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The Predicted Toxicology of Benfluralin, Dinitramine, Ethalfluralin, Oryzalin, Pendimethalin, Prodiamine, and Trifluralin Using in Silico Models s

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ABSTRACT

In modern agriculture, pesticides are indispensable chemicals for controlling and eliminating pests, which ensures high growth rates and the quantity of food. Pesticide usage is linked to managing the weeds and insect pests that impact agricultural systems. Water, soil, and air are essential media for transporting pesticides from one location to another and can further cause direct and indirect exposure to pesticides. *In silico* toxicity modeling is considered a novel computational method used to predict toxicological outcomes and endpoints related to pesticides. Two different *in silico* models were applied and compared to predict the toxicity of seven pesticides, belonging to the dinitroaniline family of herbicides. The Toxicity Estimation Software Tool (TEST) and ProTox 3.0 *in silico* platforms were utilized to estimate the toxicity of benfluralin, dinitramine, ethalfluralin, oryzalin, pendimethalin, prodiamine, and trifluralin. TEST results indicated that seven herbicides appeared to be potential developmental toxicants. According to the ProTox 3.0 *in silico* hazard results, dinitramine, ethalfluralin, and oryzalin dinitroanilines were relatively harmless (predicted toxicity class 5), while benfluralin, pendimethalin, prodiamine, and trifluralin herbicides were classified as predicted toxicity class 4.

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Introduction

Pesticides are chemical substances applied extensively in modern agriculture, including insecticides, herbicides, fungicides, nematicides, rodenticides, etc, which specifically target various types of pests or functions. The use of pesticides is an effective and cost-efficient way to enhance both the quality and quantity of crops, maintaining food security for the growing global population. Thus, pesticides, particularly in agricultural lands and gardens, helps ensure the control pests, weeds, undesirable organisms, and diseases in plants. However, the extensive use of pest-controlling agents has become a global concern due to the contamination of soil and water resources, posing a potential threat to both ecosystems and human health (Çakmak & Avcı, 2025; Erkan Can & Boğa, 2025; Hassaan & El Nemr, 2020; Sharma et al., 2019; Shekhar et al., 2024).

The accumulation of residual pesticides in soil can threaten non-target living organisms and disrupt ecosystems due to the long-term effects of pesticide contamination. Moreover, these toxic substances can bioaccumulate in the food chain, causing health problems. Pesticide exposure can occur through direct or indirect exposures, entering the dermal, respiratory, ocular, and oral routes. Direct exposure can occur through applications, especially when pesticides are sprayed without wearing protective equipment such as gloves and masks. This can lead to respiratory problems, skin and eye irritation, and headache symptoms. Indirect exposure occurs due to the accumulated pesticides in food, water supplies, and soil. Consequently, determining the acute toxicity of pesticides is essential for assessing human and environmental risks, serving as a precaution against pollution (Chia et al., 2024; Dhankhar & Kumar, 2023; Raffa & Chiampo, 2021; Shekhar et al., 2024).

Herbicides primarily serve as agricultural chemicals, comprising 40% of the global pesticide market share. Dinitroanilines are a category of pre-emergent and broad-spectrum herbicides that effectively control annual grasses and broadleaf weeds before crop germination.

These herbicides are commonly applied in cotton, peanuts, and soybeans by targeting microtubule proteins. Dinitroanilines disrupt mitosis, effectively destroying weeds while also affecting the emergence of crops. The

repeated annual application of aromatic compounds can influence their translocation and persistence in soil, which are affected by factors such as temperature, moisture, and soil type. (Giglio & Vommaro, 2022; Zhang et al., 2025; Zhang et al., 2024). Vighi et al. conducted a laboratory simulation study, and a geometric mean half-life of pendimethalin in relevant soils under aerobic conditions was found to be 76–98 days (Vighi et al., 2017). (Strandberg & Scott-Fordsmand, 2004). Arici et al. reported that pendimethalin was indicated to increase risks for certain types of cancer. They also highlighted the use and possible toxic effects of this herbicide, which can induce oxidative damage (Arici et al., 2020). Another toxicity study of the herbicides pendimethalin, butralin, and napropamid exhibited slight to moderate toxicity to egg parasitoids (Cheng et al., 2018). Park et al. investigated the toxicity of oryzalin on zebrafish embryos, highlighting potential developmental risks to vertebrates and emphasizing the necessity for caution in its widespread application (Park et al., 2025). The toxicology of ethalfluralin (Hong et al., 2023) and befuraline (Kim et al., 2023) was investigated in zebrafish, indicating developmental toxicity.

Recently, computational toxicology has been applied to the assessment of predicted *in silico* toxicity and toxicological endpoints of pesticides (Demir et al., 2023; Venko et al., 2018; Yaman, 2025). *In silico* modeling is regarded as an alternative to animal testing, utilizing various computational systems. This method predicts the toxicity or efficacy of a chemical by analyzing the relationship between its chemical structure and various algorithms (Golbamaki et al., 2014; Rim, 2020).

The current study aimed to predict the *in-silico* toxicity of seven dinitroanilines: benfluralin, dinitramine, ethalfluralin, oryzalin, pendimethalin, prodiamine, and trifluralin. The performance of two different *in silico* modeling packages, TEST and ProTox 3.0, was assessed and compared for predicting the toxicity of dinitroanilines. Additionally, the acute toxicity of these dinitroanilines was assessed using lethal dose 50 (LD_{50}) and lethal concentration 50 (LC_{50}) values.

Materials and Methods

The *in-silico* predictions were derived by computational tools, namely TEST and ProTox 3.0. The chemical structures of seven dinitroanilines (benfluralin, dinitramine, ethalfluralin, oryzalin, pendimethalin, prodiamine, and trifluralin) are presented in Figure 1. TEST (https://www.epa.gov/comptox-tools/toxicity-estimation-software-tool-test, 2020) and ProTox 3.0 (https://tox.charite.de/protox3/) *in silico* platforms were utilized to calculate the predicted toxicology and toxicological endpoints of dinitroanilines. TEST, version 5.1.2 (USEPA Toxicity Estimation Software Tool) is a quantitative structure–activity relationship (QSAR) model based on the mathematical relationships associated with the biological activity of compounds, using SMILES or CAS numbers. The predicted toxicity and acute oral LD_{50} (96 h) toxicity in rats were determined using a consensus QSAR approach, which averaged all the hierarchical, single-model, group contribution, and nearest neighbor-based methods. Therefore, the consensus method is regarded as the most reliable approach in TEST software, providing a thorough toxicity prediction. For more information on QSAR methodologies and models documented on an open software website (https://www.epa.gov/comptox-tools/toxicity-estimation-software-tool-test, 2020).

A variety of endpoints, such as *Fathead minnow* LC_{50} (96 h), *Tetrahymena pyriformis* IGC_{50}, 50% growth inhibitory concentration (48 h), *Daphnia magna* LC_{50} (48 h), developmental toxicity, and bioconcentration factor, were used to estimate the toxicity of the selected dinitroanilines.

ProTox 3.0 is an open web-based source that integrates machine learning algorithms and extensive databases based on cheminformatics principles to classify toxicity into six categories according to LD_{50} values (Banerjee et al., 2024; https://tox.charite.de/protox3/). This *in silico* approach employs different methods, such as similarity-based prediction, fragment propensities, pharmacophore models, and machine learning algorithms (CLUSTER cross-validation based on fragment similarity). The toxicological profile of dinitroanilines was assessed using selected endpoints, including acute toxicity, carcinogenicity, cytotoxicity, hepatotoxicity, and mutagenicity, and specifically predicted LD_{50} values for rats via oral route exposure. The utilization of the ProTox 3.0 platform in the analysis of seven dinitroanilines was supported by its extensive external validation, as explained in publications by Drwal et al. (Drwal et al., 2014) and Banerjee et al. (Banerjee et al., 2018), which was verified by high accuracy and reliability.

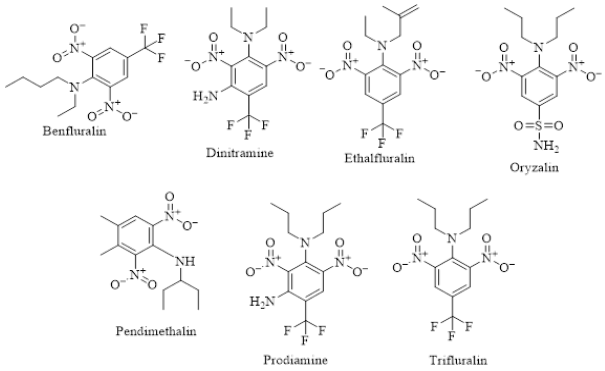

Figure 1. The chemical structures of selected dinitroanilines

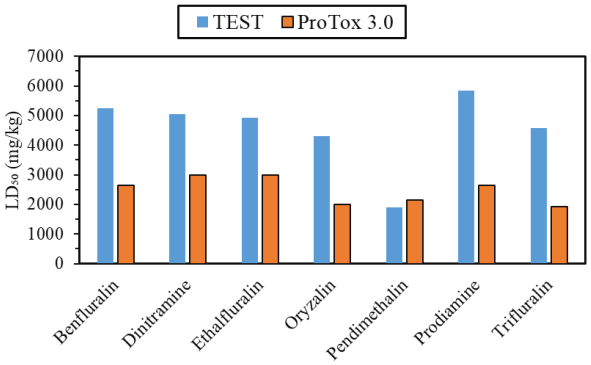

Figure 2. The predicted LD_{50} values derived using the TEST and ProTox 3.0 in silico platforms

Table 1. The predicted LD_{50} values derived from in silico tools

Dinitroanilines	LD_{50} (mg/kg)	
	TEST	ProTox 3.0
Benfluralin	5237	2650
Dinitramine	5045	3000
Ethalfluralin	4913	3000
Oryzalin	4298	2000
Pendimethalin	1898	2140
Prodiamine	5841	2650
Trifluralin	4589	1930

Table 2. The predicted toxicological risk assessments using the TEST in silico platform.

Dinitroanilines	Fathead minnow LC_{50} (96 h) mg/L	Tetrahymena pyriformis IGC_{50} (48 h) mg/L	Daphnia magna LC_{50} (48 h) mg/L	Developmental toxicityvalue	Bioconcentration factor
Benfluralin	0.22	2.06	1.45	1.14	235
Dinitramine	0.48	4.03	1.97	1.28	97
Ethalfluralin	0.11	4.21	0.76	1.21	195
Oryzalin	0.36	9.20	2.33	1.21	22
Pendimethalin	0.19	0.88	0.82	0.95	58
Prodiamine	0.22	2.19	1.16	1.34	122
Trifluralin	0.21	2.38	2.03	1.15	150

Table 3. The predicted toxicological endpoints using ProTox 3.0 in silico platform.

Dinitroaniline	Class	Carcinogenicity	Hepatotoxicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Benfluralin	4	Active	Inactive	Active	Active	Inactive
Dinitramine	5	Active	Inactive	Active	Active	Inactive
Ethalfluralin	5	Active	Inactive	Active	Active	Inactive
Oryzalin	5	Active	Inactive	Inactive	Active	Inactive
Pendimethalin	4	Active	Inactive	Inactive	Active	Inactive
Prodiamine	4	Active	Inactive	Active	Active	Inactive
Trifluralin	4	Active	Inactive	Active	Active	Active

Table 4. The selected experimental and predicted LD_{50} and LC_{50} values

	LD_{50}/LC_{50} values	References
Benfluralin	LC_{50} > 2.16 mg/L, rat, air	(Authority et al., 2019).
Dinitramine	LD_{50}: 3700 mg/kg, rat, oral	(Karmaus et al., 2022)
Ethalfluralin	LC_{50}: 18.49 mg/L, zebrafish embryos	(Hong et al., 2023)
Oryzalin	LD_{50}> 10000 mg/kg, rat, oral	(Francis et al., 1985)
Pendimethalin	LC_{50}: 3.55 mg/L, *Clarias batrachus,* LD_{50}> 5000 g/kg b.wt, rat	(Gupta & Verma, 2022), (Gad et al., 2022)
Prodiamine	LC_{50}: 10.4 mg/L	(Park & Lees, 2005)
Trifluralin	LC_{50}: 3.48 mg/L	(Park & Lees, 2005)

In ProTox 3.0, the assessment of acute oral toxicity was determined by comparing the two-dimensional similarity of compounds with known LD_{50} values (mg/kg) and identifying structural fragments associated with toxicity. A leave-one-out cross-validation technique, which calculated the three nearest neighbors for each chemical compound in the training dataset regarding the similarity of their fingerprints, was used as the validation methodology.

Results and Discussion

The predicted LD_{50} values for seven dinitroanilines, using TEST and ProTox 3.0, are summarized in Table 1. This critical acute toxicity value refers to the toxic dose relative to the body weight of the organism. The TEST *in silico* model estimated the LD_{50} value of benfluralin to be 5237 mg/kg, while ProTox 3.0. determined as the LD_{50} value to be 2650 mg/kg.

The toxicological effects of dinitroanilines were assessed using TEST and ProTox 3.0 software, as shown in Tables 2 and 3, respectively, and a comparison was also presented in Figure 1. Besides, Table 4 provides detailed information on various experimental LD_{50} and LC_{50} values obtained from different species for a comparison with the predicted LD_{50} and LC_{50} values derived from *in silico* methods, as shown in Tables 1-3.

According to the TEST *in silico* tool, benfluralin was identified as having developmental toxicant effects.

This pesticide is considered slightly toxic, classified as predicted toxicity class 4 by ProTox 3.0. The toxicity of benfluralin was studied on zebrafish embryos, revealing an impact on liver and cardiovascular development in the larvae. They reported that benfluralin induced a smaller liver size, which was approximately 59.81% of the normal liver size (Kim et al., 2023). Strupp et al. reported that benfluralin acts specifically on rats for thyroid and liver

carcinogenesis, which was not relevant for human cancer risks based on the weight of the approach (Strupp, Quesnot, Richert, et al., 2020; Strupp, Quesnot, Weber-Parmentier, et al., 2020). The toxicology of benfluralin on rat LC_{50} inhalation (dust, nose only) was greater than 2.16 mg/L in air/4h (Authority et al., 2019).

The estimated LD_{50} values (rat, oral) for dinitramine, derived from TEST and ProTox 3.0 *in silico* tools, were 5045 mg/kg and 3000 mg/kg, respectively. Karmaus et al. reported that the LD_{50} (rat, oral) value of dinitramine was 3700 mg/kg (Karmaus et al., 2022). This experimental data was close to the predicted LD_{50} (rat, oral) value obtained from ProTox 3.0. Rani et al. investigated the *in silico* modelling analysis of dinitramine using ADMET application, and found a predicted LD_{50} value for oral rats of 2.079 log mol/kg (Rani et al., 2024). Park et al. investigated the effects of dinitramine on developing zebrafish and calculated the 96-hour post-fertilization (hpf) LC_{50} value of 15.1 mg/L from the acute mortality rate (Park et al., 2021).

The calculated LC_{50} value of ethalfluralin for Fathead minnow (96 h) via TEST software was 0.11 mg/L. Hong et al. investigated the toxicity of ethalfluralin by using zebrafish embryos, and the LC_{50} value was 18.49 mg/L. Ethalfluralin was reported to cause developmental changes in the morphology of zebrafish embryos (Hong et al., 2023).

The acute oral LD_{50} value of oryzalin in rats was found to be higher than 10000 mg/kg (Francis et al., 1985). The potential toxicity of oryzalin was determined by using zebrafish embryos, causing lethality in the embryos (Park et al., 2025). The predicted LD_{50} value (oral, rat) was 4298 mg/kg as determined by TEST software, and the oral LD_{50} value for rat (2000 mg/kg) was estimated by ProTox 3.0, which notably deviated from the experimental data. According to the ProTox 3.0 *in silico* tool, oryzalin herbicide exhibited potential carcinogenic and mutagenic activities.

Pendimethalin is genotoxic to freshwater fish *Clarias batrachus,* and the LC_{50} value was determined as 3.55 mg/L for 96 h (Gupta & Verma, 2022). The LC_{50} value was 3.6 mg/L, which was nearly identical to another freshwater fish, *Channa punctatus* (Ahmad & Ahmad, 2016). The LC_{50} prediction values assessed by *Fathead minnow* and *Daphnia magna* species obtained by TEST software were 0.19 mg/L and 0.82 mg/L, respectively. Gad et al. examined the acute oral toxicity of pendimethalin and reported that the LD_{50} value was greater than 5000 g/kg b.wt for rats (Gad et al., 2022).

The acute toxicity tests of both trifluralin and pendimethalin were performed on the Collembolan species *Proisotoma minuta*, and the LC_{50} values for trifluralin and pendimethalin herbicides in an artificial sea salt solution for seven days were 3.48 mg/L and 10.4 mg/L, respectively (Park & Lees, 2005). The acute toxicities of trifluralin and prodiamine were assessed on the soil invertebrate *Eisenia fetida*, and the LC_{50} (95% CI) values were determined to be greater than 1000 µg/cm^2, indicating they were relatively non-toxic (Wang et al., 2012). Using the ProTox 3.0 *in silico* method, this herbicide exhibited potential toxic effects, including carcinogenicity, immunotoxicity, and mutagenicity.

The estimated oral LD_{50} value for rats was 1930 mg/kg using the online ProTox 3.0 *in silico* tool, while this predicted value was 4589 mg/kg using TEST software. ProTox *in silico* tool indicated the possible toxic effects of trifluralin herbicide, such as carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. A toxicity assessment study of trifluralin tested on laboratory animals revealed that sub-chronic oral toxicity resulted in hemotoxicity. They determined the no-observed-effect level of 41 mg/kg body weight per day in rats exposed to trifluralin (Ebert et al., 1992). Byrd et al. investigated the potential development of toxicity of trifluralin, conducted on pregnant rats and rabbits. They observed maternal toxicity in both specimens and reported non-selective toxicity towards developing concepts (Byrd et al., 1995). In toxicological research on trifluralin using a Chagas disease mouse model, it was found to be a moderately toxic drug (Zaidenberg et al., 2007). Additionally, trifluralin was also tested against *Trypanosoma cruzi, Plasmodium falciparum, and Toxoplasma gondii* parasites, which were responsible for Chagas disease. It was reported that the LD_{50} value in rats was 500 mg/kg, exhibiting low toxicity (Bogitsh et al., 1999; Stokkermans et al., 1996; Werbovetz et al., 1999). The oral LD_{50} values of trifluralin were higher than 500 mg/kg in *Mus musculus* (laboratory mice) and exceeded 10000 mg/kg in *Rattus norvegicus* (laboratory mice) (Marin-Morales et al., 2013).

Conclusion

The predicted toxicity of the herbicides trifluralin, pendimethalin, oryzalin, prodiamine, ethalfluralin, benfluralin, nitrilin, and dinitramine, which belong to the dinitroaniline family, was calculated by using ProTox 3.0 and TEST *in silico* platforms compared with the experimental data from the literature. According to the TEST *in silico* approach, all dinitroaniline herbicides were identified as potential developmental toxicants. Based on the ProTox 3.0 *in silico* toxicity results, three dinitroanilines were relatively harmless (dinitramine, ethalfluralin, and oryzalin) and classified in predicted toxicity class 5. Benfluralin, pendimethalin, prodiamine, and trifluralin herbicides were categorized as predicted toxicity class 4, indicating they were potentially slightly toxic. Among the seven dinitroanilines, the herbicide trifluralin showed potential toxicity effects, including carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. This toxicity study presented a green strategy, highlighting the reduction of animal testing. However, differences were noted between the predicted LD_{50} values of TEST, ProTox *in silico* platforms, and experimental data. Therefore, this study will serve as a guide for further investigations needed to confirm the toxicity profiles of these dinitroanilines using computational predictions.

Declarations

Ethical Approval Certificate

Not applicable.

Author Contribution Statement

N.T.: Conceptualization, writing the original draft, review and editing

Y.K.: Conceptualization, writing the original draft, review and editing

Y.Y.G.: Writing the original draft, review and editing, software

S.K.: Supervision, writing the original draft, review and editing software

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Conflict of Interest

The authors declare that they have no conflict of interest.

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