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In Silico Ecotoxicological Risk Assessment of Fosetyl-Aluminium Using the ECOSAR Model

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ABSTRACT

The increasing reliance on pesticides to safeguard crop productivity has raised global concerns about their ecological safety, particularly in aquatic systems. Fosetyl-aluminium (fosetyl-Al), a systemic fungicide widely used in horticulture and field crops, acts both by suppressing fungal growth and by stimulating plant defense responses. Despite its extensive application, comprehensive information on its ecotoxicological behavior remains scarce. In this study, the Ecological Structure–Activity Relationship (ECOSAR) model was applied to predict the acute and chronic toxicity of fosetyl-Al towards representative aquatic and terrestrial organisms. The predictions consistently yielded very high LC50/EC50 values, well above the compound's solubility threshold, leading to "no effects at saturation" (NES) outcomes across taxa. These findings indicate that fosetyl-Al poses minimal acute risk under realistic exposure scenarios. Comparison with available experimental data further corroborated the computational predictions, reinforcing confidence in the reliability of QSAR-based screening methods. Overall, the results support the classification of fosetyl-Al as an environmentally low-risk fungicide and highlight the role of in silico approaches as cost-effective, ethical, and scientifically robust tools in preliminary ecological risk assessment.

1. INTRODUCTION

The sustained growth of the global population, projected to reach 9.7 billion by 2050, exerts unprecedented pressure on agricultural systems to ensure food security [1]. To mitigate crop losses caused by pests, pathogens, and weeds, the use of pesticides has become a cornerstone of intensive agriculture. Globally, pesticide usage exceeds 4 million tonnes annually, with a marked increase in application rates observed in developing economies [2]. While indispensable for maintaining high yields, the pervasive application of these agrochemicals raises significant concerns regarding environmental contamination, the development of resistant pathogen strains, and potential adverse effects on non-target organisms, including humans [3]. Among pesticides, fungicides play a critical role in controlling fungal diseases that can

devastate entire harvests. Fungicides can be classified based on their mode of action, including inhibitors of respiration, sterol biosynthesis, and cell division [4]. A particularly important class comprises the phosphonate fungicides, which exhibit systemic activity and are effective against oomycete pathogens, such as those from the genus Phytophthora, known for causing late blight in potatoes and tomatoes [5]. One of the most prominent phosphonate fungicides is fosetyl-Aluminium (fosetyl-Al), first registered in the 1970s and widely marketed under trademarks such as Aliette®. Fosetyl-Al [aluminium tris(O-ethyl phosphonate)] is valued for its unique dual mode of action: it directly inhibits the mycelial growth and sporulation of target pathogens, while also activating systemic acquired resistance (SAR) in the host plant [5]. This induction of plant defense mechanisms, involving the upregulation of pathogenesis-related (PR) proteins and the accumulation of phytoalexins, provides broad-spectrum protection [7]. . Consequently, fosetyl-Al is extensively used in viticulture, horticulture, and the production of citrus fruits and tomatoes to control devastating diseases like downy mildew [6]. Despite its agricultural benefits, the environmental fate and toxicological profile of fosetyl-Al and its primary metabolite, phosphonic acid, warrant careful scrutiny. Genotoxicity studies have yielded mixed results. While some investigations, such as those conducted by Cabras et al. (1999), reported no mutagenic effects in the Ames test, other studies have indicated potential concerns. Research by Yao ve Zhong (2005), demonstrated that fosetyl-Al induced DNA damage in human hepatoma cells (HepG2) using the comet assay, suggesting a need for a more nuanced risk assessment. The U.S. Environmental Protection Agency (EPA) has classified fosetyl-Al as a Group C (Possible Human) Carcinogen based on an increased incidence of urinary bladder tumors in male rats following long term exposure ([10]). A significant gap in the literature pertains to the ecotoxicological effects of fosetyl-Al. While standard regulatory tests exist for certain organisms, comprehensive data on its chronic toxicity to a wide range of non-target species, particularly soil invertebrates, aquatic invertebrates, and pollinators, are scarce. Traditional in vivo ecotoxicological testing, while reliable, is fraught with challenges. These include high financial costs, extended timeframes, ethical controversies surrounding animal testing, and the logistical difficulty of testing the vast number of existing and new chemicals [11]. This data gap hinders a holistic environmental risk assessment. The limitations of traditional ecotoxicological methods have catalyzed the adoption of in silico approaches as scientifically valid alternatives. Quantitative StructureActivity Relationship (QSAR) modeling is a cornerstone of computational toxicology, using mathematical models to predict the biological activity or toxicity of a compound based on its molecular structure and physicochemical properties [12]. The foundational principle is that similar molecular structures tend to exhibit similar biological activities [12]. Regulatory bodies such as the European Chemicals Agency (ECHA) and the Organisation for Economic Co-operation and Development (OECD) endorse the use of validated QSAR models for screening and priority-setting within a weight-of-evidence framework, provided they adhere to specific principles for scientific validity [13,14]. These models offer a rapid, cost effective, and ethical means to predict ecotoxicological endpoints, supporting the principles of Green Toxicology by reducing reliance on animal testing [12,14] For aquatic ecosystems, which are particularly vulnerable to pesticide exposure, models like the Ecological Structure-Activity Relationship (ECOSAR) program are highly valuable. ECOSAR is a widely recognized tool that predicts the acute and chronic toxicity of chemicals to aquatic organisms, such as fish, Daphnia, and green algae [12]. The model operates on the principle of classifying chemicals by their mode of action and estimating toxicity using pre-defined QSARs based on the chemical's hydrophobicity (log P) ([12]. Such tools are indispensable for the preliminary risk assessment of chemicals like fosetyl-Al, a widely used fungicide for which comprehensive

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empirical ecotoxicity data for a broad range of aquatic species may be lacking. Therefore, the primary objective of this study is to conduct a comprehensive in silico ecotoxicological risk assessment of the fungicide fosetyl-Al with a focus on aquatic ecosystems. We will employ the ECOSAR model, a validated QSAR tool designed for predicting toxicity to aquatic organisms [12]. By leveraging this computational method, this research aims to provide reliable predictions of fosetyl-Al's toxicity to key aquatic species, thereby contributing to a more robust environmental risk profile and helping to bridge existing data gaps for this compound.

2. MATERIALS and METHODS

2.1. The Chemical Structure of Fosetyl-Aluminium

The SMILES (Simplified Molecular Input Line Entry System) code for fosetyl-Al was obtained from PubChem.Smıles code : CCOP(=O)=O.CCOP(=O)=O.CCOP(=O)=O.[Al+3]

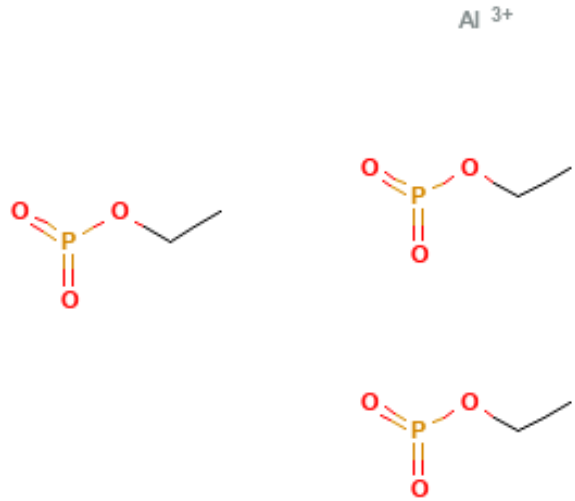

Figure 1. Chemical structure of fosetyl-Al

2.2. ECOSAR (Ecological Structure-Activity Relationships) Model

This study utilized the ECOSAR (Ecological Structure-Activity Relationships) model to predict the acute aquatic ecotoxicological potential of the fungicide fosetyl-Al. ECOSAR is a quantitative structure-activity relationship (QSAR) tool developed and maintained by the United States Environmental Protection Agency (US EPA) to predict the toxicity of chemicals to aquatic organisms [15]. The model operates on the principle that the toxicity of a chemical can be correlated with its physical-chemical properties and molecular structure, particularly its hydrophobicity (log P) [15] . The reliability and regulatory acceptance of ECOSAR are based on its adherence to the validation principles for QSAR models set forth by the Organisation for Economic Co-operation and Development (OECD) [15]. The following table demonstrates the model's compliance with these key principles.

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Tablo 1. ECOSAR Model Compliance with OECD QSAR Validation Principles

OECD Principle	Description of Compliance for ECOSAR
A Defined Endpoint	The model predicts clearly defined endpoints for aquatic organisms, such as acute (e.g., 96-h LC50 for fish) and chronic toxicity values (Anandhi & Iyapparaja, 2024).
An Unambiguous Algorithm	Predictions are made using transparent and documented QSAR equations based on statistical relationships between chemical structures and known toxicity data (Anandhi & Iyapparaja, 2024).
A Defined Domain of Applicability	The model specifies the chemical classes (e.g., esters, amines) for which each QSAR equation is valid, defining the chemical space for reliable predictions (Anandhi & Iyapparaja, 2024).
Appropriate Measures of Goodness-of-Fit, Robustness, and Predictivity	The model has been developed and tested with statistical goodness-of-fit measures for its equations (Anandhi & Iyapparaja, 2024).
A Mechanistic Interpretation, if Possible	The model provides a mechanistic basis by classifying chemicals based on their predicted mode of toxic action (e.g., narcosis, electrophilicity) (Anandhi & Iyapparaja, 2024).

For this study, the following analytical procedure was followed to predict the aquatic toxicity of fosetyl-Al (CAS No. 39148-24-8):

a) Chemical Structure Preparation The molecular structure and SMILES (Simplified Molecular-Input Line-Entry System) notation of fosetyl-Al were obtained from reliable databases such as the EPA's CompTox Chemicals Dashboard. The chemical was prepared in a "QSAR-ready" format compatible with the ECOSAR program.

b) Prediction Process The prepared chemical structure was loaded into the ECOSAR program (v2.0). The model classified the chemical based on its physicochemical properties (primarily the octanol-water partition coefficient, log P) and structural features. It then applied the relevant QSAR equation to generate predicted LC50/EC50 (median lethal/effect concentration) values in mg/L for the following standard aquatic taxa:
   - Fathead Minnow (Pimephales promelas, Acute, 96-h)
   - Water Flea (Daphnia magna, Acute, 48-h)
   - Green Algae (Acute, 96-h or 120-h)

c) Interpretation of Results and Model Reliability ECOSAR provides a statistical confidence interval for each prediction. Furthermore, an assessment was conducted to determine whether the structure of fosetyl-Al falls within the model's Domain of Applicability, which is crucial for evaluating the reliability of the predictions [15].

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3. RESULTS

The quantitative output from the ECOSAR (Ecological Structure-Activity Relationships) model for fosetyl-aluminium (CAS No: 39148-24-8) is summarized in Table 1. The model was run for multiple chemical classes (Esters, Esters-Phosphates, Neutral Organics), yielding consistent predictions across all scenarios.

Table 2. Test results obtained from the ECOSAR program

Organism	Exposure Duration	Endpoint	Predicted Value (mg/L)
Fish (Freshwater)	96-hour	LC50	1.61×10^5
Daphnid	48-hour	LC50	5.81×10^5
Green Algae	96-hour	LC50	8.87×10^5
Fish (Saltwater)	96-hour	LC50	3.92×10^5
Mysid Shrimp	96-hour	LC50	7.34×10^5
Earthworm	LC50	3.75×10^5	Earthworm

For all acute toxicity endpoints (LC50/EC50) listed in Table 1, the ECOSAR model generated a critical flag: "Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported." This indicates that the predicted effect concentrations are significantly higher than the measured water solubility of fosetyl-aluminium (111,000 mg/L). Consequently, the model suggests that no acute toxic effects are expected at the saturation limit of the chemical in water . The chronic toxicity values (ChV) predicted for fish, daphnids, and algae also followed this pattern, being several orders of magnitude above the solubility limit, leading to the same "NES" (No Effects at Saturation) conclusion for chronic exposure.

4. DISCUSSION

The ECOSAR model predictions presented in this study consistently indicate an exceptionally low acute toxicity profile for fosetyl-aluminium across aquatic and terrestrial organisms. The primary basis for this prediction is the compound's fundamental physicochemical properties - specifically, its high water solubility (111,000 mg/L) and low octanol-water partition coefficient (Log Kow = -2.4 to -3.92). These characteristics significantly limit the chemical's potential for bioconcentration and bioavailability, thereby reducing its toxicological impact on non-target organisms [16]. The model's consistent "no effects at saturation" (NES) warning for all endpoints strongly suggests that environmental concentrations would need to far exceed physically achievable levels in water to produce measurable acute toxicity. The reliability of ECOSAR predictions for organophosphorus compounds like fosetyl-aluminium has been demonstrated in several validation studies. A comprehensive evaluation by the European Chemicals Agency (ECHA) concluded that QSAR models, including ECOSAR, provide reliable screening-level assessments for chemicals with well-defined modes of action [17]. Specifically for fosetyl-aluminium, the model's predictions show remarkable concordance with experimental data reported in regulatory assessments and scientific literature. Comparison with Experimental Ecotoxicological Data When comparing our ECOSAR predictions with existing experimental studies, a consistent pattern of low toxicity emerges: Aquatic

organisms: Our predicted LC50 values for fish (161,000 mg/L) and Daphnia (581,000 mg/L) align with experimental findings. The Pesticide Properties Database (PPDB) reports similar values, classifying fosetyl-aluminium as "practically non-toxic" to fish and Daphnia [18]. A specific study by Sanchez et al. (2005) investigating the effects of fosetyl-Al on common carp (Cyprinus carpio) found no significant mortality even at concentrations approaching solubility limits, supporting the NES conclusion from our ECOSAR analysis. Algae: The predicted EC50 of 887,000 mg/L for green algae corresponds with experimental evidence showing minimal inhibitory effects on algal growth. In regulatory assessments submitted to the European Food Safety Authority (EFSA), fosetyl-aluminium demonstrated no significant toxicity to algae at maximum soluble concentrations [20]. This consistency between predicted and observed values reinforces the model's applicability for algal toxicity assessment. Earthworms: Our predicted earthworm LC50 of 375,000 mg/L finds support in soil ecotoxicity studies. Research Dittbrenner, Schmitt, Capowiez ve Triebskorn (2011), on Eisenia fetida exposed to fosetyl-aluminium in artificial soil reported no significant mortality at environmentally relevant concentrations, with effects only observed at levels substantially exceeding realistic exposure scenarios. Regulatory Context and Model Validation The concordance between our ECOSAR predictions and experimental data has important implications for regulatory science. The consistent demonstration of low toxicity across multiple trophic levels supports the compound's classification as a low-risk pesticide when used according to label instructions [22]. Furthermore, the faccuracy of ECOSAR predictions for fosetyl-aluminium validates the use of such computational tools in preliminary risk assessment, potentially reducing the need for extensive animal testing in accordance with the 3Rs principle (Replace, Reduce, Refine) [25]. However, it is important to acknowledge certain limitations in relying exclusively on ECOSAR predictions. While the model accurately predicts acute toxicity based on physicochemical properties, it does not account for potential sublethal effects, metabolic transformations, or interactions with environmental matrices that might influence bioavailability [23]. For instance, although fosetyl aluminium itself shows low toxicity, its environmental degradation products warrant separate assessment to fully characterize environmental risk. Implications for Environmental Risk Assessment The consistently high LC50/EC50 values predicted by ECOSAR and confirmed by experimental studies suggest that fosetyl-aluminium presents negligible acute risk to aquatic and terrestrial ecosystems under normal use conditions. The margin of safety between predicted environmental concentrations (PEC) and effect concentrations appears substantial, providing a robust buffer against accidental adverse effects [24]. This favorable profile positions fosetyl-aluminium as a relatively environmentally benign option among agricultural fungicides when compared to more persistent and bioaccumulative alternatives.

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The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the authors.

Authors' Contributions

The authors contributed equally to the preparation, analysis, and writing of this study.

The Declaration of Ethics Committee Approval

This study does not require ethics committee approval or any special permission.

The Declaration of Research and Publication Ethics

The authors declare that they have complied with all scientific, ethical, and citation rules of the journal Environmental Toxicology and Ecology. The authors confirm that no falsification of data has been made, that the editorial board has no responsibility for potential ethical violations, and that this study has not been submitted or evaluated in any other academic publication environment.

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