Toxicological Insights into Broflanilide: A Novel Meta-Diamide Pesticide with Potential Health Risks in Mammals

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Abstract: Broflanilide, a meta-diamide insecticide launched in 2021 by Mitsui Chemical Agro Inc., represents a major breakthrough in pest management due to its potent action on insect γ-aminobutyric acid receptors (GABARs). Classified under Group 30 by the Insecticide Resistance Action Committee (IRAC) as a GABA-gated chloride channel allosteric modulator, it represents a major breakthrough in pest control strategies. Lindane and cyclodienes, such as dieldrin and α-endosulfan represent the first generation of noncompetitive antagonist (NCAs), but pests developed resistance to cyclodienes. It provides effective control of Lepidopteran, Coleopteran, and Thysanopteran pests. However, despite its agricultural significance, concerns remain about its impact on non-target organisms, particularly mammals. Recently, it has been demonstrated that Broflanilide exhibits potent chronic metabolic impacts on aquatic species such as *Danio rerio*, as reflected by moderate bioaccumulation of this pesticide and the induction of detoxification enzymes including CYP450 and GST. In spite of bioaccumulation of these hazardous pesticides in environment, very limited information is available regarding its toxicity in living system and environment.

This review consolidates current evidence on broflanilide's toxicity, biochemical alterations, and anticipated health risk. By integrating findings from environmental, biochemical, and animal studies, this review bridges critical gaps between pesticide chemistry, mammalian toxicology, and public health. The analysis highlights an urgent need for comprehensive in vivo mammalian studies and risk assessment frameworks to ensure safe regulatory use of broflanilide and to guide evidence-based policy development.

Keywords: Broflanilide, insect γ-aminobutyric acid receptor (GABAR), noncompetitive antagonist (NCAs), zebrafish, mice, *in silico*, hepato-renal toxicity, cytogenetic endpoints, and bioaccumulation toxicology.

1. Introduction

The use of pesticides has become an essential part of contemporary agriculture, as it helps to reduce the losses of crops due to pests and improves the production. They have been used on a large scale to cater the food needs in the world. Global pesticide usage surpasses two million tons annually, with Europe accounting for nearly half and India contributing around 3.75 % [1]. Between 2001 and 2020, pesticide consumption rose by approximately 58 % and causes pesticides resistance [2].

Due to their increased use, resistance to pesticides still poses a threat to the sustainable pest management [3]. The identification of new compounds and their new action sites, like Broflanilide (Fig.1), is a plausible move in the direction of conquering cross-resistance. The insecticide broflanilide, a metamorph of flubendiamide is very potent on resistant Lepidopteran, Thysanopteran and Coleopteran pests [4]. Broflanilide has a high octanol-water partition coefficient (log P = 5.2 at pH 7), low aqueous solubility (0.71 mg/L at 20°C), and high solubility in organic solvents such as acetone [5]. Nonetheless, it is lipophilic meaning that it has high bioaccumulative potential and has a persistent behavior in the environment. In comparison to other pesticides, Broflanilide has less mammalian toxicity and minimal cross-resistance but have greater environmental persistence [6]. Its ability to bioaccumulate in aquatic organisms has also been observed experimentally, and this highlights the necessity to monitor residues continuously and assess its dietary-exposure [7]. In addition, Broflanilide residues are found in aquatic sediments and this aids in trophic transfer and disruption of food webs. Its bioaccumulation by primary consumers can cause imbalance in the eco system, low biodiversity and stress of the ecological system. Hence, there is a need to carry out long-term studies to study about its toxicity and environmental impact.

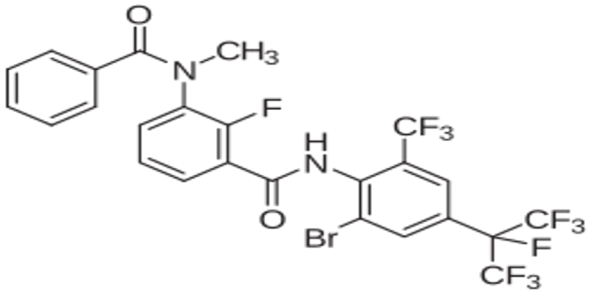

Fig. 1: Structural formula of Broflanilide ((N[2Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl) phenyl]-2-fluoro-3-(N-methylbenzamido) benzamide) (PubChem CID 53341374)

2. Mode of Action

2.1. GABA-Gated Chloride Channel Modulation

Broflanilide, a meta-diamide insecticide, acts as a negative allosteric modulator of GABA-gated chloride channels [8]. Its metabolite, desmethyl-broflanilide (DMBF), binds to a region of the insect GABA-gated chloride channel that is spatially distinct from the binding sites of conventional noncompetitive antagonists such as fipronil and cyclodienes, indicating a different mode of inhibitory action on the receptor [9]. By preventing chloride channel opening, it induces continuous neuronal firing, paralysis, and death in pests.

Broflanilide exhibits minimal cross-resistance with other GABAergic insecticides. Comparative bioassays demonstrate superior control of *Spodoptera litura* and *Plutella xylostella* even in resistant populations [3].

3. Toxicity in Mammals

The toxicity of broflanilide has been reported in mammals and aquatics animals due to its potent ability of bioaccumulation [7]. An *in vivo* study by Nakao and Banba 2016 demonstrated that broflanilide exposure develop neurological signs such as tremors, reduced locomotion, and ataxia, consistent with the compound's interaction with γ-aminobutyric acid (GABA) receptors [10]. Moreover, broflanilide shows low systemic acute oral and dermal absorption. An *in vivo* study has reported LD_{50} values exceeding 2000 mg/kg body weight, showing minimal acute oral toxicity. [11].

It has been demonstrated that chronic exposure of this compound in rodents has been associated with specific organ damage especially liver and kidney. Sub-chronic studies suggest that the toxicological effects of broflanilide are primarily concentrated in the hepatocellular and renal systems [12]. In aquatic models such as *Danio rerio*, broflanilide shows moderate bioconcentration and active elimination following exposure, with significant increase in detoxification enzymes system particularly cytochrome P450 and glutathione-S-transferase [7].

The World Health Organization (2023) reported about the toxicological evaluation of VECTRON T500, the indoor residual spraying formulation of broflanilide [12]. This report suggests that this spray formulation increases the activity of hepatic enzymes that are involved in thyroid hormone metabolism. Hence, these findings conclude that broflanilide may modulate the thyroid–liver axis, which plays a crucial role in maintaining metabolic hormone homeostasis [12]. Moreover, Broflanilide acts selectively on insect GABA receptors (RDL subunit) at a novel binding site. Although its selectivity for mammalian receptor is high, chronic exposure to this compound or its active metabolites may significantly disrupt mammalian GABA_A receptor activity. Moreover, its major metabolite, desmethyl-broflanilide has demonstrated partial permeability across the blood–brain barrier at elevated systemic concentrations, suggesting potential for mild neurobehavioral alterations (Table.1).

Recently *in silico* study including molecular docking and homology modeling (Surflex, Swiss-Model) provide insight into Broflanilide's neuronal interactions. Gao et al. (2020) demonstrated hydrogen bond formation between Broflanilide metabolite and G277 (glycine-277 at GABARs) of insect GABARs. Extending these models to mammalian receptors can predict neurotoxicity potential of this compound. Recently, Wang et al. (2023) suggests that exposure to broflanilide can lead to a formation of reactive oxygen species and hence, increasing oxidative stress at cellular level. This increased oxidative stress cause mitochondrial membrane depolarization and eventually signal the cells to

undergo mitochondria mediated apoptosis. These findings support oxidative stress and mitochondrial dysfunction as secondary mechanisms underlying tissue injury [13]. Meanwhile, certain genotoxicity assays like the Ames test for bacteria confirm that broflanilide does not cause genetic mutations under the specific conditions evaluated [11].

Certain studies also demonstrated the embryotoxic effect Broflanilide on developing fetus. Developmental and reproductive studies suggested decreased pup body weight and delayed growth at maternally toxic doses, though teratogenic malformations have not been consistently observed. Tests on aquatic life show that exposure to broflanilide can spike oxidative stress markers, like malondialdehyde and reactive oxygen species [12].

Table 1: Table showing the toxic effect of Broflanilide.

Toxicological Domain	Findings	Mechanism / Biological Basis	References
Neurotoxicity (Acute Exposure)	Tremors, reduced locomotion, ataxia observed in vivo.	Interaction with γ-aminobutyric acid (GABA) receptors; selective binding to insect RDL subunit at a novel site; potential partial modulation of mammalian GABA_A receptors at high exposure levels.	[10]
Acute Oral Toxicity	LD50 > 2000 mg/kg body weight in rats; minimal acute oral hazard.	Low systemic absorption following single oral exposure.	[11]
Dermal Toxicity	Limited dermal uptake; negligible systemic effects via inhalation under controlled conditions.	Poor percutaneous absorption; low systemic bioavailability.	[12]
Liver and Kidney Toxicity	Hepatocellular hypertrophy and renal tubular degeneration in rodents. Liver and kidney identified as primary target organs.	Organ-specific toxicity associated with hepatic metabolism and renal accumulation. Accumulation in hepatocytes and renal tissues.	[12]
Endocrine-Related Effects	Induction of hepatic enzymes involved in thyroid hormone metabolism, lipid accumulation; altered transcription of hormone-related genes.	Potential interference with thyroid–liver axis; weak endocrine-modulating activity.	[6], [12]
Genotoxicity	Negative in Ames test and mammalian gene mutation assays.	No evidence of mutagenicity under standard test conditions.	[11]
Metabolite (DM-8007) Neurobehavioral Potential	Partial blood–brain barrier permeability at elevated systemic	Systemic distribution of desmethyl-broflanilide (DM-8007) to CNS.	[10]

	concentrations; possible mild neurobehavioral alterations.		
Developmental & Reproductive Toxicity	Decreased pup body weight; delayed growth at maternally toxic doses; no consistent teratogenic malformations.	Developmental effects secondary to maternal toxicity; further DNT studies required.	[12]
Embryotoxicity	Reported adverse effects on developing fetus in experimental studies.	Likely linked to systemic toxicity and oxidative stress mechanisms.	[12]

4. Ecotoxicology in Aquatic Vertebrates

Zebrafish (Danio rerio) act as a major aquatic model for evaluating Broflanilide's toxicity. According to research by Duan et al. (2021), exposure to this chemical leads to developmental deficits, including a slower heartbeat, stunted body length, and edema (fluid buildup) in both the heart area and the yolk sac in developing embryo of zebrafish. LC_{50} (**Lethal Concentration**) values of 3.72 mg/L for embryos and 1.28 mg/L for larvae were reported after 96-hour exposure [14]. Exposure to this pesticide results in caspase-9 activation and upregulation of *tbx5* genes (responsible for heart formation) in embryo of zebrafish, confirming apoptotic and cardiotoxic pathways [7]. Moreover, chronic exposure to developing embryo not only enhances oxidative stress, lipid peroxidation but also results in disruption of antioxidant enzymes (SOD, CAT, and GST) [7].

5. Regulatory Status and Safety Evaluation

The U.S. Environmental Protection Agency (2021) approved broflanilide as a new active ingredient, with safety measures for occupational use. [11]. Additionally, the World Health Organization (2023) evaluated it for public health use specifically in products like VECTRON T500 (indoor residual spraying insecticide) and determined that it poses a low acute risk when used in these specific disease-control formulations [12]. The Australian Pesticides and Veterinary Medicines Authority (APVMA, 2019) have arrived at comparable findings [15]. However, both agencies emphasize the need for additional studies to evaluate its toxicity on human health and environment. However, elaborated experimental studies, environmental impact assessments, and biomonitoring are required to assess safe exposure thresholds and regulatory standards to use this compound as pesticides.

6. Conclusion

Broflanilide exemplifies a dual nature of modern pesticide innovation that offer duality of providing powerful control over resistant pest species with novel gamma aminobutyric acid (GABA) receptor modulation, but also raising new concerns for ecological and mammalian safety. As a Fluorinated meta-diamide insecticide, it shows high efficacy and selectivity but lipophilicity and environmental persistence, increases its bioaccumulation in ecosystem.

Research involving both aquatic life and vertebrates shows that this compound can trigger oxidative stress, heart issues, and growth defects by disrupting mitochondrial and apoptotic pathways. Additionally, *in silico* and preliminary mammalian studies further suggest hepatic, renal, and cytogenetic alterations following exposure to this compound, indicating the need for deeper mechanistic exploration.

While regulatory agencies currently label its immediate risk as low, but the effects of chronic exposure on the immune system, hormones and other organs are still elusive.

A comprehensive understanding of Broflanilide's toxicological behavior requires integration of experimental toxicology, computational modeling, and omics-based approaches. Long-term mammalian studies, interspecies comparative assessments, and biomonitoring are essential to refine safe exposure thresholds and regulatory standards.

Broflanilide represents both innovation and uncertainty. Its sustainable use depends on rigorous scientific evaluation, responsible regulation, and adherence to the precautionary principle—ensuring that agricultural progress aligns with environmental integrity and human health protection.

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