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Integrative *In Silico* Toxicity Assessment of Chlorfenapyr Using AI-Driven Platforms

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Abstract

Chlorfenapyr is a pyrrole-class pesticide with a unique mechanism of action that disrupts mitochondrial oxidative phosphorylation. Despite its broad-spectrum insecticidal use, publicly available toxicological data on chlorfenapyr remain limited, particularly regarding organ-specific and long-term effects. To address this data gap, the present study implements a multi-model *in silico* toxicity assessment using three AI-based platforms—SwissADME, ProTox-II, and ADMETlab 2.0—to predict key toxicokinetic and toxicodynamic properties from the compound's SMILES representation. Physicochemical and pharmacokinetic parameters such as molecular weight, lipophilicity, gastrointestinal absorption, and cytochrome P450 inhibition were consistently predicted across platforms. However, notable discrepancies emerged in blood–brain barrier (BBB) permeability and hepatotoxicity outcomes. Acute toxicity was estimated with a predicted LD_{50} of 55 mg/kg (Class 3), while organ-specific risks included neurotoxicity, hepatotoxicity, and respiratory toxicity. Both platforms highlighted mitochondrial membrane potential disruption and oxidative stress pathways as probable mechanisms of toxicity. Toxicophore analysis further revealed substructures associated with non-genotoxic carcinogenicity, aquatic toxicity, and poor biodegradability, raising environmental safety concerns. By combining complementary model outputs, this AI-supported approach allows for scalable, reproducible, and ethically favorable screening of chemical hazards despite inherent limitations associated with model training data and prediction variability. The findings demonstrate that multi-endpoint *in silico* toxicology workflows can effectively identify early warning signals of compound toxicity and guide future experimental priorities—particularly for chemicals like chlorfenapyr, where experimental data are scarce and regulatory insight is urgently needed.

Keywords: ADMETlab 2.0, Chlorfenapyr, Computational Toxicology, ProTox-II, Pesticide Risk Assessment, SwissADME.

1. Introduction

Pesticides are among the most widely used chemical agents in agriculture, public health, and vector control. While their effectiveness in controlling pests is well established, their potential risks to human health and the environment have led to increased regulatory attention. Chlorfenapyr, a pro-insecticide of the pyrrole class, has gained significant attention due to its broad-spectrum insecticidal activity and unique mechanism of action, which involves the disruption of mitochondrial oxidative phosphorylation [1]. Despite its increasing usage, the long-term toxicological profile of chlorfenapyr remains incompletely understood, especially in terms of chronic toxicity and potential organ-specific effects. This makes chlorfenapyr an ideal candidate for computational toxicity modeling, particularly for exploring data-poor endpoints such as chronic toxicity and carcinogenicity.

Traditional toxicity testing methods, particularly in vivo animal studies, are time-consuming, costly, and ethically constrained. Moreover, they often fail to keep pace with the growing number of chemicals introduced into the environment. In this context, computational toxicology has emerged as a powerful alternative, enabling the prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties through structure-based and data-driven models. Although these tools are not without limitations, they facilitate early-stage hazard identification, reduce the need for animal testing, and support risk assessment strategies by generating reproducible and scalable predictions [2].

Although the development of computational models for toxicity prediction dates back to the early use of Quantitative Structure–Activity Relationship (QSAR) methods in the 1960s, their practical application remained limited for decades due to insufficient data and computational power [3]. In recent years, however, the field has advanced rapidly with the integration of machine learning, large chemical databases, and open-access platforms. Today's models operate using a variety of approaches, including descriptor-based algorithms, graph neural networks, and multi-task learning frameworks. Several *in silico* platforms have been developed to estimate

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toxicological endpoints using molecular descriptors and machine learning algorithms in response to these needs. SwissADME provides physicochemical and pharmacokinetic parameters such as lipophilicity, gastrointestinal absorption, and blood-brain barrier permeability [4]. ProTox-II enables the prediction of acute toxicity and organ-specific toxicities through structural similarity-based modeling [5]. ADMETlab 2.0, on the other hand, offers an extended suite of predictive models, including those for metabolism, distribution, and long-term toxicity endpoints such as carcinogenicity [6]. The integration of outputs from these complementary tools allows for a broader and more reliable toxicity profiling of chemical compounds. Furthermore, comparing these computational predictions with available in vitro and in vivo data is essential to assess model validity and to identify where experimental validation is still lacking.

The integration of outputs from these complementary tools allows for a broader and more reliable toxicity profiling of chemical compounds. These platforms employ artificial intelligence techniques—including descriptor-based models, ensemble machine learning methods, and graph neural networks—to perform multi-endpoint toxicity prediction [4-6]. While comparing these computational results with experimental data remains essential for validation, such AI-driven approaches increasingly bridge the gap between early discovery and toxicological screening.

This study aims to construct a multi-model *in silico* toxicity assessment workflow to evaluate the potential health risks associated with chlorfenapyr exposure. By integrating predictions from SwissADME, ProTox-II, and ADMETlab 2.0, the toxicological profile of chlorfenapyr is analyzed in terms of its physicochemical behavior, absorption and distribution characteristics, acute and organ-specific toxicities, and long-term hazard endpoints. The outcomes are further interpreted in the context of existing literature to identify knowledge gaps—particularly regarding chronic toxicity and carcinogenic potential—and to propose future directions for research.

2. Material and Methods

2.1. Compound Selection and SMILES Retrieval

Chlorfenapyr (PubChem CID: 9579305) was selected as the model compound for this study due to its increasing agricultural use, unique mode of action, and limited availability of long-term experimental toxicity data. Its canonical SMILES string (CCOCN1C(=C(C(=C1C(F)(F)F)Br)C#N)C2=CC=C(C=C2)Cl) and molecular descriptors (e.g., molecular weight, LogP, TPSA) were retrieved from the PubChem database. The SMILES code serves as the structural input for all computational platforms used in this study.

2.2. *In Silico* Tools and Workflow

To assess the toxicological profile of chlorfenapyr, a combination of three widely recognized *in silico* tools was employed, each offering complementary perspectives to the evaluation process.

SwissADME was utilized to examine physicochemical characteristics and pharmacokinetic behavior, including lipophilicity, gastrointestinal absorption, and blood-brain barrier permeability. These features are essential for understanding how chlorfenapyr may interact with biological systems and whether it can access sensitive tissues such as the central nervous system. ProTox-II was selected for its ability to estimate acute toxicity (LD_{50}), assign toxicity classes, and identify target organ toxicities and mechanistic pathways through structural similarity analysis. This tool provided insight into the potential systemic and organ-specific effects of the compound. To extend the analysis, ADMETlab 2.0 was used due to its broad coverage of endpoints, including cytochrome P450 inhibition profiles, hepatotoxicity, carcinogenicity, and other ADME-related parameters. This allowed for a more comprehensive evaluation of long-term toxicity and metabolic interactions.

All predictions were conducted through the official web interfaces of each platform using the compound's SMILES notation. The workflow was organized in a stepwise and integrative manner. It began with the evaluation of fundamental absorption and distribution properties, continued with the assessment of acute and organ-specific toxicities, and concluded with the prediction of long-term hazard endpoints. The results were subsequently interpreted and compared in the context of available experimental literature.

All tools were accessed via their respective web platforms: SwissADME (accessed March 13, 2025), ProTox-II (accessed March 28, 2025), and ADMETlab 2.0 (accessed April 4, 2025).

2.3. Prediction Parameters and Comparison Strategy

The analysis focused on a range of parameters representing different aspects of toxicokinetics and toxicodynamics. From SwissADME, key descriptors such as molecular weight, topological polar surface area (TPSA), lipophilicity (LogP), and blood-brain barrier (BBB) permeability were evaluated to infer absorption and

tissue distribution potential. ProTox-II was employed to obtain predicted LD_{50} values, toxicity class, and organ-specific toxicity outcomes, particularly regarding hepatotoxicity and neurotoxicity. ADMETlab 2.0 provided additional insights, including cytochrome P450 enzyme inhibition, hERG liability, skin sensitization, and carcinogenicity predictions. Each output parameter was categorized by endpoint type (e.g., acute toxicity, organ-specific effects, genotoxicity), and overlapping predictions across platforms were assessed for consistency. Parameters without consensus were flagged for further interpretation, and endpoints that consistently appeared across tools were prioritized in the mechanistic discussion. This approach enabled a cross-validated, AI-driven assessment of the toxicological potential of chlorfenapyr.

3. Results

3.1. Physicochemical and pharmacokinetic properties

A summary of key physicochemical and pharmacokinetic parameters predicted by SwissADME and ADMETlab 2.0 is provided in Table 1.

The physicochemical properties of chlorfenapyr were assessed using both SwissADME and ADMETlab 2.0. The molecular weight was estimated as 407.61 g/mol by SwissADME and 405.97 g/mol by ADMETlab, with both platforms agreeing on a topological polar surface area (TPSA) of 37.95 $Å^2$, indicative of favorable membrane permeability. The compound exhibited moderate lipophilicity, with a consensus LogP of approximately 4.8. Hydrogen bond analysis revealed no donors and a slight variation in acceptor count between platforms (5 vs. 3), although this difference is unlikely to influence passive diffusion significantly.

Regarding pharmacokinetics, both platforms predicted high gastrointestinal absorption and agreed that chlorfenapyr is not a substrate for P-glycoprotein. However, their predictions differed concerning BBB permeability. SwissADME suggested that the compound would not cross the BBB, whereas ADMETlab indicated a positive prediction (++), highlighting a model-based discrepancy. Protein binding was only evaluated by ADMETlab, which estimated a plasma protein binding (PPB) rate of 99.04%, suggesting a limited free circulating fraction. Additionally, the skin permeation coefficient (Log Kp) was calculated as –5.36 cm/s, reflecting poor dermal absorption potential.

Metabolic predictions revealed strong inhibition of several cytochrome P450 enzymes, particularly CYP1A2 and CYP2C9, across both tools. ADMETlab additionally suggested moderate inhibition of CYP2C19 and negligible inhibition of CYP3A4 and CYP2D6, pointing to a potential for selective metabolic interactions.

Table 1. *Comparison of physicochemical and pharmacokinetic properties of chlorfenapyr predicted by SwissADME and ADMETlab 2.0.*

Parameter	**SwissADME**	**ADMETlab**	**Interpretation**
Molecular weight (g/mol)	407.61	405.97	Consistent; minor variation due to rounding
Topological Polar Surface Area (Å²)	37.95	37.95	Identical
Consensus LogP	4.8 (approx.)	4.839	Consistent lipophilicity
H-bond Donors / Acceptors	0 / 5	0 / 3	Slight difference in HBA count
GI Absorption	High	---	Predicted only by SwissADME
P-gp Substrate	No	---	Consistent (not a substrate)
*BBB Permeability**	No	++	Conflicting predictions
Plasma Protein Binding (%)	—	99.04%	Only available in ADMETlab
Log Kp (Skin Permeation)	-5.36 cm/s	-5.36 cm/s	Consistent
CYP1A2 Inhibition	Yes	+++	Strong inhibitor; potential interaction
CYP2C9 Inhibition	Yes	+++	Strong inhibitor; potential interaction
CYP2C19 Inhibition	Yes	++	Moderate inhibitor
CYP2D6 Inhibition	Yes	--	Low inhibition potential
CYP3A4 Inhibition	No	--	Low inhibition potential

An asterisk (*) denotes parameters for which SwissADME and ADMETlab 2.0 produced differing predictions, reflecting possible methodological differences between platforms. For the classification endpoints, the prediction probability values are transformed into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).

3.2. Acute toxicity and organ-specific predictions

The acute toxicity potential of chlorfenapyr was predicted using ProTox-II, which estimated an LD_{50} value of 55 mg/kg and classified the compound in toxicity class 3, indicating a moderate level of acute oral toxicity. As detailed in Table 2, organ-specific toxicity predictions revealed a high probability of neurotoxicity (0.79) and

Table 2. *Comparative predictions of acute toxicity and organ-specific toxicological endpoints for chlorfenapyr, based on ProTox-II and ADMETlab 2.0 outputs.*

Parameter	**ProTox-II**	**ADMETlab 2.0**	**Interpretation**
LD50 (mg/kg)	55	—	Moderate acute toxicity (ProTox-II only)
Toxicity Class	Class 3	—	Toxic if swallowed (GHS Class 3)
Neurotoxicity	Active (0.79)	—	Consistently predicted across tools
Respiratory Toxicity	Active (0.67)	+++	Consistently predicted across tools
Hepatotoxicity	Inactive (0.67)	+++	Discrepant prediction (ProTox-II: Inactive, ADMETlab: +++)
Nephrotoxicity	Inactive (0.66)	—	Both models indicate low risk
Carcinogenicity	Inactive (0.58)	–	Predicted inactive by both tools
Mutagenicity (AMES)	Inactive (0.68)	--	Predicted non-mutagenic by both tools
Drug-Induced Liver Injury (DILI)	Not available	+++	Strong DILI signal from ADMETlab
BBB Permeability	Active (0.90)	++	Conflicting predictions with SwissADME (No)

Discrepancies between models are marked with interpretation comments. LD_{50} and toxicity class values are available only from ProTox-II. '+++' indicates high confidence prediction in ADMETlab; probability values are shown in parentheses for ProTox-II.

respiratory toxicity (0.67), while hepatotoxicity and nephrotoxicity were predicted to be inactive by ProTox-II. In contrast, ADMETlab 2.0 predicted a high likelihood (+++) for both hepatotoxicity and respiratory toxicity, reflecting a model-based divergence in liver-specific toxicity outcomes.

Both platforms consistently predicted negative results for mutagenicity (AMES test) and carcinogenicity, indicating low genotoxic potential. ADMETlab 2.0 additionally flagged chlorfenapyr with a high risk for drug-induced liver injury (DILI), further supporting hepatotoxicity concerns. Notably, BBB permeability predictions showed convergence between ProTox-II and ADMETlab (++/active) but were inconsistent with SwissADME, which predicted no BBB penetration.

These findings were further visualized through the ProTox-II radar chart (Figure 1), which showed extended projections for neurotoxicity and respiratory toxicity, indicating strong model confidence in these endpoints. Structural toxicity risks were also explored through toxicophore analysis. ADMETlab 2.0 identified specific substructures associated with non-genotoxic carcinogenicity, aquatic toxicity, and environmental persistence. These flagged motifs are shown in Figure 2, providing mechanistic insight into structural features potentially linked to adverse effects.

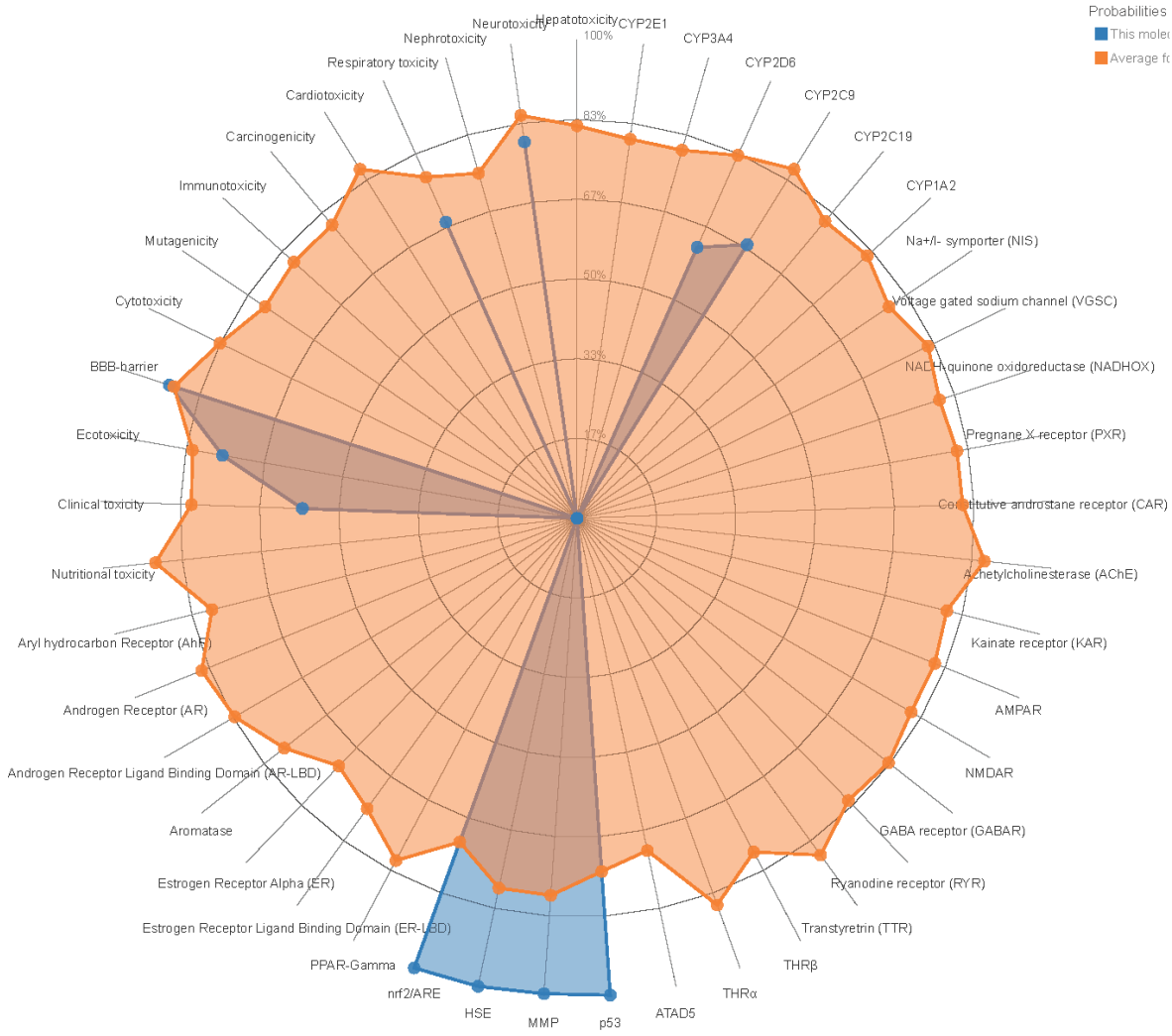

Figure 1. *Radar chart generated by ProTox-II illustrating the confidence levels of predicted toxicological endpoints for chlorfenapyr.*

3.3. Mechanistic Toxicity and Stress Pathway Activation

The mechanistic toxicity profile of chlorfenapyr was explored using ProTox-II and ADMETlab 2.0, both of which predicted notable activation of key cellular stress response pathways. ProTox-II identified strong activation for the antioxidant response element (Nrf2/ARE), mitochondrial membrane potential disruption (MMP), heat shock response element (HSE), and the p53 tumor suppressor pathway, all with high probability scores (>0.99). These findings suggest that chlorfenapyr may induce oxidative stress, mitochondrial dysfunction, and apoptosis-related processes.

ADMETlab 2.0 provided complementary evidence by confirming activation of the p53 pathway (+++), heat shock protein signaling (++), and mitochondrial toxicity risk (++). Additionally, chlorfenapyr was predicted to activate peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor associated with lipid metabolism and inflammation. These converging results support the hypothesis that chlorfenapyr may exert its toxic effects through combined oxidative and metabolic stress mechanisms.

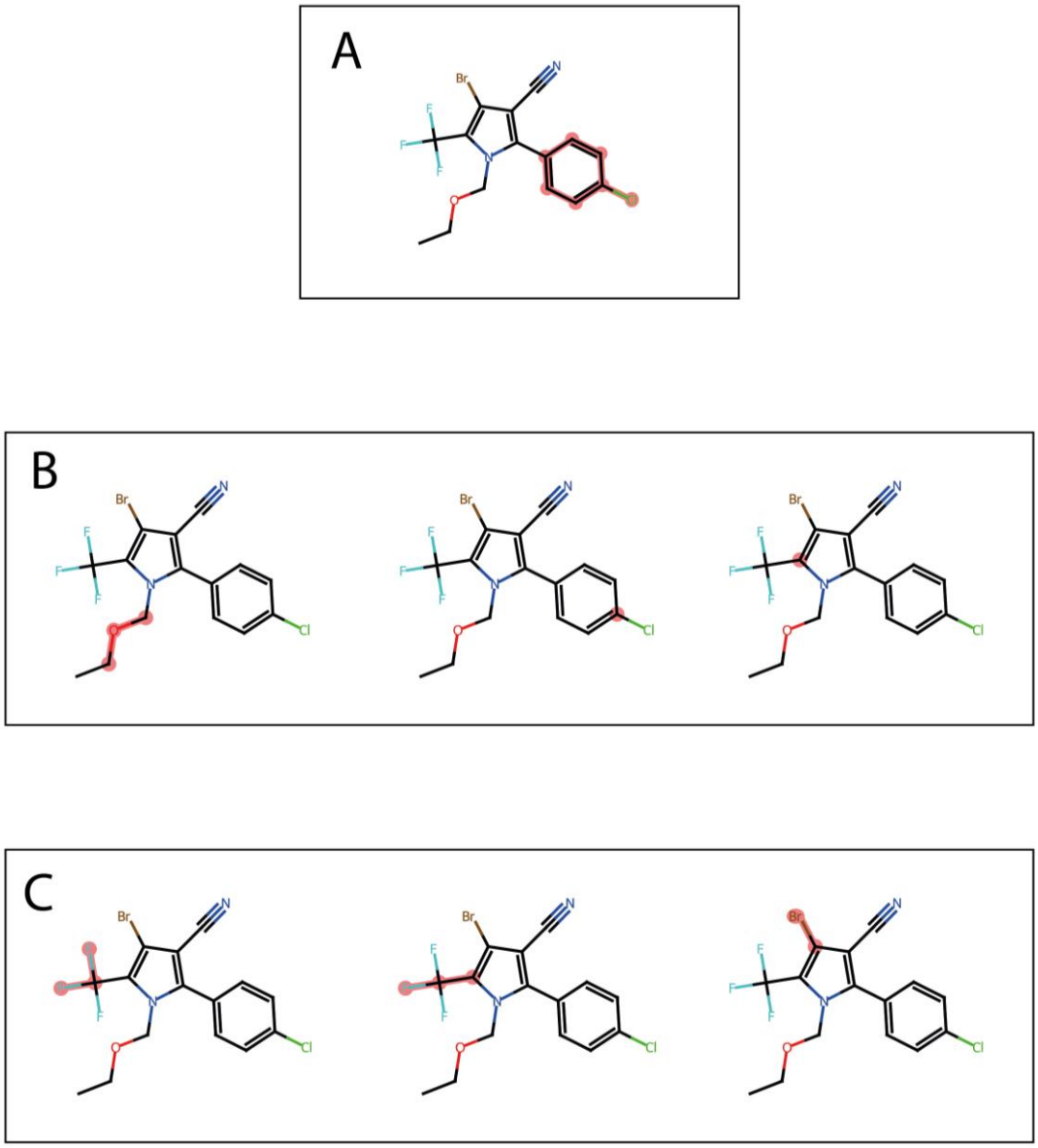

Figure 2. *Structural alerts identified by ADMETlab 2.0 in the chlorfenapyr molecule. Three key toxicophoric substructures are highlighted: (A) a non-genotoxic carcinogenicity-associated motif commonly found in compounds with chronic hazard potential; (B) a non-biodegradable fragment indicating environmental persistence risk; and (C) a structural feature linked to aquatic toxicity, based on established cheminformatic rules. These motifs contribute to the compound's predicted long-term health and environmental risks.*

While no strong activity was observed on endocrine-related targets such as estrogen or androgen receptors, ADMETlab flagged a weak aromatase interaction (+), which may warrant further investigation. Importantly, most molecular initiating events (MIEs), including interactions with thyroid hormone receptors and neurotransmitter receptors, were predicted to be inactive, suggesting a degree of target selectivity.

The integrated results indicate that chlorfenapyr may trigger a multifaceted stress response involving mitochondrial, oxidative, and inflammatory pathways—potentially underlying the observed neurotoxic and hepatotoxic predictions in earlier models.

Table 3. *Mechanistic toxicity and stress pathway activation predictions for chlorfenapyr based on outputs from ProTox-II and ADMETlab 2.0.*

Target / Pathway	**ProTox-II**	**ADMETlab 2.0**	**Interpretation**
*Nrf2/ARE (oxidative stress)**	Active (1.00)	—	Strong oxidative stress signal
*Mitochondrial Membrane Potential (MMP)**	Active (0.99)	++	Mitochondrial stress confirmed by both
*Heat Shock Element (HSE)**	Active (1.00)	++	Consistent heat shock response
*p53 (tumor suppressor)**	Active (0.99)	+++	Strong activation across tools
*PPAR-γ (metabolic regulation)**	—	+++	Activation confirmed by ADMETlab
*Aromatase (hormonal)**	—	+	Weak hormonal interaction
Estrogen Receptor	Inactive (0.88 / 0.92)	-	No significant endocrine effect
Androgen Receptor	Inactive (0.98 / 0.92)	--	No androgenic activity
Thyroid Hormone Receptors (α/β)	Inactive (0.90 / 0.78)	--	Inactive thyroid-related events
Neurotransmitter Receptors (GABA, NMDA, AMPA)	Inactive (0.92–0.99)	--	No CNS receptor interaction predicted
CAR, PXR (xenobiotic sensors)	Inactive (0.92 / 0.98)	--	No activation of detox sensors

Pathways predicted as active by either tool are emphasized in the table by (*). ProTox-II provides probabilistic scores, while ADMETlab 2.0 uses a qualitative scale (+++ to ---).

3.4. Toxicophore alerts and structural liabilities

Structural alert analysis was conducted using ADMETlab 2.0, which flagged several toxicophoric fragments in the chlorfenapyr molecule. These substructures were associated with risks of non-genotoxic carcinogenicity, aquatic toxicity, and non-biodegradability. Such fragments are commonly flagged in cheminformatics-based toxicity filters due to their known association with long-term or environmental hazards.

In particular, one alert was triggered under the non-genotoxic carcinogenicity rule, indicating the presence of a substructure that may induce carcinogenesis through mechanisms other than direct DNA damage. Additionally, three separate alerts were detected for aquatic toxicity, and three for poor biodegradability, suggesting that chlorfenapyr may pose environmental persistence and ecotoxicity risks. These features are visualized in Figure 2, where the flagged chemical motifs are shown in relation to their associated toxicity categories. While the compound showed acceptable drug-likeness in initial filters (e.g., Lipinski and PAINS), the FAF-Drugs4 rule identified two substructures considered undesirable in drug development contexts due to their potential reactivity or off-target effects.

Together, these toxicophore findings provide a structural basis for interpreting some of the predicted toxicological behaviors discussed in earlier sections, particularly regarding carcinogenic potential and environmental impact.

4. Discussion

In this study, a comprehensive *in silico* workflow was developed to evaluate the toxicological profile of chlorfenapyr using three established AI-powered platforms: SwissADME, ProTox-II, and ADMETlab 2.0. The integration of diverse prediction models enabled a multidimensional assessment of physicochemical, pharmacokinetic, acute toxicological, organ-specific, and mechanistic endpoints. To the best of the author's knowledge, while previous studies have applied AI-driven techniques such as molecular docking or predictive modeling to investigate Chlorfenapyr [7-9], no comprehensive toxicity screening has been conducted using an integrated multi-platform *in silico* workflow. This underscores the novelty and added value of the current study within the expanding field of computational toxicology.

The physicochemical and pharmacokinetic properties of chlorfenapyr suggest high lipophilicity, efficient gastrointestinal absorption, and extensive plasma protein binding. Despite its low polar surface area, predictions regarding BBB permeability were inconsistent between SwissADME and ADMETlab, highlighting the importance of cross-platform evaluation when interpreting distribution-related endpoints [10-12]. CYP450 inhibition predictions suggested the compound may interact with major metabolic enzymes such as CYP1A2 and CYP2C9, posing a potential for drug–drug interactions [13]. These findings align with the known metabolic characteristics of chlorfenapyr, which is bioactivated to a mitochondrial uncoupler compound in vivo [14-15].

Toxicity predictions revealed a moderate acute toxicity profile (LD_{50} = 55 mg/kg; Class 3) and high-confidence organ-specific toxicities in the nervous and respiratory systems. The stress response pathway analysis provided additional mechanistic insights, with activation of mitochondrial dysfunction (MMP), oxidative stress (Nrf2/ARE), and the tumor suppressor pathway (p53) being prominent. These outputs suggest that chlorfenapyr may exert its toxicity through mitochondrial disruption and oxidative imbalance, consistent with its proposed mechanism of action as a pro-insecticide targeting mitochondrial ATP synthesis [16, 17]. Interestingly, while organ toxicity predictions were robust, both mutagenicity and genotoxicity endpoints were consistently negative across platforms. Toxicophore alerts further supported concerns about non-genotoxic carcinogenicity and environmental impact. Alerts were triggered for substructures associated with poor biodegradability and aquatic toxicity, pointing to ecological risks that may be overlooked in human health assessments alone. These findings are particularly important given the increasing focus on environmental safety in pesticide regulation [18-21]. Incorporating toxicophore-based filters allows for early identification of structural liabilities and aligns with green chemistry principles [22].

One notable strength of this study is the simultaneous use of multiple AI-driven tools, each relying on different algorithms such as graph-based neural networks, support vector machines, and ensemble learning models. This redundancy not only improves confidence in overlapping predictions but also identifies inconsistencies that may reflect model limitations. For example, the conflicting BBB permeability outputs underscore the need for harmonized training datasets and model interpretability in regulatory applications [23-26].

Despite the comprehensive scope, the study has limitations. Predictions were not validated against in vitro or in vivo experimental data due to limited publicly available toxicological datasets for chlorfenapyr. As such, the results should be considered as a high-throughput hypothesis-generating framework rather than definitive toxicological evidence. Future studies should focus on experimentally confirming key endpoints such as neurotoxicity, hepatotoxicity, and mitochondrial impairment, especially using human-relevant models. Moreover, the current workflow could be extended to include population-level toxicogenomic analyses or adverse outcome pathway (AOP) mapping to better understand long-term and low-dose effects. Expanding the approach to structurally related pesticides may also reveal structure–toxicity relationships and inform safer chemical design strategies.

In conclusion, this work demonstrates the utility of integrative *in silico* toxicology workflows for early hazard identification of chemical compounds. Nonetheless, it is important to recognize that the reliability of these AI-driven predictions is inherently limited by the quality and scope of training datasets, as well as the lack of systematic experimental validation for many endpoints. These limitations underline the necessity of integrating computational assessments with confirmatory *in vitro* or *in vivo* studies, especially in regulatory contexts. The findings provide a predictive toxicological map of chlorfenapyr and highlight the potential of combining AI-driven tools to strengthen chemical safety evaluation in the absence of wet-lab data.

Declaration of Interest

The author declares that there is no conflict of interest.

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Author Contributions

The author was solely responsible for the conception, design, execution, data analysis, interpretation, and writing of this manuscript.

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