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Morphometric Changes in Internal Organs and Hematological Alterations Induced by TOPIK80EC Exposure in Domestic Rabbits.

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Abstract
This study is part of a broader investigation into the toxicological impact of the herbicide TOPIK® 80EC, which contains clodinafop-propargyl, in domestic rabbits (Oryctolagus cuniculus). A total of 24 male rabbits were randomly divided into four groups: a control group and three experimental groups receiving oral doses of 1, 4, and 20 mg/kg body weight of TOPIK® 80EC daily for 30 consecutive days. A significant dose-dependent reduction in body weight gain was observed throughout the treatment period ($p \leq 0.05$). While the control group exhibited normal weight progression, Groups II (4 mg/kg/day) and III (20 mg/kg/day) showed significantly reduced final body weights compared to the control ($p < 0.01$), with Group III displaying the most pronounced effect. Hematological analysis revealed statistically significant decreases in red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), and platelet (PLT) levels in Groups II and III ($p \leq 0.05$), indicating hematotoxic effects. In contrast, white blood cell (WBC) and lymphocyte counts were significantly elevated in Groups I and II ($p < 0.05$), suggesting immune stimulation, but were significantly decreased in Group III ($p < 0.01$), indicative of bone marrow suppression or systemic toxicity. Morphometric analysis of vital organs demonstrated significant increases in the weight, length, width, and volume of the liver, kidneys, and spleen in Groups II and III compared to controls ($p < 0.01$), confirming organomegaly and suggesting potential toxicity. The liver and spleen exhibited the most pronounced changes, with Group III showing the greatest enlargement ($p < 0.001$). Overall, these findings demonstrate the multi-systemic toxic potential of TOPIK® 80EC, even at sub-lethal doses, and underscore the need for cautious herbicide use.
Keywords: *Clodinafop-propargyl; Herbicide toxicity; Hematological alterations; Liver damage; Spleen; Rabbits.*

INTRODUCTION

Over the past several decades, herbicides have become a cornerstone in modern agricultural practices due to their efficiency in managing unwanted weed growth. Their increasing use worldwide is largely attributed to rising labor costs, ease of application, and their ability to provide rapid and effective weed control in both crop and non-crop environments (Benbrook, 2016). Since the post-World War II discovery and application of 2,4-D, the development of new herbicidal molecules has accelerated remarkably, driven by extensive research into their modes of action (ACTA, 2006). Today, herbicides account for approximately 44% of global pesticide consumption, surpassing insecticides (22%) and fungicides (27%). According to the World Health Organization (WHO), herbicide residues are defined as any substance or mixture found in food for humans or animals resulting from pesticide use, including degradation products, metabolites, and other derivatives of toxicological concern. Algeria, as a major consumer of phytosanitary products, is not exempt from the negative consequences associated with herbicide use. Annual pesticide consumption in Algeria ranges between 6,000 and 10,000 tons, representing approximately 15 to 20% of national agricultural needs. Herbicides, along with fungicides and insecticides, are among the most widely utilized chemical agents in the country. While the western regions of Algeria show high usage of fungicides and insecticides, herbicide application is particularly prevalent in the eastern regions (Lagadic et al., 1997; Bordjiba, 2009). The overuse of herbicides in these areas contributes not only to the contamination of soil and water bodies but also to the degradation of biodiversity and ecosystem health (Naz et al., 2023). In addition to their environmental persistence, numerous herbicides have been shown to exert genotoxic, cytotoxic, and reproductive toxic effects on non-target organisms, including mammals. Studies have reported adverse impacts on reproductive functions, such as disrupted spermatogenesis, impaired steroidogenesis, decreased sperm viability and motility, and disturbances in the estrous cycle of females (Muczynski, 2011; Ferdinand et al., 2017; Al-Hamdani & Yajurvedi, 2017). TOPIK®80EC is a systemic, post-emergence herbicide widely used in cereal crops such as wheat and rye. It contains clodinafop-propargyl (80 g/L) and cloquintocet-mexyl (20 g/L). Clodinafop-propargyl, a FOP-family herbicide, acts by inhibiting acetyl-CoA carboxylase (ACCase)—disrupting fatty acid synthesis and causing rapid death of grassy weeds (Chen et al., 2005; OEHHA, 2011). Its high lipophilicity aids plant penetration and soil binding, though residual activity is low (Takano et al., 2019b; Lancaster et al., 2018). Despite its efficacy, clodinafop-propargyl shows acute and chronic toxicity in animals. It exhibits oral and dermal toxicity, and is classified under H302 (harmful if swallowed) and H317 (skin sensitizer) (ECHA, 2017). Subchronic exposure in rodents and dogs has caused liver damage and hematological alterations, including anemia. Long-term studies have also linked it to benign and malignant liver tumors in rodents, likely due to peroxisome proliferation, a mechanism not directly relevant to humans (EFSA, 2012; SANCO, 2003).While these toxicological data are available for laboratory rodents, and a study have done in Algeria by Rebahi et al. (2024), still a notable lack of research on the effects of clodinafop-propargyl-based herbicides such as TOPIK®80EC in other mammalian species, particularly domestic rabbits. Given their physiological sensitivity and frequent use in toxicology, rabbits represent a relevant model for assessing systemic toxicity, especially with regard to hematological changes and organ-specific effects. The objective of the present experimental study is to conduct a comprehensive evaluation of the toxicological impact of the herbicide TOPIK®80EC on domestic rabbits, focusing on general health status, hematological alterations, and histopathological changes in key target organs, including the liver, kidneys, and spleen.

MATERIALS AND METHODS

Experimental Animals

The study was conducted on 24 male rabbits of the *Oryctolagus cuniculus* strain, aged between 5 and 6 months, with an average body weight ranging from 1.8 to 2 kg. These animals, originating from the Sétif region, are commonly used in scientific research due to their well-established biological characteristics, rapid reproductive cycle, and status as a livestock species. Puberty in these rabbits typically occurs between the 4th and 6th month, and all individuals included in the study were pubescent. Upon arrival at the laboratory, the rabbits were housed in metal cages (three animals per cage), each equipped with a pellet dispenser (complete feed composed of corn, barley, and straw) and a water bottle system. The animals were fed and watered *ad libitum* throughout the experimental period. The study took place between February and March, during which the ambient temperature ranged from 20 to 25°C, with relative humidity varying from 60% to 80%. A 15-day acclimatization period preceded the start of treatment. Throughout the study, the following parameters were monitored: daily weighing of the rabbits (kg/week), and daily observation of general condition, including behavioral signs (stress, anorexia) and morphological signs (skin lesions, inflammation).

Experimental Design and Test Substance

After the adaptation phase, the 24 rabbits were randomly divided into four homogeneous groups of six animals each: the control group, which received only physiological water (daily gavage) for four weeks; Group I, which received 1 mg/kg/day of Topik® 80EC; Group II, which received 4 mg/kg/day of Topik® 80EC; and Group III, which received 20 mg/kg/day of Topik® 80EC. The treatment was administered daily by gavage for four weeks. The tested product, Topik® 80EC, is an herbicide based on clodinafop-propargyl, an active substance belonging to the aryloxyphenoxypropionic acid family. Its

IUPAC name is *(R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy) phenoxy]* propanoic acid, and its chemical formula is $C_{14}H_{11}ClFNO_4$. This phytosanitary product is commonly recommended for weed control.

Sacrifice and Sample Collection

At the end of the treatment, the rabbits were fasted overnight. The following morning, blood samples were collected via venous puncture into EDTA tubes for hematological analysis. The animals were then sacrificed according to the halal method by exsanguination.

Organ Morphometry

The liver, kidneys, and spleen were carefully dissected from each rabbit for morphometric evaluation. For each organ, the following parameters were assessed: length (cm), weight (g), volume (cm^3), and thickness (cm). Organ weight was measured using an electronic precision balance, while volume was determined through the water displacement method (WDM). Thickness measurements were taken using a digital caliper.

Hematological Parameter Assay

Hematological analyses were performed at the private laboratory REOLAB – Dr. Ben Aissa in Bordj Bou Arréridj. The blood samples were analyzed using a hematology analyzer, providing the following values, Red blood cells (RBC), White blood cells (WBC), Hemoglobin (Hb), Hematocrit (HCT), Platelets (PLT).

Statistical analysis

Statistical differences between groups were assessed using descriptive statistics followed by two-way ANOVA. Post hoc comparisons for hematological and organ morphometric variables (liver, kidney, spleen) were performed using Tukey's HSD or Tamhane's test, as appropriate, with R software. A *p*-value ≤ 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Over the 30-day treatment period, body weight increased progressively in all experimental groups, with clear dose-dependent trends (Figure 1). Rabbits in the control group exhibited consistent and natural weight gain, increasing from an initial average of 1.898 g on Day 1 to 2.82 g by Day 30. In the low-dose group (1 mg/kg), weight gain was also observed, but the final body weights were slightly lower than those of the control animals, indicating a mild effect of Topik80 EC on growth. More pronounced effects emerged in the 4 mg/kg group, where body weight gains were noticeably reduced, particularly toward the experiment's end. The most severe impact was recorded in the high-dose group (20 mg/kg), where reduced weight gain was evident from Day 10 onward, culminating in significantly lower final weights compared to all other groups. These findings suggest a dose-dependent inhibition of growth, likely associated with herbicide-induced disruptions to metabolic processes, gastrointestinal function, or increased catabolic activity aimed at detoxification (Bosy-Westphal et al., 2009). Our results align with those of Heba et al. (2023), who reported significant weight loss in rats treated with clodinafop-propargyl, attributing the effect to dehydration, reduced activity, and appetite loss. El-Abd et al. (2022) and the EFSA (2020), who noted reduced body weight in rodents exposed to the same compound, also documented similar findings. The impact on weight gain is consistent with outcomes from studies on other herbicides, including metribuzin (Derouiche et al., 2018; Morgan, 2001), where reduced food intake contributed to diminished growth, and long-term exposure to xenobiotics induced herbicide-related anorexia (Zaheer et al., 2013).

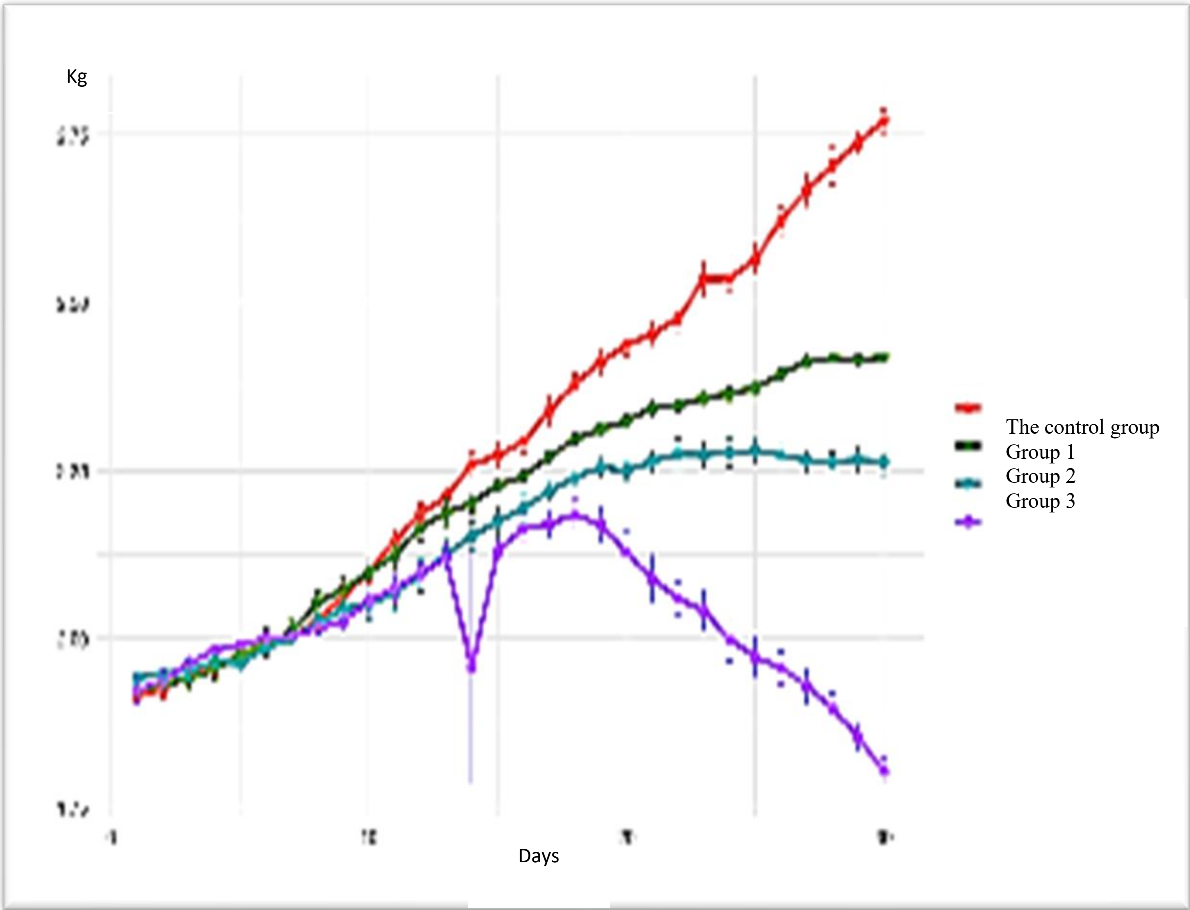

Figure 1: Temporal Evolution of Body Weight in Domestic Rabbits Following Exposure to TOPIK® 80EC. The control group received only physiological water via daily gavage for four weeks. Group 1 received 1 mg/kg/day of TOPIK® 80EC, Group 2 received 4 mg/kg/day, and Group 3 received 20 mg/kg/day of TOPIK® 80EC.

Hematological parameters also revealed marked alterations across treated groups (Figure 2). Tukey's post-hoc analysis showed significant dose-related decreases in red blood cell (RBC) counts, hemoglobin (HGB), hematocrit (HCT), and platelets (PLT). In contrast, white blood cell (WBC) and lymphocyte counts exhibited a biphasic pattern: Groups 1 and 2 had elevated values compared to the control, suggesting early immunostimulation, while Group 3 experienced significant reductions, indicating possible bone marrow suppression or systemic cytotoxicity. These findings are comparable to those of Ati (2024), who noted hematological suppression in glyphosate-treated rabbits. Decreases in erythroid parameters suggest myelotoxicity, similar to observations in metribuzin-exposed animals (Medjdoub et al., 2018; Derouiche, 2019). The transient lymphocytosis observed in the low-dose groups may reflect a compensatory response to oxidative or inflammatory stress (Khan et al., 2013; Jasper et al., 2012). Similar hematological disruptions are well documented with various pesticides, including glyphosate (George & Shukla, 2013), malathion (Riaz & Yousefzay, 2017), and atrazine (Martinez et al., 2010), reinforcing the hematotoxic potential of Topik80 EC.

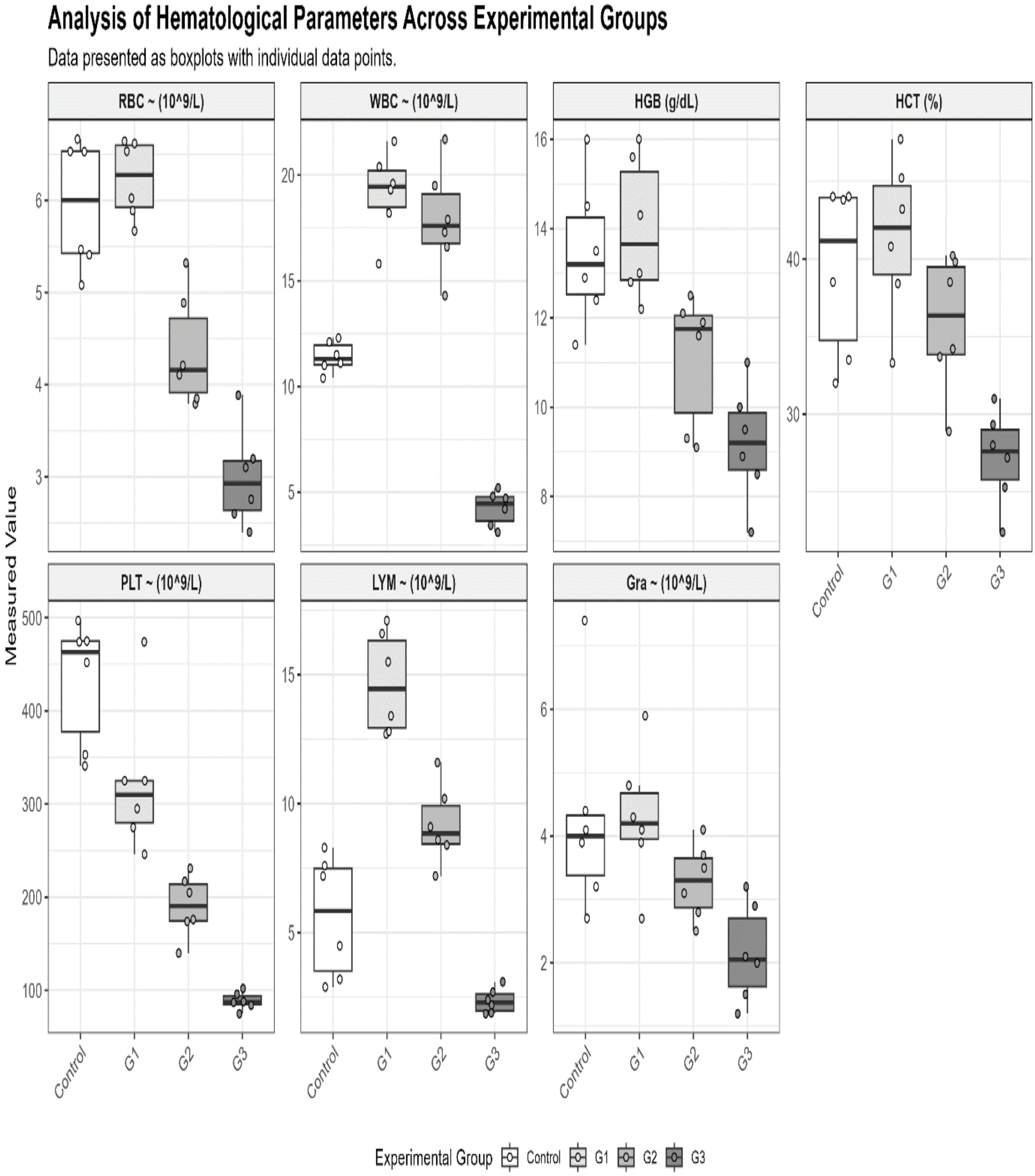

Figure 2: Analysis of hematological parameters across different groups of domestic rabbits following exposure to TOPIK® 80EC. The control group received only physiological water via daily gavage for four weeks. Group 1 received 1 mg/kg/day of TOPIK® 80EC, Group 2 received 4 mg/kg/day, and Group 3 received 20 mg/kg/day of TOPIK® 80EC.

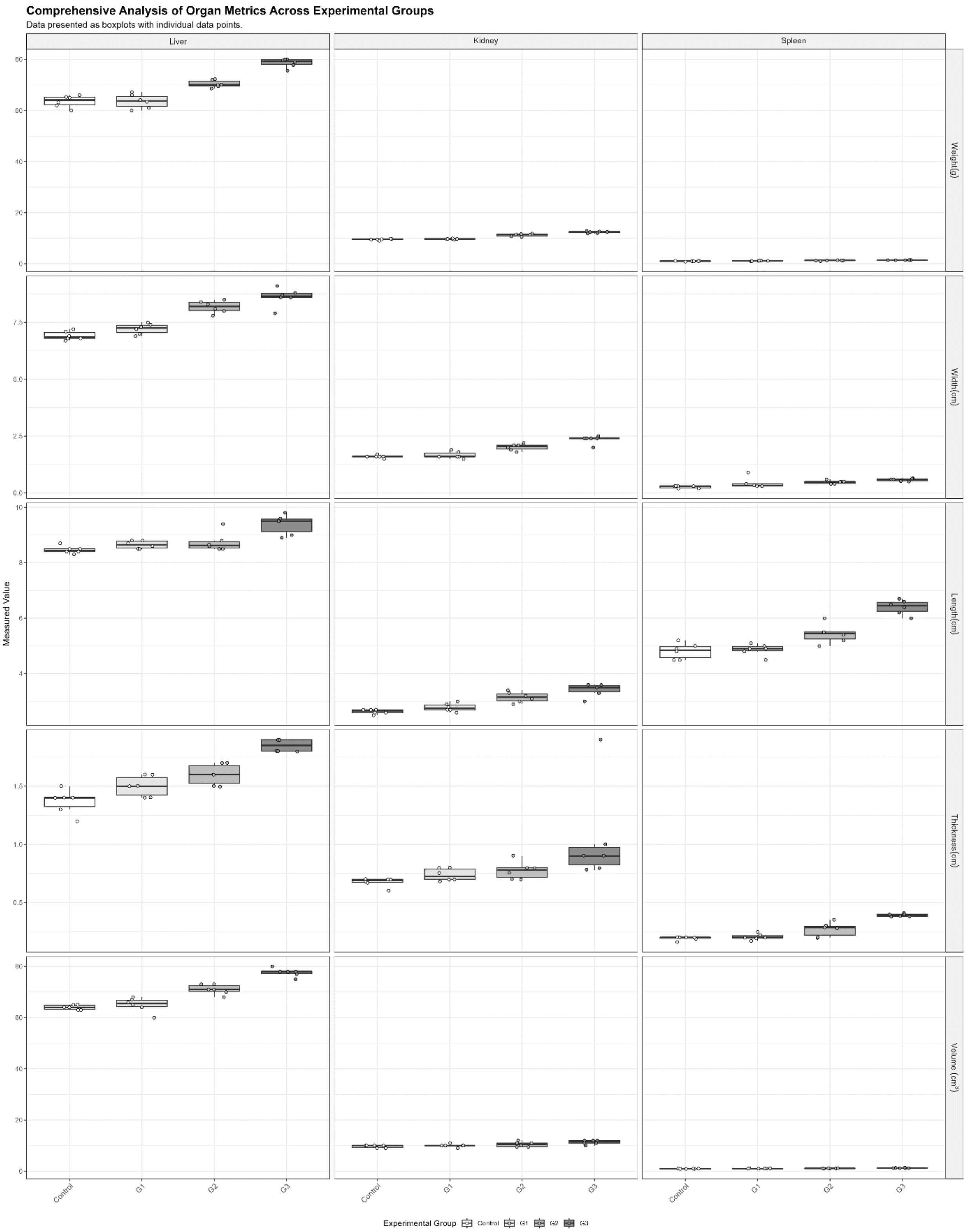

Figure 3: Differences in liver, kidney, and spleen parameters (length, weight, volume, and thickness) across different groups of domestic rabbits following exposure to TOPIK® 80EC. The control group received only physiological water via daily gavage for four weeks. Group 1 received 1 mg/kg/day of TOPIK® 80EC, Group 2 received 4 mg/kg/day, and Group 3 received 20 mg/kg/day of TOPIK® 80EC.

For the organs analysis (Figure 3), Liver morphometric analysis demonstrated significant increases in weight, length, width, thickness, and volume in the treated animals, with more pronounced changes at higher doses. Post-hoc Tamhane analysis confirmed significant enlargement in liver parameters for Groups 2 and 3 compared to the control, with Group 3 exhibiting the most substantial alterations. The observed hepatomegaly may be attributed to toxicant-induced cellular hypertrophy, compensatory hyperplasia, or lipid accumulation—mechanisms typical of hepatic response to toxic insult (Trefts et al., 2017; Manfo et al., 2014). These results are consistent with prior reports by Heba et al. (2023), who identified hepatomegaly and elevated hepatic enzymes following clodinafop-propargyl exposure, indicating hepatocellular damage (Vagvala & O'Connor, 2018). Comparable hepatotoxic effects have been reported for haloxyfop-methyl (Olayinka & Ore, 2015), metribuzin (Derouiche et al., 2018), and atrazine (Jestadi et al., 2014; Khozimy et al., 2022). While hepatocellular hypertrophy and even tumor development have been noted in long-term rodent studies (ECHA, 2017), species-specific metabolic differences complicate extrapolation to human risk. The spleen, a critical immunological organ, also exhibited dose-dependent increases in morphometric parameters. Post-hoc analysis revealed significant elevations in spleen weight, length, width, thickness, and volume, particularly in Groups 2 and 3. These changes likely reflect splenic hypertrophy driven by heightened lymphocyte activity or immune cell proliferation in response to systemic herbicidal stress (Mebius & Kraal, 2005). Ge et al. (2021), who observed increased spleen indices following low-dose atrazine exposure. However, conflicting data exist, as some studies describe immunosuppression and lymphoid organ atrophy in response to herbicides like atrazine (Zhao et al., 2013). The nature of the splenic response may thus depend on dose, duration, and species sensitivity. Finally, The kidneys, as primary organs for the excretion of xenobiotics and their metabolites via urine, are particularly susceptible to damage from toxic compounds such as pesticides (Brzóska et al., 2003). In the present study, animals treated with Topik80EC at doses of 4 mg/kg and 20 mg/kg exhibited a significant increase in kidney weight and morphometric parameters compared to the control group. These findings indicate that higher doses of the product induce notable structural alterations in renal tissue, suggesting a potential nephrotoxic effect of Topik80EC. Such kidney hypertrophy might be a compensatory response to oxidative stress or cellular damage. This hypothesis is supported by the findings of Derouiche (2019), who observed increased relative kidney weights in pregnant rabbits exposed to Metribuzine (3.22 and 6.44 mg/kg). This enlargement was attributed to renal necrosis due to Metribuzine accumulation in renal cells. Similar histopathological signs, including necrosis and inflammation, were also observed. Further evidence from Dedek et al. (2018) demonstrated renal biomarker alterations in rats exposed to Roundup (a glyphosate formulation), corroborating its nephrotoxic potential. Likewise, Oliveira et al. (2007) observed increased creatinine and urea concentrations in rats treated with diminazene aceturate, pointing to a shared mechanism of renal dysfunction triggered by various toxicants. Riaz et al. (2018) further confirmed such disruptions in male rabbits, with glyphosate exposure leading to marked elevations in renal function biomarkers. Moreover, Heba et al. (2023) reported that clodinafop-propargyl significantly increased urea, uric acid, and creatinine levels, suggesting impaired renal filtration, possibly due to accumulation of the compound in renal cells leading to tubular dysfunction. Collectively, these findings strongly suggest that Topik80EC, likely due to its active ingredient clodinafop-propargyl, may exert dose-dependent nephrotoxic effects characterized by oxidative stress, morphometric change, and impaired renal function.

CONCLUSION

This study demonstrates that exposure to the herbicide Topik® 80EC induces significant, dose-dependent toxic effects in rabbits. Treated animals, particularly at higher doses, showed reduced body weight gain, indicating disruptions in growth and general metabolism. Hematological analysis revealed marked decreases in red blood cells, hemoglobin, hematocrit, and platelets, along with a dose-related biphasic alteration in white blood cell counts, suggesting immune system disturbances. Morphometric evaluations of the liver, kidneys, and spleen showed significant increases in organ weight, size, and volume, especially in the higher dose groups, indicating hepatotoxicity, nephrotoxicity, and possible immune activation. These findings reflect the systemic toxicity of Topik® 80EC and underscore the potential health risks associated with its exposure. Further studies, including histopathological assessments and chronic exposure trials, are recommended to clarify its toxicological profile and define safe exposure limits.

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ETHICS DECLARATION
Not applicable.

CONFLICT OF INTEREST
Authors declare no conflict of interest, financial or otherwise.

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