ACTA VETERINARIA INDONESIANA

Vol. 14, No. 2: 184-193, July 2026
DOI : 10.29244/avi.14.2.184-193
P-ISSN 2337-3202, E-ISSN 2337-4373

Review Article

OPEN ACCESS

Anthelmintics as Hidden Toxins in Small Ruminants and Cattle: A Systematic Review

Albiruni Haryo[1]*, Jayusman Arsiyanti Joesoef[2]

[1]Laboratory of Pathology, Faculty of Veterinary Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[2]Department of Clinical Medicine, Reproduction, Pathology, and Nutrition, Veterinary Medicine Study Program, Universitas Nusa Cendana, Kupang, Indonesia

*Corresponding author: albiruni.haryo@ub.ac.id

Article history:
Received: 6 December 2025
Revised : 11 February 2026
Accepted: 5 March 2026

Keywords:
anthelmintic overdose
small ruminants
cattle
veterinary toxicology
parasite control

ABSTRACT

Background: Gastrointestinal nematode infections remain a major constraint on productivity and welfare in sheep, goats, and cattle. Routine anthelmintic administration is central to parasite control; however, reports of intoxication associated with overdose and misuse have raised safety concerns.

Aims: This study aimed to synthesize published evidence on documented anthelmintic intoxication in domestic ruminants.

Methods: A systematic literature search was conducted in Scopus, PubMed/MEDLINE, and Web of Science following PRISMA guidelines. Studies reporting confirmed or strongly suspected intoxication in sheep, goats, or cattle were included. Fifteen studies met the eligibility criteria and were analyzed qualitatively. The search strategy used combinations of keywords related to anthelmintics, toxicity or intoxication, and domestic ruminant species. Titles and abstracts were screened for relevance, followed by full-text evaluation of potentially eligible articles. Data extracted from the included studies covered animal species, type of anthelmintic involved, exposure circumstances, clinical manifestations, and reported pathological findings to enable a descriptive synthesis of intoxication patterns.

Results: Most intoxication events involved overdose or inaccurate weight-based dosing. Macrocyclic lactones and levamisole were primarily linked to neurological dysfunction, including ataxia and tremors. Closantel was consistently associated with optic nerve degeneration and blindness, whereas nitroxinil exposure resulted in acute hepatic and renal injury with high mortality in outbreak settings. High extra-label benzimidazole dosing was reported to cause intestinal crypt necrosis and bone marrow suppression.

Conclusion: The findings indicate that clinically significant toxicity arises mainly under misuse conditions rather than routine labeled administration, emphasizing accurate dosing and veterinary oversight to improve drug safety in ruminant production systems.

INTRODUCTION

Gastrointestinal nematode infections are a major constraint on the health, productivity and welfare of small ruminants and cattle globally (1) Parasitic gastroenteritis is responsible for impaired weight gain and milk yield, reproductive failure and increased mortality in many production systems, especially those located within the tropics and subtropics (VanHoy, 2025). As a result, the routine use of broad-spectrum anthelmintics has become a fundamental principle in parasite management within modern herd and flock health programs. There are several frequently used classes of anthelmintics for the control of ruminant parasites (Oliveira et al., 2022; Virkel et al., 2025).

However, the increasing prevalence of anthelmintic resistance among gastrointestinal nematodes has

altered treatment practices in many livestock systems. Treatment failure and multidrug resistance have encouraged more frequent dosing, shortened retreatment intervals, and occasional off-label drug use or dose escalation (Oliveira et al., 2022). Under such circumstances, anthelmintics should also be considered biologically active xenobiotics whose toxicological effects may emerge when therapeutic safety margins are exceeded.

Studies specifically addressing ruminant intoxication syndromes demonstrate clinically important toxicological outcomes associated with anthelmintic overdose and misuse. Overdoses or other inappropriate drug administration of a number of compounds used for antiparasitic purposes in small ruminants resulted in neurological, renal, locomotor and reproductive effects under different circumstances, according to a systematic review on small ruminant intoxications by antiparasitic drugs (Oliveira et al., 2022).

Outbreaks of intoxications associated with improper practices in dosages have also been reported from field investigations. Overdose of salicylanilides, such as closantel in sheep, has been associated with optic nerve degeneration and irreversible blindness (Pohl et al. 2020; Athar et al. 2022).

However, the literature on anthelmintic toxicity in ruminants is scarce and fragmented. The majority of the literature comes from either case reports, outbreak investigations or localized diagnostic surveys which limits generalisation of toxicology pathways. Furthermore, the majority of veterinary parasitology syntheses focus on drug efficacy and resistance, while safety outcomes have not been as uniformly interrogated. Consequently, the current study sought to collate published evidence on reported instances of anthelmintic toxicity and misuse in sheep, goats and cattle via a systematic review of the literature.

By synthesising knowledge across case reports, outbreak investigations and diagnostic studies, this review aims to describe the drug classes implicated, exposure scenarios encountered, toxicity symptoms observed and pathological consequences reported with toxic events to achieve safer and more rational anthelmintic use in ruminant production systems.

MATERIALS AND METHODS

Study Design

In this study, a systematic review was performed to provide synthesized evidence regarding anthelmintic intoxication and misuse in sheep, goats, and cattle based on the published literature. The review was planned and reported per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) statement (Page et al., 2021) to ensure transparency of literature identification, screening, eligibility assessment and study inclusion. Because the majority of available evidence in this area consists of case reports, outbreak investigations, and retrospective necropsy series, the review was conducted as a qualitative evidence synthesis. Heterogeneity of study designs, exposure definitions and outcome measures precluded formal quantitative meta-analysis.

Review Question

The review addressed the following question:
What toxicological outcomes have been reported in sheep, goats, and cattle following overdose, cumulative exposure, or misuse of anthelmintic drugs?
Primary outcomes of interest included:

- Clinical signs attributable to intoxication
- Mortality associated with drug exposure
- Clinicopathological abnormalities
- Histopathological lesions
- Organ-specific toxic syndromes

Only studies reporting extractable safety or toxicity endpoints were eligible for inclusion.

Information Sources and Search Strategy

A formal literature search was performed in Scopus, PubMed/MEDLINE, and Web of Science. To include contemporary evidence most relevant to existing production systems and drug use patterns, publications from January 2000 to December 2025 were included.

Search strategies combined terms related to ruminant species, anthelmintic compounds, and toxicity outcomes using Boolean operators. A representative search string used in PubMed was:

("anthelmintic" OR ivermectin OR closantel OR nitroxinil OR levamisole OR albendazole OR benzimidazole OR "macrocyclic lactone")
AND
(sheep OR goat OR cattle OR ruminant)
AND
(toxicity OR intoxication OR overdose OR poisoning OR misuse OR "adverse effect")

Booleans operators were utilized to combine terms associated with ruminant species, anthelmintic compounds, and toxicity outcomes. Equivalent search strategies were adapted for Scopus and Web of Science according to database-specific syntax. We also manually screened reference lists of other relevant review

articles to find additional eligible studies. The retrieved records were exported into reference management.

Eligibility Criteria

Eligibility criteria were defined a priori to ensure transparent and consistent study selection. Studies were eligible if they investigated sheep, goats, or cattle and reported confirmed or suspected intoxication associated with anthelmintic exposure, or provided safety data related to overdose, adverse effects, or toxicological outcomes. Only studies describing overdose, dosing miscalculation, cumulative exposure, or extra-label administration with extractable clinical, pathological, or mortality outcomes were included. Studies focusing exclusively on drug efficacy, parasite resistance, pharmacokinetics, or residue analysis without safety outcomes were excluded. Reports involving only non-ruminant species, narrative reviews, opinion articles, and studies lacking sufficient methodological detail were also excluded. When eligibility was uncertain, full-text assessment was performed to determine whether reported findings were plausibly linked to anthelmintic exposure.

Study Selection

Study selection was performed in two stages. First, titles and abstracts were screened to exclude clearly irrelevant records. Second, full-text articles were assessed against the predefined eligibility criteria. Reasons for exclusion at the full-text stage were recorded to ensure transparency and auditability. The numerical flow of records through identification, screening, eligibility assessment, and final inclusion is presented in the PRISMA flow diagram (Figure 1) in the Results section.

Data Extraction

Data extraction was performed using a structured framework developed specifically for this review to allow systematic comparison across heterogeneous study designs. For each included study, descriptive and clinical variables were recorded, including publication year, geographic context when available, ruminant species involved, anthelmintic compound or drug class, type of exposure (e.g., overdose, cumulative dosing, outbreak event, extra-label use), and reported dose and route of administration when specified.

Clinical manifestations were well characterized, including the organ system involved and severity. Pathological findings (gross lesions and histopathology), when reported, and mortality rates or case-fatality data were extracted. If studies reported contextual data and information on management practices, dosing errors, environmental stressors or herd-level factors this was also documented to assist epidemiological interpretation. Information gathered was tabulated to allow for comparison across drug classes and species. Also, the approach enabled determination of patterns related to toxicology and characterization of exposure contexts and durable differentiations between acute fatal intoxications versus non-fatal or sub-clinically defined adverse response.

Evidence Appraisal

Given that the majority of included studies were descriptive case reports or outbreak investigations rather than controlled trials, formal quantitative risk-of-bias tools were not applied. Instead, methodological quality was assessed qualitatively by evaluating clarity of exposure documentation, consistency between clinical and pathological findings, and consideration of alternative diagnoses where reported.

Data synthesis

Due to heterogeneity in study design, exposure definitions, dosing practices, and outcome reporting, pooled quantitative meta-analysis was not performed. Instead, findings were synthesized qualitatively.

Toxicological manifestations were categorized according to:

- Drug class
- Species
- Exposure context
- Organ system involvement
- Severity spectrum (reversible signs to fatal intoxication)

Major toxicity patterns were grouped into neurological, hepatic, renal, ocular, hematological, and reproductive/teratogenic syndromes to identify recurring clinical and pathological themes across studies.

RESULTS AND DISCUSSION

Study Selection

The systematic search across Scopus, PubMed/MEDLINE, and Web of Science identified 330 records. After removal of 40 duplicate entries, 290 records remained for title and abstract screening. During initial screening, 235 records were excluded

because they focused on efficacy or resistance studies without safety outcomes, involved non-ruminant species, or did not describe overdose, misuse, or intoxication contexts relevant to this review.

Subsequently, 55 full-text articles were assessed for eligibility. Of these, 40 articles were excluded due to absence of toxicity endpoints, lack of documented overdose or misuse context, insufficient evidence linking clinical signs to anthelmintic exposure, or exclusive reporting of pharmacokinetics or therapeutic safety at recommended doses. A total of 15 studies met the inclusion criteria and were included in the qualitative synthesis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

Characteristics of Included Studies

The 15 included studies were published between 2015-2025 and consisted primarily of case reports, outbreak investigations, retrospective necropsy series, and safety analyses. Most reports involved small ruminants (sheep and goats), whereas direct cattle-specific intoxication reports were comparatively limited. Reported drugs included macrocyclic lactones, salicylanilides, nitro compounds, imidazothiazoles, and benzimidazoles. Most exposure events involved overdose, dosing errors, extra-label administration, or cumulative drug use. Key characteristics of the included studies, including species, drug class, exposure type, clinical findings, and pathological lesions, are summarized in Table 1.

Exposure Context and Patterns of Misuse

Most intoxication events were linked to preventable management errors rather than intrinsic drug toxicity. Causes included inaccurate weight assessments, flock-level dosing with no individual weights taken, increasing the dose empirically after perceived treatment failure and treating weak or stressed animals. In multiple outbreak investigations, administered doses were approximately double or more than the recommended levels owing to miscalculations in dosing.

Clinical and Pathological Manifestations

Toxicological manifestations clustered into organ-system syndromes that were largely consistent across geographic contexts.

Neurological Toxicity

Neurological signs were the most frequently reported clinical presentation. Macrocyclic lactones were associated with ataxia, tremors, hypersalivation, depression, and recumbency, occasionally progressing to coma or death. CNS lesions were often minimal, suggesting functional neurotoxicity related to excessive penetration across the blood–brain barrier. Closantel intoxication in sheep has been consistently linked to optic nerve degeneration and retinal damage, resulting in irreversible blindness. An overdose of levamisole induces cholinergic-type symptoms, including tremors, convulsions, hypersalivation, and rapid collapse.

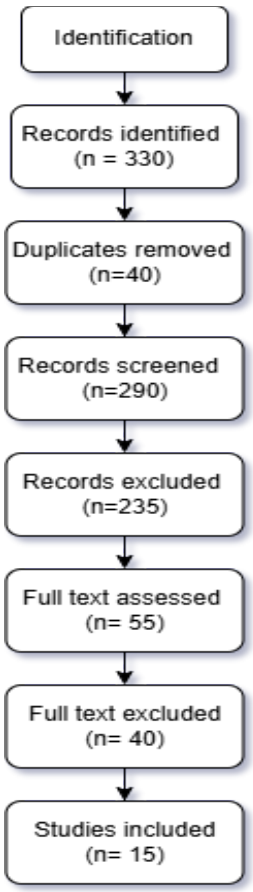

Figure 1. PRISMA flow diagram of the study selection process.

Table 1. Characteristics of included studies on anthelmintic overdose and misuse in domestic ruminants

Author (Year)	Species	Drug/Class	Evidence Type	Exposure	Main Clinical Findings	Pathology
Silva et al. (2024)	Sheep/Goat	Ivermectin, Nitroxinil, Disophenol	Necropsy series	Overdose/ outbreak	Ataxia, tremors, dyspnea, hyperthermia	Hepatic & renal necrosis; CNS vascular congestion
Júnior et al. (2021)	Goat	Nitroxinil	Outbreak + experimental	~2× recommended dose	Weakness, staggering, rapid death	Centrilobular hepatic necrosis; tubular nephrosis
Harm et al. (2022)	Goat	Albendazole	Case report	35.7 mg/kg × 3 days	Severe diarrhea	Intestinal crypt necrosis; bone marrow hypoplasia
Nürnberger et al. (2021)	Goat	Doramectin	Adverse drug reaction	Extra-label administration	Ataxia, tremor, mydriasis	Functional neurotoxicity (no structural lesions)
Pohl et al. (2020)	Sheep	Closantel	Field intoxication	Accidental overdose	Blindness	Optic neuropathy
Rivero et al. (2015)	Sheep	Closantel	Outbreak	Drench overdose	Blindness, neurologic signs	Optic nerve degeneration
Cantón et al. (2022)	Sheep	Doramectin	Iatrogenic toxicity	Overdose	Neurological depression	Neurofunctional toxicity
Oliveira et al. (2022)	Sheep/Goat	Multiple anthelmintics	Systematic review	Overdose/ misuse	Neurological, renal, locomotor signs; teratogenic effects	Multi-organ involvement
CABI Compendium (2022)	Sheep/Goat	Levamisole	Toxicity database	Overdose	Salivation, tremors, collapse	Cholinergic toxidrome
Susar & Karahan (2025)	Sheep	Levamisole	Pharmacokinetic safety study	7.5 mg/kg	No clinical toxicity	No significant pathological findings
Susar et al. (2025)	Sheep	Levamisole	Safety study	7.5 mg/kg	Hematologic changes without clinical illness	No significant pathology
Glamazdin (2024)	Sheep	Albendazole	Safety margin study	3×–5× dose	No overt illness	Mild biochemical alterations
Kutahya et al. (2022)	Sheep	Oxfendazole	PK interaction study	7.5 mg/kg	No toxicity reported	No pathological changes reported
Virkel et al. (2025)	Sheep	Benzimidazoles	Metabolism study	Experimental	Mechanistic relevance	Hepatic CYP3A-mediated metabolism
Eriksson & Nylén (2024)	Experimental model (neurotox context)	Ivermectin	Mechanistic neurotoxicity study	High dose model	Tremor, ataxia	Functional CNS toxicity

Hematological and Gastrointestinal Effects

The administration of high extra-label doses of albendazole in goats was associated with severe necrosis of intestinal crypts and bone marrow hypoplasia, indicating a dose-dependent myelotoxic potential. While benzimidazoles are generally considered safe at recommended dosages, significant overdoses may lead to clinically relevant hematological suppression and gastrointestinal damage.

Epidemiological Context and Severity Spectrum

Necropsy-based surveillance suggested that anthelmintic intoxication represented a small proportion of diagnostic submissions, although individual outbreaks were associated with substantial within-flock mortality. The severity of intoxication ranged from reversible neurological depression to irreversible blindness, multi-organ failure, and death. Although global prevalence cannot be estimated from the available data, the evidence indicates that intoxication events occur across multiple production systems and are frequently associated with preventable management practices.

Interpretation of the Evidence

This systematic review synthesizes available evidence on anthelmintic intoxication in sheep, goats, and cattle and identifies recurring toxicological patterns associated with several commonly used drug classes. Although intoxication events appear relatively uncommon at the population level, the reviewed studies demonstrate that severe morbidity and mortality can occur when dosing accuracy or management practices are compromised. Accurate pathological investigation plays an essential role in confirming toxicological diagnoses in veterinary cases. The significance of macroscopic or microscopic lesions has previously been emphasized in distinguishing toxic, infectious and parasitic conditions in animals (Haryo 2019; Haryo et al., 2021).

The literature captured is dominated by case reports, outbreak investigations, and necropsy-based studies which reflects the episodic nature of anthelmintic intoxication. Previous analyses have likewise found that the majority of documented cases stem from overdose or misuse rather than adverse reactions under recommended therapeutic circumstances (Oliveira et al., 2022). Surveillance based on necropsy has indicated that anthelmintic poisoning accounts for only a small portion of diagnostic submissions, but individual outbreaks can cause significant within-flock mortality (Silva et al., 2024). Because toxicological risk itself is highly context-specific and management-dependent, these findings highlight the need of considering both at once.

A Conceptual Framework for Anthelmintic Hidden Toxicity

The findings of this review support the development of a conceptual framework that reframes anthelmintics not merely as therapeutic agents but as conditionally toxic xenobiotics whose safety is contingent on adherence to dosing principles. As synthesized across the included studies, the pathway to clinically significant toxicity follows a consistent trajectory: management errors lead to supratherapeutic drug exposure, which exceeds organ-specific safety thresholds, ultimately resulting in organ-targeted toxic syndromes. The conceptual framework for anthelmintic can be seen in Figure 2.

Within this framework, the term "hidden toxin" is not a claim that routine anthelmintic use is inherently dangerous. Rather, it encapsulates the concept that the toxicological potential of these drugs is latent under standard conditions yet becomes manifest when dosing safeguards fail. This reframing has practical implications: it positions anthelmintic safety as a management problem amenable to intervention, rather than an intrinsic pharmacological hazard. Recognition of this conditional toxicity should prompt a shift in how anthelmintic use is communicated to livestock producers — moving beyond efficacy-centered messaging toward a balanced, risk-aware framework that incorporates weight-based dosing, retreatment intervals, and veterinary oversight as non-negotiable safety elements.

Neurological Toxicity: Mechanistic Perspective

Neurological dysfunction was reported as the most commonly observed clinical manifestation among multiple drug classes. Ataxia, tremors, hypersalivation, depression, and recumbency were frequently associated with macrocyclic lactones and sometimes progressed to coma or death. These clinical signs are consistent with over-penetration of macrocyclic lactones at the blood–brain barrier. In many reports only minor structural lesions were identified in the CNS indicating primarily functional neurotoxic effects.

In contrast to macrocyclic lactone toxicity, where ocular signs are absent, closantel intoxication is characterised by optic nerve degeneration and retinal damage leading to irreversible blindness, as consistently observed in field studies and experimental settings (Pohl et al., 2020). This has been consistently

observed in field studies and experimental settings (Eröksüz et al., 2023; Pohl et al., 2020). Levamisole overdose also caused Neurological manifestations (tremors, convulsions and hypersalivation) characteristic of cholinergic overstimulation.

Mechanistic Basis of Organ-Specific Toxicity

A deeper understanding of the mechanisms underlying each toxidrome strengthens the clinical and diagnostic value of this review. For macrocyclic lactones, neurotoxicity arises primarily from potentiation of gamma-aminobutyric acid (GABA)-mediated chloride conductance in the central nervous system. Under normal conditions, the blood–brain barrier (BBB) restricts drug penetration via P-glycoprotein efflux transporters encoded by the *MDR1* (ABCB1) gene. Overdose conditions, or genetic/breed-associated P-glycoprotein deficiency, overwhelm this barrier, resulting in excessive GABA-ergic inhibition manifest as ataxia, tremors, and progressive CNS depression (Nürnberger et al., 2021; Eriksson & Nylén, 2024).

For levamisole, toxicity reflects cholinergic overstimulation. As a nicotinic acetylcholine receptor agonist, levamisole at supratherapeutic concentrations produces sustained receptor activation, resulting in the characteristic syndrome of salivation, tremors, convulsions, and cardiovascular collapse. The cholinergic toxidrome observed clinically mirrors the pharmacological mechanism closely, making dose history an important diagnostic clue.

Closantel-induced ocular toxicity operates through a distinct mechanism: as a proton ionophore, closantel disrupts mitochondrial oxidative phosphorylation in cells with high metabolic demands. The retinal ganglion cells and optic nerve, which have particularly high energy requirements, are preferentially affected, leading to axonal degeneration and irreversible blindness. This mechanism explains the characteristic dissociation between systemic signs and ocular pathology observed in field cases (Pohl et al., 2020; Rivero et al., 2015).

Nitroxinil, as an uncoupler of mitochondrial oxidative phosphorylation, similarly disrupts cellular

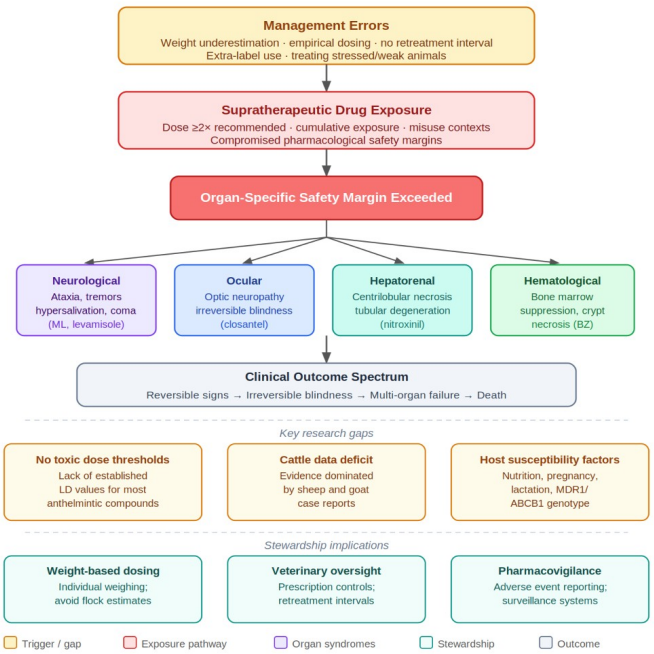

Figure 2. Conceptual framework illustrates the conditional toxicological pathway of anthelmintic agents in domestic ruminants. Clinically significant toxicity does not arise from routine therapeutic use but emerges predictably when management errors lead to supratherapeutic exposure exceeding organ-specific safety margins. The framework identifies four principal toxic syndromes and highlights unresolved research gaps alongside evidence-based stewardship measures. ML: macrocyclic lactones, BZ: benzimidazoles, MDR1/ABCB1: multidrug resistance gene encoding P-glycoprotein.

energy metabolism, but with predominant affinity for hepatic and renal parenchymal cells. The resulting centrilobular hepatic necrosis and renal tubular injury reflect the drug's metabolic activation and accumulation in these organs (Júnior et al., 2021). For benzimidazoles, myelotoxicity and intestinal crypt necrosis at high doses likely reflect interference with tubulin polymerization in rapidly dividing cell populations, consistent with the drug class's mechanism of action against nematode tubulin (Harm et al., 2022; Virkel et al., 2025).

Hepatic and Renal Injury in Nitroxinil Exposure

Evidence from both experimental and field investigations indicates that nitroxinil intoxication may produce severe hepatic and renal injury. Cases reported in goats were characterized by acute centrilobular hepatic necrosis and renal tubular degeneration, frequently accompanied by high mortality rates during outbreak events (Júnior et al., 2021; Silva et al., 2024). These findings suggest that certain anthelmintic compounds may have relatively narrow safety margins when dosing limits are exceeded.

Although benzimidazoles are typically regarded as having wide therapeutic safety margins, rare toxic reactions have been described after high extra-label dosing. High exposure to albendazole in goats causing severe enteropathy and bone marrow hypoplasia shows that even good safety profile drugs can be toxic at beyond prescribed doses (Harm et al., 2022).

Management-Related Risk Factors

Management factors were consistently identified in intoxication events across the literature reviewed. Weight underestimation, flock-level treatment without body-weight assessment, retreatment intervals shorter than currently recommended intervals and step-wise empirical dosing after perceived treatment failure were the most common attributable factors identified (Oliveira et al., 2022; Silva et al., 2024).

Implications for Anthelmintic Stewardship

The results of this review suggest that the concept of anthelmintics as "hidden toxins" should be interpreted cautiously. Available evidence does not support the view that routine therapeutic use inevitably leads to toxicity. Rather, toxicological outcomes appear to arise primarily when recommended dosing principles are not followed. From a practical standpoint, enhanced management of anthelmintic application may mitigate both the development of resistance and the risk of toxicity. Implementing accurate weight-based dosing, pharmacokinetically informed treatment strategies, targeted selective treatment approaches, and improved pharmacovigilance systems could augment the safety of parasite control programs within ruminant production systems.

Gap Analysis and Research Priorities

Despite the patterns identified in this review, several critical knowledge gaps limit the development of evidence-based safety guidelines. First, consistent toxic dose thresholds have not been established for most anthelmintic compounds in ruminant species. The majority of included studies reported approximate or estimated doses, and controlled dose-escalation studies with systematic clinicopathological endpoints remain scarce. For compounds such as closantel and nitroxinil, the margin between the recommended therapeutic dose and the dose associated with severe toxicity appears narrow, yet precise threshold values derived from ruminant-specific experimental studies are lacking in the current literature.

Second, the evidence base for cattle-specific intoxication is substantially underdeveloped relative to small ruminants. Most included studies involved sheep or goats, and direct cattle-specific intoxication reports were comparatively limited. Given the scale of anthelmintic use in cattle production systems globally, this represents an important evidence gap that warrants dedicated surveillance and reporting.

Third, the mechanisms by which subclinical or repeated subtherapeutic overdosing may accumulate to produce organ damage over time remain poorly defined. Chronic low-level exposure scenarios, which may be particularly relevant in intensive production systems with frequent treatment intervals, have not been systematically studied.

Fourth, the interplay between animal-level risk factors — including nutritional status, concurrent disease, physiological state (pregnancy, lactation), and genetic variation in drug metabolism or BBB transport — and susceptibility to intoxication is incompletely characterized. These factors are likely to modulate individual vulnerability substantially but are rarely reported in field case series.

Addressing these gaps would require prospective surveillance programs, standardized reporting frameworks for anthelmintic adverse events in veterinary practice, and collaborative multi-site studies capable of generating sufficient case numbers for quantitative analysis.

Geographic and Regulatory Context

The studies included in this analysis originate from a variety of regulatory environments, encompassing regions with differing levels of veterinary oversight and pharmacovigilance infrastructure. In settings where over-the-counter access is prevalent and weight-based dosing equipment is scarce, the risk of dosage miscalculation may be heightened. Conversely, systems characterized by structured veterinary supervision may experience a reduced incidence of severe intoxication events, even in settings where anthelmintic resistance is prevalent.

Limitations

Several limitations should be acknowledged. Most included studies consisted of descriptive case reports or outbreak investigations, and standardized exposure data were often unavailable. Publication bias toward severe intoxication cases is also possible, and subclinical adverse effects may therefore be underreported. In addition, uneven geographic representation limits the ability to estimate global prevalence of anthelmintic intoxication.

A further consideration is diagnostic validity. Many included studies relied on clinical presentation and circumstantial dose history rather than confirmed analytical toxicology, and the threshold for attributing clinical signs to anthelmintic exposure varied across reports. In field settings, differentiation of anthelmintic intoxication from concurrent infectious disease, nutritional deficiency, or other toxic exposures may be challenging without systematic exclusion of alternative diagnoses. This diagnostic uncertainty is an inherent limitation of case-based evidence and may contribute to misclassification in either direction — both underreporting of genuine intoxication and occasional misattribution of multifactorial presentations.

Publication bias is also likely to disproportionately favour severe or fatal intoxication cases. Mild-to-moderate adverse reactions that are resolved without veterinary intervention, subclinical biochemical alterations, or non-fatal within-flock events are substantially less likely to reach formal publication. The true incidence and full severity spectrum of anthelmintic-associated adverse effects in ruminant populations therefore remain underestimated. Future pharmacovigilance systems that capture a broader range of adverse event severities would provide a more representative picture of the actual risk profile of these compounds under field conditions.

CONCLUSION

This systematic review demonstrates that anthelmintic intoxication in sheep, goats, and cattle is an uncommon but clinically significant event that occurs primarily under conditions of overdose, dosing miscalculation, cumulative exposure, or extra-label misuse. The reviewed evidence indicates that toxicity is not an inherent consequence of recommended therapeutic use but is largely associated with preventable management errors. When intoxication occurred, it produced distinct toxicological patterns across multiple organ systems, typically producing neurological, hepatic, renal and ocular systems. These events ranged from reversible neurological signs to severe outcomes including blindness and death. In summary, the results demonstrate the emergence of anthelmintic resistance in ruminant production systems and the need for prudent usage. Developing weight-based dosing with proper veterinary supervision, and monitoring adverse drug events on an individual animal basis in practice is crucial to help prevent unnecessary intoxications while ensuring the effectiveness of parasite control.

ACKNOWLEDGMENTS

The author would like to thank colleagues at Department of Anatomical Pathology, Faculty of Veterinary Medicine, Brawijaya University for their support during the preparation of this manuscript. The author also thank the anonymous reviewers for their valuable comments and suggestions, which helped improve the quality of this article.

AUTHORS CONTRIBUTION

A.H. conceived the study, conducted the literature search, performed data extraction and analysis, and prepared the initial manuscript draft. J.A.J. contributed to the study design, supervised the review process, assisted in data interpretation, and provided critical revisions to the manuscript. Both authors reviewed and approved the final version of the manuscript.

REFERENCES

Athar, H., Parrah, J. D., Hussain, S. A., & Dar, M. U. (2022). Ultrasonographic evaluation of blindness in sheep due to inadvertent closantel overdose.

Asian Journal of Animal and Veterinary Advances, 17(4), 132–136. https://doi.org/10.3923/ajava.2022.132.136.

CABI. (2022). Levamisole toxicity in goats and sheep. CABI Compendium. https://doi.org/10.1079/cabicompendium.77349.

Eriksson, M., & Nylén, S. (2024). Case report: C57BL/6NTac and C57BL/6NCrl mice displaying neurological signs after deworming with ivermectin. *Laboratory Animals*. https://doi.org/10.1177/00236772241286214.

Glamazdin, I. (2024). Effect of albendazole supramolecular complex on sheep organism. *Russian Journal of Parasitology*. https://doi.org/10.31016/1998-8435-2024-18-4-427-432.

Harm, T., Radke, S., Burns, L., & Schrunk, D. (2022). Enteropathy and bone marrow hypoplasia associated with presumptive albendazole toxicosis in a juvenile Boer goat. *Journal of Veterinary Diagnostic Investigation*, 34, 1015–1019. https://doi.org/10.1177/10406387221121122.

Haryo, A. (2019). Case report: Canine toxication food allergic. *Jurnal Medik Veteriner*, 2(2), 158–161. https://doi.org/10.20473/jmv.vol2.iss2.2019.158-161.

Haryo, A., Br Ginting, I. A., & Oktavianie, D. A. (2021). Macroscopic and microscopic identification in native chicken (Gallus domesticus) organ with helminthiasis. *Jurnal Medik Veteriner*, 4(1), 160–164. https://doi.org/10.20473/jmv.vol4.iss1.2021.160-164.

Júnior, J., Soares, K., Soares, Y., Oliveira, F., Alves, R., Neto, E., Dantas, A., & Galiza, G. (2021). Spontaneous and experimental poisoning by nitroxinil at 34% in goats. *Pesquisa Veterinária Brasileira*. https://doi.org/10.1590/1678-5150-pvb-6935.

Kutahya, O., Kandir, S., Faki, E., et al. (2022). Pharmacokinetics of oxfendazole and oxyclozanide in sheep. *Journal of Veterinary Pharmacology and Therapeutics*. https://doi.org/10.1111/jvp.13096.

Nürnberger, D., Müller, S. F., Hamann, M., et al. (2021). First sequencing of caprine Mdr1 mRNA due to suspected neurological adverse drug reaction following doramectin. *Frontiers in Veterinary Science*. https://doi.org/10.3389/fvets.2021.682393.

Oliveira, C., Costa, D., Limeira, C., Nogueira, D., Nascimento, B., & Vaz, A. (2022). Anthelmintic intoxication in goats and sheep: A systematic review. *Research in Veterinary Science*, 152, 657–662. https://doi.org/10.1016/j.rvsc.2022.09.038.

Pohl, C. H., et al. (2020). Closantel intoxication in sheep. *Acta Scientiae Veterinariae*. https://doi.org/10.22456/1679-9216.101078.

Rivero, R., et al. (2015). Closantel intoxication in sheep. *Pesquisa Veterinária Brasileira*. https://doi.org/10.1590/s0100-736x2015000100004.

Silva, C., Oliveira, G., Soares, L., Soares, Y., Soares, K., Olinda, R., Silva, T., Dantas, A., & Galiza, G. (2024). Anthelmintic intoxication in small ruminants diagnosed in Northeastern Brazil. *Pesquisa Veterinária Brasileira*, 44, e07416. https://doi.org/10.1590/1678-5150-pvb-7416.

Susar, H., & Karahan, I. (2025). Pharmacokinetics of liposomal levamisole after oral, intramuscular, and subcutaneous administration in sheep. *Turkish Journal of Veterinary & Animal Sciences*. https://doi.org/10.55730/1300-0128.4364.

Susar, H., Özüiçli, M., Çelebi, M., Çelebi, Ç., & Karahan, I. (2025). Effects of orally administered free and liposomal levamisole on hematological and biochemical parameters in sheep. *Revista Científica de la Facultad de Ciencias Veterinarias*. https://doi.org/10.52973/rcfcv-e35589.

VanHoy, G. (2025). Overview of gastrointestinal parasites of ruminants. MSD Veterinary Manual. https://www.msdvetmanual.com

Virkel, G., Maté, L., Ichinose, P., et al. (2025). Further insights into the hepatic metabolism of benzimidazole anthelmintics in sheep. *Research in Veterinary Science*. https://doi.org/10.1016/j.rvsc.2025.105589.