbrek, beyin ve ince bağırsak dokularında LDH enzim aktivitesinde artışlar istatistiksel olarak önemli kaydedilmiştir.*

*3- Fenarimol uygulamasının incelenen tüm dokularda hücresel hasar meydana getirdiği düşünülmektedir.*

# The Changes in LDH Activity in Various Tissues of Rats Exposed to Fenarimol


## Abstract

*Fenarimol is a fungicide widely used in fruit and vegetable cultivation, particularly in vineyards, to combat fungal diseases. Exhibiting both estrogenic and antiandrogenic activities, this compound also influences several key enzymes, including gamma-glutamyltransferase, glucose-6-phosphatase, and alkaline phosphatase. In the present study, the enzyme lactate dehydrogenase (LDH) was selected as a biochemical marker to evaluate tissue-specific effects of Fenarimol exposure.*

*Fenarimol was administered intraperitoneally to both male and female rats at its $LD_{50}$ dose (200 mg/kg). Following administration, changes in LDH enzyme activity were assessed in liver, kidney, brain, and small intestine tissues at various time intervals: 2, 4, 8, 16, 32, 64, and 72 hours.*

*The results indicated a significant increase in LDH activity in all examined tissues post-exposure. However, this elevated enzyme activity gradually declined toward the 72-hour mark in both sexes. These increases in LDH activity suggest that Fenarimol induces notable tissue damage, reflecting its toxicological impact on vital organs.*



***Keywords***

fenarimol, liver, kidney, brain, small intestine, lactate dehydrogenase


***Highlights***

*1- Fenarimol application caused increases in LDH activity in both male and female rats.*

*2- Statistically significant increases in LDH enzyme activity were recorded in the liver, kidney, brain, and small intestine tissues of rats.*

*3- Fenarimol application is thought to cause cellular damage in all tissues examined*

## 1. Introduction

The human population in the world is increasing very rapidly. This increase also causes an increase in food demand. This situation directs the agricultural and livestock industries to produce more food. Increasing agricultural areas in this sense and uncontrolled use of pesticides lead to the destruction of natural habitats and loss of biodiversity. Pesticide use is increasing every year in the world and in Turkey [1]. It has been announced that Turkey's pesticide imports have increased by 52.15% and the amount of pesticide use has increased by 39.21% in recent years [2]. It has been shown that the most used among these pesticides are fungicides with 38.4% [3]. In addition, it is known that such excessive and unconscious use of pesticides causes damage to water, soil, fruits, and vegetables, reaches people through the food chain, and causes serious health problems [4].

Fenarimol, a pyrimidine derivative, has a chemical formula of $C_{17}H_{12}Cl_2N_2O$. Fenarimol is a fungicide used in the agricultural sector for the control of plant diseases. It is widely used against fungal diseases in fruits and vegetables, such as grape vineyards. Among these diseases, we can mention mildew, anthracnose, and other fungal infections. Fenarimol is a substance classified as a sterol biosynthesis inhibitor (SBI) and exhibits

antifungal effects by inhibiting the synthesis of ergosterol, an important component of the fungal cell membrane [5, 6].

Fenarimol has been shown to interfere with hepatic biotransformation processes, potentially slowing the elimination of certain toxins. Prolonged exposure may place a significant burden on liver function. In humans, it has been demonstrated to inhibit the cytochrome P450 enzyme system, particularly impacting steroid metabolism, which could result in drug interactions and the accumulation of toxic compounds in the body [7].

As an endocrine-disrupting chemical, fenarimol inhibits key enzymes such as Cytochrome P450 Family 19 (CYP19, aromatase) and Cytochrome P450 Family 17 (CYP17), thereby impairing the biosynthesis of estrogen and testosterone. This disruption of androgen-to-estrogen conversion may lead to imbalances in hormonal regulation. Animal studies have reported that fenarimol exposure in males leads to reduced testosterone levels and impaired spermatogenesis [8, 9].

Similarly, studies in female mice have indicated reproductive irregularities, decreased fertility, and potential transgenerational effects on the reproductive capacity of offspring during gestation and lactation [10]. Although its neurotoxic potential has not been conclusively established, some evidence suggests that fenarimol may pose a risk of developmental neurotoxicity, particularly when exposure occurs during critical periods of fetal development.

Given its potential to disrupt hormonal balance, modulate hepatic enzymes, and impair reproductive function, fenarimol is considered a fungicide of concern. Long-term exposure is associated with significant health risks, and as a result, its use has been restricted or banned in certain countries [11, 12].

Lactate dehydrogenase (LDH) is one of the crucial enzymes in metabolism. Under hypoxic conditions, it catalyzes the conversion between lactic acid and nicotinamide adenine dinucleotide ($NAD^+$) in the body. During this conversion, pyruvic acid is transformed into lactic acid, while the NADH molecule converts to $NAD^+$ and a hydrogen ion ($H^+$). This conversion is important for the continuity of glycolysis. LDH is involved in cellular energy production when oxygen levels in the cells are low or absent. For example, during intense exercise when oxygen becomes depleted in muscle cells, pyruvic acid is converted to lactic acid, and this conversion is utilized to sustain energy production [13].

Even though this enzyme is present in all cells, it is primarily found in the liver, muscle, kidney, and heart tissues. Variations in LDH enzyme levels are typically linked to tissue damage. LDH is also found in the blood. Measurement of LDH levels during blood tests serves as a diagnostic tool, especially in conditions such as heart attack, liver diseases, and other tissue damage. The organism attempts to repair the damage as quickly as possible using the metabolic energy produced rapidly by the LDH enzyme [14]. However, the use of LDH alone as a diagnostic tool is not common. It is usually evaluated in conjunction with many other tests and interpreted alongside clinical symptoms.

The specific effects of pesticides, especially their effects on enzymes, vary depending on the components used, their doses, and the duration of exposure. Therefore, the biochemical and physiological effects of pesticide exposure encompass a wide range. In this study, the effect of Fenarimol, commonly used in agricultural fields, on the activity of the LDH enzyme, which plays a significant role in the metabolic pathway, was investigated. LDH activity was assessed in the liver, kidney, brain, and small intestine tissues of male and female rats following exposure to fenarimol. This research will contribute to studies exploring the effects of fenarimol on metabolism.

## 2. Material and method

### 2.1. Material

The project was completed with Rattus norvegicus rats weighing 200-250g obtained from Bursa Uludağ University's experimental animal breeding center. The rats were kept under standard laboratory conditions until they were taken into the experiment. The laboratory environment was sterile and hygienic. Feeding programs were organized according to the needs of the rats. Water was given freely. Ethical rules were followed in experimental techniques.

### 2.2. Method

In the study, two groups of rats were considered for each experimental period: a control group consisting of 2 rats (1 male; 1 female) and an experimental group consisting of 4 rats (2 males; 2 females). Experimental animals were kept under control in separate cages during the test periods of 2, 4, 8, 16, 32, 64, and 72 hours. A total of 42 rats were used in the experiments. Fenarimol (Sigma-Aldrich, St. Louis, MO) was administered intraperitoneally to the experimental groups at a dose of 200mg/kg ($LD_{50}$), while the control groups received an equivalent volume of corn oil. To ensure metabolic synchronization, rats in both groups were subjected to 24 hours of fasting and water deprivation prior to injection. After the injection, food and water were given regularly throughout the experiment. The animals were humanely euthanized by cervical dislocation at 2, 4, 8, 16, 32, 64, and 72 hours following the injection. Tissues from the small intestine, brain, kidney, and liver were carefully collected in a cold environment and then infused in 0.15 M KCl. The tissues were homogenized in a T-line laboratory shaker-type homogenizer (model No: 136-2) at 2000 rpm. Each homogenate was centrifuged at 48000g for 30 minutes in an RC-5 super-speed refrigerated centrifuge (Dupont Instruments Sorvall), and the supernatants were used as the enzyme source. Enzymatic reaction rates were determined using freshly prepared samples, and centrifugation and homogenization were carefully performed at 0-4°C. Protein amounts in the resulting homogenates were determined using the Bradford method with standard bovine serum albumin [15]. The Boehringer & Mannheim method was used for the calculation of LDH activity [16]. The activity determination was spectrophotometrically assessed at a wavelength of 340nm.

### 2.3. Statistical Analysis

The experimental data were analyzed using the GraphPad Prism 8 software for Windows (Demo Version; GraphPad, San Diego, CA). The effect of Fenarimol between the experimental and control groups was evaluated using an independent t-test. Statistical significance was determined through a one-way analysis of variance (ANOVA). p-values of <0.05, <0.01, and <0.001 were considered statistically significant

## 3. Result and discussion

### 3.1. The Impact of Fenarimol on LDH Activity in Liver Tissue

Fenarimol significantly increased LDH enzyme activity in liver tissue compared to the control group, beginning as early as 2 hours in both male and female rats ($p<0.05$, $p<0.01$, and $p<0.001$). The highest enzyme activity was observed in both groups at 32 hours (Figure 1A and 1B). While it was 146.46±54.98 U $mg^{-1}$ protein in males, it was 199.56±56.8 U $mg^{-1}$ protein in females.

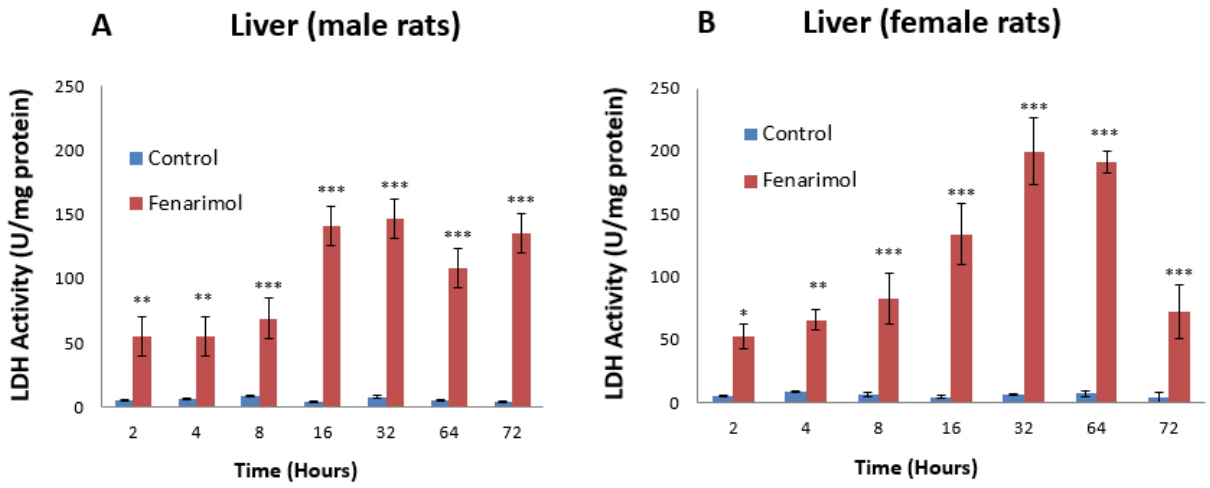


**Figure 1.** LDH activity (U $mg^{-1}$ protein) in male (A) and female (B) rat liver tissue under the influence of Fenarimol. Statistically significant differences, *($p<0.05$); **($p<0.01$); ***($p<0.001$).

$^{\gamma}$ For each supernatant, activity values were measured in triplicate using spectrophotometer, and the averages were calculated.

### 3.2 Effect of Fenarimol on LDH Activity in Kidney Tissue

Fenarimol increased LDH enzyme activity in the kidney tissue of both male and female rats compared to the control group. This activation was statistically significant starting from the 2nd hour ($p<0.001$). Notably, the highest levels of LDH activity were reached at 32 hours in male rats (87,12±6,19 U $mg^{-1}$ protein) and 64 hours in female rats (105,42±13,4 U $mg^{-1}$ protein). Although there was a decrease in LDH activity from these time periods onwards, the activation continued until the end of the experimental period (Figure 2A and 2B).

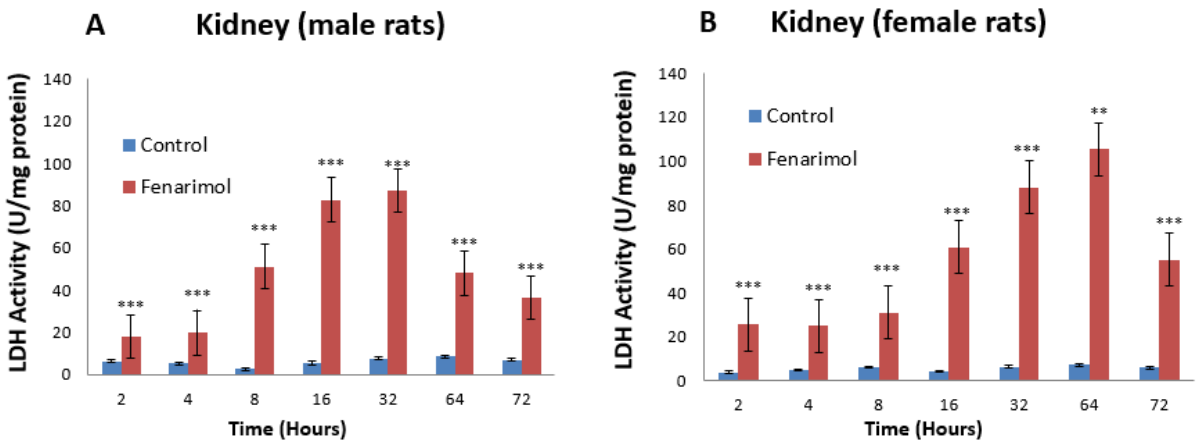


**Figure 2.** LDH activity (U $mg^{-1}$ protein) in male (A) and female (B) rat kidney tissue under the influence of Fenarimol. Statistically significant differences, **($p<0.01$); ***($p<0.001$).

$^{\gamma}$ For each supernatant, activity values were measured in triplicate using spectrophotometer, and the averages were calculated.

### 3.3. Effect of Fenarimol on LDH Activity in Brain Tissue

When the effect of Fenarimol on LDH enzyme activity in brain tissues was examined, increases in LDH activity were observed in both male and female rats during all experimental periods studied. Despite a decrease in LDH activity from 32 hours onwards, the activation was observed to continue until the end of the experimental period. In male rats, LDH activity was found to significantly increase in all periods except for the 2nd hour ($p<0.01$ and $p<0.001$). The highest LDH activity was measured at 8 hours (Figure 3A) (55,58±9,17 U $mg^{-1}$ protein). In female rats, LDH activity in the brain was found to significantly increase from the 1st hour onwards, reaching its peak at 32 hours (57,94±5,20 U $mg^{-1}$ protein), $p<0.001$; Figure 3B).

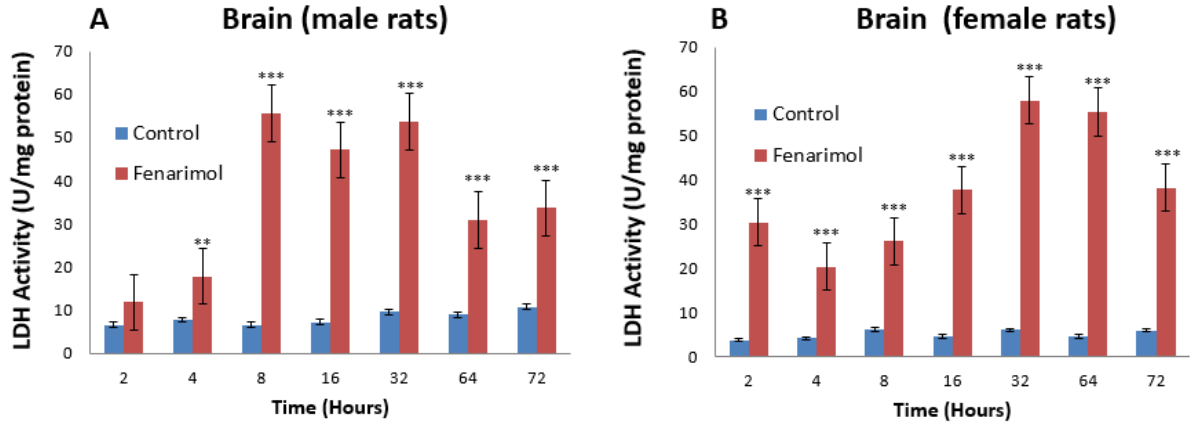


**Figure 3.** LDH activity (U $mg^{-1}$ protein) in male (A) and female (B) rat brain tissue under the influence of Fenarimol. Statistically significant differences, **($p<0.01$); ***($p<0.001$).

$^{\gamma}$ For each supernatant, activity values were measured in triplicate using spectrophotometer, and the averages were calculated.

### 3.4. Effect of Fenarimol on LDH Activity in Small Intestine Tissue

When the LDH enzyme activity in the small intestine tissues of rats exposed to Fenarimol was evaluated, an increase was observed in both male and female rats from the early period (2 hours) compared to the control group. This increase in LDH activity was statistically significant in all experimental periods, except for the last time period, in all rats (Figure 4A and 4B). The highest activity was reached at the 8th hour in male rats (6.57±2.57 U mg-1 protein), while it was reached at the 2nd hour in female rats (5.30±2.71 U mg-1 protein).

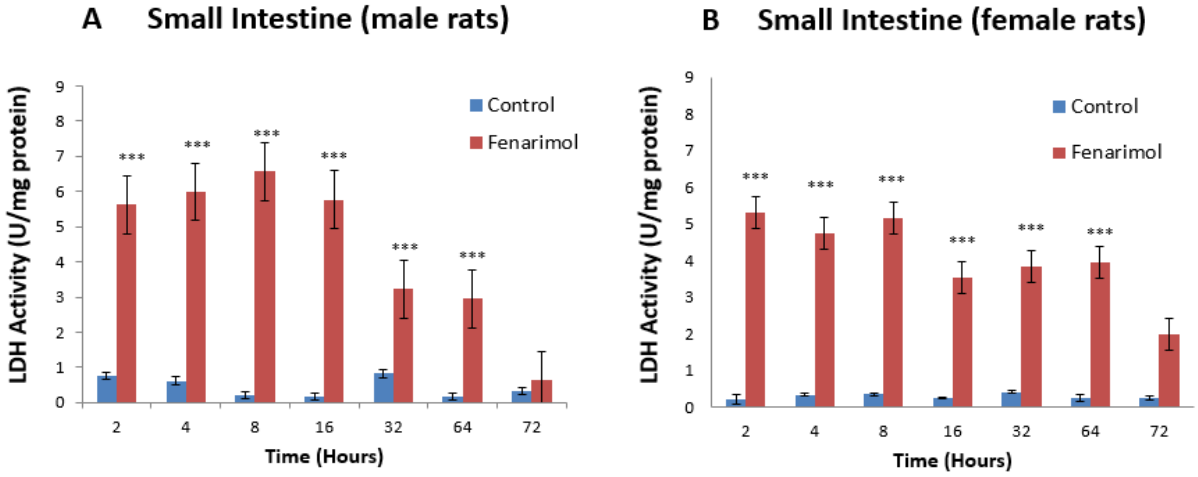


**Figure 4.** LDH activity (U mg$^{-1}$ protein) in male (A) and female (B) rat small intestine tissue under the influence of Fenarimol. Statistically significant differences, ***($p<0.001$).

$^{\gamma}$ For each supernatant, activity values were measured in triplicate using spectrophotometer, and the averages were calculated.

Fenarimol is an agricultural pesticide used as a fungicide. Fungicides disrupt the integrity of the fungal cell membrane or increase its permeability by targeting the fungal cell membrane. This causes an imbalance in ions and molecules within the cell, leading to disruption of energy metabolism in the cell. Additionally, they can interfere with the respiratory processes of the fungus, thereby inhibiting energy production. They disrupt the working system of electron carriers in the respiratory chain by inhibiting or activating enzymes involved in respiratory processes [17]. There is limited information on the effects of fenarimol on humans, and it is a chemical that requires careful use. Prolonged or intense exposure to fenarimol can cause irritation in the respiratory tract, skin, and eyes. Fungicides particularly affect processes such as growth, development, and energy production, especially in the muscle and nervous systems [18].

In the study, it was found that LDH enzyme activity in the liver tissue increased statistically significantly in both male and female rats from the beginning of the experimental period (2 hours) until the end period, especially reaching the highest activity level at 32 hours ($p<0.001$, Figure 1A and 1B). Fenarimol may cause damage to liver cells and increase LDH activity. Cellular damage can occur when the liver tissue is not provided with sufficient oxygen (ischemia), leading to an increase in LDH activity. It has been shown that liver weight increases in rats, and serum enzymes, which are indicators of liver toxicity, also increase [19]. A study showed that exposure to fenarimol resulted

in activation of the GST enzyme in the small intestine, kidney, and liver tissues of rats, while it caused inhibition in brain tissue [20]. In another study, an increase in cholinesterase activity was suggested. In the same study, it was histologically shown that the portal of the liver of animals given fenarimol was blocked with infiltration of lymphocytes, indicating portal inflammation [21].

Similarly, in the study, LDH enzyme activity in the kidney tissue was observed to increase consistently in male rats until 32 hours ($p<0.001$) and in female rats until 64 hours ($p<0.01$), after which the activity levels decreased in the subsequent hours. However, it was determined that activations in LDH enzyme activity continued until the end of the experimental period compared to the control group in both male and female rats (Figure 2A and 2B). While metabolizing in the liver, fenarimol may have caused damage, either itself or its metabolites, to the kidney, leading to cellular damage. Ahmed et al. (2002) showed in their studies that fenarimol caused moderate swelling of kidney epithelium and glomerular obstruction [21].

When the effect of fenarimol on LDH enzyme activity in small intestine and brain tissues was examined, it was found that there was an increase in both male and female rats compared to the control group in all experimental periods. Although there was a decrease in LDH activity in the brain tissue from 32 hours onwards, activation continued until the end of the experimental period. In male rats, LDH activity was found to increase significantly in all periods except the 2nd hour (4th hour $p<0.01$ and other hours $p<0.001$). The highest LDH activity was measured at 8 hours. In female rats, brain LDH activity was found to increase statistically significantly from the 1st hour and peaked at 32 hours ($p<0.001$; Figure 3A and 3B). Since the brain tissue is the control center of the body hormonally, it can be considered that the necessary energy to send signals to the relevant organs for pesticide detoxification is required, and this energy need may be met through the LDH enzyme [22]. The maximum level of LDH enzyme activation in the small intestine was observed around 8 hours, followed by a decrease in activation. However, LDH enzyme activity in the small intestine was lower compared to other tissues (Figure 4A and 4B). This observation may be due to the relatively small role of the small intestine in the detoxification mechanism due to its function in chemical digestion processes [23]. A study by Arı et al. (2017) showed that exposure to methyl parathion and fenarimol increased glucose-6-phosphate dehydrogenase enzyme activity, which plays a role in the metabolic pathway, in small intestine and brain tissues of rats. In another study, exposure to fenarimol resulted in increased activities of serum creatine kinase (CK), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) in rats [24, 25]. Dehydrogenase enzymes play crucial roles in detoxification, metabolism, and various fundamental biological processes, including the biosynthesis of energy macromolecules [26]. These enzymes are considered specific indicators of damage for many tissues, especially hepatic dysfunction [27]. Increases in LDH activity result in elevated levels of lactate and ATP [28]. Thus, it can be said that the energy required by the liver and kidney tissues, primarily responsible for the detoxification and elimination of pesticides, is obtained through the LDH enzyme.

One possible reason for the increase in LDH activity observed in different tissues may be the effect on chromosomes and DNA. It has been shown that fenarimol affects DNA in the leukocytes of rats and mice. This fungicide may cause DNA damage in a dose-

dependent manner [29]. In a previous study, fenarimol was shown to induce DNA damage in rat hepatocytes, leading to a significant increase in DNA opening [30]. Short-term genotoxicity tests showed DNA damage, point mutations, and chromosomal abnormalities [31, 32, 33]. An in vitro study conducted with rat and mouse leukocytes also demonstrated that fenarimol affected the DNA of more than 50% of the cells and caused damage [29]. It has been proposed that Fenarimol causes damage by inducing oxidative stress [34].

During the experimental periods in our study, female rats exhibited higher LDH activity in liver, kidney, brain, and small intestinal tissues compared to male rats. This difference may be attributed to gender-specific metabolic and hormonal variations. In particular, female hormones such as estrogen are known to influence tissue stress responses, enzyme expression, and cell membrane stability. These findings suggest that female subjects may respond differently to cellular damage or elicit a more pronounced enzymatic reaction to toxic effects. Furthermore, this highlights the importance of considering sex-based differences when evaluating toxicological outcomes.

## 4. Conclusion

In conclusion, it should be considered that exposure to fenarimol may be one of the reasons for the high LDH activity observed in laboratory tests. It is possible to minimize the harm to human health caused by fenarimol, widely used in agricultural fields, through the food chain. Therefore, the amounts of fenarimol used in the fields must be determined by agricultural engineers. Agricultural workers should also comply with these rules. Additionally, pesticide residues in agricultural fields in Turkey must be controlled. Pesticide use should be regulated to meet the maximum limits set by the European Union for pesticide residues [35].

## Conflict of interest

There is no conflict of interest between the author and those who support the article

## Funding

This study was supported by Bursa Uludağ University Animal Care and Use Committee in accordance with the decision of the Ethics Committee dated 3 June 2003 (Decision No: 2003/3) and scientific research fund (grant no: F (U) -2003/65).

## 5. References

[1] FAO, Statistical yearbook, world food and agriculture 2023. Food and agriculture organization of the United Nations Rome, (2023a). ISBN 978-92-5-138262-2 https://doi.org/10.4060/cc8166en

[2] Yılmaz A.M., Tomar O., Çağlar A. Evaluatıon of pesticide use and trade in Turkey. 8th international new york conference on evolving trends in interdisciplinary research &

practices. Conference paper, Manhattan, New York City, May 1-3, (2023). https://www.researchgate.net/publication/377241148

[3] Özercan B., Taşcı R. Türkiye'de pestisit kullanımının iller, bölgeler ve pestisit grupları açısından incelenmesi. Ziraat mühendisliği 375, 75-88, (2022). https://doi.org/10.33724/zm.1120599

[4] Kuruta B., Kilin M. Pestisitlerin biyolojik sistemler üzerine etkisi. Arşiv kaynak tarama dergisi, 12:3, 215–228, (2003). https://doi.org/10.17827/aktd.33853

[5] Siegel M.R. Sterol inhibiting fungicides: Effects on sterol biosynthesis and sites of action. Plant diseases, 65:12, 986-989, (1981). https://doi.org/10.1094/PD-65-986

[6] Stenzel K., Vors J.P. Sterol Biosynthesis Inhibitors In book: Modern Crop Protection Compounds, (2019). doi:10.1002/9783527699261.ch19

[7] Paolini M., Mesirca R., Pozzetti L., Maffei F., Vigagni F., Hrelia P., Cantelli-Forti, G. Genetic and non-genetic biomarkers related to carcinogenesis in evaluating toxicological risk from Fenarimol, Mutation Research, 368, 27-39, (1996a). https://doi.org/10.1016/s0165-1218(96)90037-3.

[8] Sanderson J.T., Boerma J., Lansbergen G.W.A., van den Berg M., Induction and Inhibition of Aromatase (CYP19) Activity by Various Classes of Pesticides in H295R Human Adrenocortical Carcinoma Cells. Toxicology and Applied Pharmacology 182:1, 44-54, (2002).

[9] Andersen H.R., Bonefeld-Jørgensen E.C., Nielsen F., Jarfeldt K. Estrogen effects in vitro and in vivo of the fungicide fenarimol. Toxicology Letters 163:2, 142-152, (2006). doi:10.1016/j.toxlet.2005.10.004

[10] Han J., Park M., Won M., Kim J-H., Ko J.J., Bae, J. Transgeneration Effects of Fenarimol on Reproductive Health in Female Mice. Biology of Reproduction 78:1, 115, (2008). doi:10.1093/biolreprod/78.s1.115

[11] WHO FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment, (1995)

[12] Bellisai G., Bernasconi G., Binaglia M., Cabrera L.C., Castellan I., Castoldi A.F., Chiusolo A., Crivellente F., Aguila M.D., Ferreira L., Santonj, G.G., Greco L., Istace F., Jarrah S., Lanzoni A., Leuschner R., Mangas I., Miron I., Nave S., Panzarea M., Morte J.M.P., Pedersen R., Reich H., Ruocco S., Santos M., Scarlato A.P., Terron A., Theobald A., Tiramani M., Verani A., Targeted review of maximum residue levels (MRLs) for fenarimol. European Food Safety Authority. Open Access. (2023). doi.org/10.2903/j.efsa.2023.8113

[13] Hargreaves M., Spriet L.L. Skeletal muscle energy metabolism during exercise. Nature metabolism, 2, 817–828, (2020). https://doi.org/10.1038/s42255-020-0251-4

[14] Bradford M.M.A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Analytical biochemistry, *72*:1-2, 248–254, (1976). https://doi.org/10.1006/ABIO.1976.9999

[15] Klein R., Nagy O., Tóthová C. Chovanová F. Clinical and diagnostic significance of lactate dehydrogenase and its isoenzymes in animals. Veterinary medicine international, 11. Article ID 5346483, (2020). https://doi.org/10.1155/2020/5346483

[16] Hodges R.S. Boehringer Mannheim award lecture 1995. La conference Boehringer Mannheim 1995. De novo design of alpha-helical proteins: basic research to medical applications. Biochemistry and cell biology = Biochimie et biologie cellulaire, 74:2, 133-154, (1996). https://doi.org/10.1139/O96-015

[17] Ivanov M., Ciric,A., Stojkovic D. Emerging Antifungal Targets and Strategies. International journal of molecular sciences, 23, 2756, (2022) https://doi.org/10.3390/ijms23052756

[18] Lushchak V.I., Matviishyn T.M., Husak V.V., Storey J.M., Storey K.B. *Pesticide toxicity:* A mechanistic approach. EXCLI Journal, 17, 1101-1136, (2018). https://doi.org/10.17179/excli2018-1710

[19] EPA, Fenarimol summary, United State Environmental Protection Agency. Docket Number: EPA-HQ-OPP-2006-0241, (2007). www.regulations.gov

[20] Özcelebi H., Ari F., Dere E. Glutathione S-transferase activity in tissues of rats exposed to fenarimol. Brazilian archives of biology and technology, 64, 1-8, (2021). https://doi.org/10.1590/1678-4324-2021200751

[21] Ahmed F.A.M., Zein A.A., Tag El-Din, M.H., El-naggar J.B. Toxicological studies of some pesticides on certain vegetable crops pests. III-Side effects of some compounds used to control certain vegetable crops pests on white rats. Journal of agricultural sciences, 27:12, 8645-8654, (2002). https://doi.org/10.21608/jppp.2002.256220

[22] Kori R.K., Singh M.K., Jain A.K., Yadav R.S. Neurochemical and behavioral dysfunctions in pesticide exposed farm workers: A clinical outcome. Indian journal of clinical biochemistry, 33:4, 372-381, (2018). https://doi.org/10.1007/s12291-018-0791-5

[23] Giambò F., Teodoro M., Costa C., Fenga C. Toxicology and microbiota: How do pesticides influence gut microbiota? a review. International journal of environmental research and public health, *18:*11, 5510, (2021). https://doi.org/10.3390/ijerph18115510

[24] Arı F., Dere E., Tosunoglu H. The Effects of Fenarimol and Methyl Parathion on Glucose 6-Phosphate Dehydrogenase Enzyme Activity in Rats. Türkiye tarımsal araştırmalar dergisi, 4:3, 275-280, (2017). https://doi.org/10.19159/tutad.310371

[25] Arı F., Dere E. Effect of the sterol demethylation-inhibiting fungicide fenarimol on selected biochemical parameters in rats. Acta veterinaria, 60:1, 31-38, (2010). https://doi.org/10.2298/AVB1001031A

[26] Jain M., Nagar P., Sharma A., Batth R., Aggarwal S., Kumari S., Mustafiz A. GLYI and D-LDH play key role in methylglyoxal detoxification and abiotic stress tolerance. Scientific reports, 8:1, (2018). https://doi.org/10.1038/s41598-018-23806-4

[27] Karaca M., Martin-Levilain J., Grimaldi M., Li L., Dizin E., Emre Y., Maechler P. Liver glutamate dehydrogenase controls whole-body energy partitioning through amino acid-derived gluconeogenesis and ammonia homeostasis. Diabetes, 67:10, 1949-1961, (2018). https://doi.org/10.2337/db17-1561

[28] Valvona C.J., Fillmore H.L., Nunn P.B., Pilkington G.J. The regulation and function of lactate dehydrogenase A: Therapeutic potential in brain tumor. Brain Pathalogy, 26:1, 3-17, (2016). https://doi.org/10.1111/bpa.12299

[29] Poli P., de Mello M.A., Buschini A., de Castro V.L.S.S., Restivo F.M., Rossi C., Zucchi T.M.A.D. Evaluation of the genotoxicity induced by the fungicide fenarimol in mammalian and plant cells by use of the single-cell gel electrophoresis assay. Mutation Research, 9;540:1 57-66, (2003). https://doi.org/10.1016/s1383-5718(03)00165-7

[30] Paolini M., Pozzetti L., Mesirca R., Sapone A., Cantelli-Forti G. Testosterone hydroxylase in evaluating induction and suppression of murine CYP isoenzymes by fenarimol. Archives of Toxicology 70, 451–456, (1996b). [Medline] [CrossRef]

[31] Grilli S., Ancora G., Rani P., Valenti A.M., Mazzullo M., Colacci A. In vivo unwinding fluorimetric assay as evidence of the damage induced by fenarimol and DNOC in rat liver DNA, Journal of toxicology and environmental health, 34, 485-494, (1991). https://doi.org/10.1080/15287399109531584

[32] de Castroa VLSS, de Mello MA, Poli, P., Zucchi T.M.A.D. Prenatal and perinatal fenarimol-induced genotoxicity in leukocytes of in vivo treated rats Mutation Research 583, 95-104, (2005) doi:10.1016/j.mrgentox.2005.02.001

[33] Hai D.Q., Varga S.I., Matkovics B. Organophosphate Effects on Antioxidant System of Carp (Cyprinus carpio) and Catfish (Ictalurus nebulosus). Biochemistry, 117:1, 83-89, (1997). https://doi.org/10.1016/s0742-8413(96)00234-4.

[34] Ojha A., Yaduvanshi S.K., Pant S.C., Lomash V., Srivastava N. Evaluation of DNA damage and cytotoxicity induced by three commonly used organophosphate pesticides individually and in mixture, in rat tissues. Environmental toxicology, 28:10, 543-552, (2013). https://doi.org/10.1002/tox.20748

[35] FAO, The state of food security and nutrition in the World. Urbanization, agrifood systems transformation and healthy dıets across the rural–urban continuum. Food and

agriculture organization of the United Nations, International fund for agricultural development, United nations children's fund, world food programme, World health organization, Rome, (2023b). ISBN 978-92-5-137226-5