METRIBUZIN-INDUCED OXIDATIVE STRESS, ENDOCRINE DISRUPTION, AND CANCER: ADVANCES IN COMPUTATIONAL TOXICOLOGY

Boulaares Islam[1,2] Derouiche Samir[1*,2]
[1]*Department of Cellular and Molecular Biology, Faculty of Natural Sciences and Life, University of El-Oued, El-Oued 39000, Algeria*
[2]*Laboratory of Biodiversity and Application of Biotechnology in the Agricultural Field, Faculty of Natural Sciences and Life, University of El-Oued, El-Oued 39000, Algeria*
**Corresponding*

Abstract
Metribuzin is classified as a systemic herbicide, belonging to the triazinone chemical group. Its effectiveness stems from its ability to disrupt photosynthesis of plants. It is widely used in agriculture to manage the growth and spread of broad-leaved weeds and grasses. Pesticides are known to induce oxidative stress by generating free radicals and altering the body's antioxidant or oxygen-free radical scavenging enzyme systems. Different types of pesticides share a common ability to cause oxidative stress in various cell types and animal models. The toxic effects of Metribuzin have shown increased oxidative stress and alterations in antioxidant levels in both laboratory settings and living organisms. In the other hand, Pesticides are known to function as endocrine disrupting chemicals interfering with the regular operation of natural hormones. The origin of endocrine disorders can be traced to the hormone-mimicking effects of pesticides at low doses, which lead to changes in the production and breakdown of the body's innate hormones. Exposure to pesticides may increase cancer risk including prostate, lung, ovarian, rectal, testicular, skin, and breast cancers. The toxicity of Metribuzin varies, but it can cause acute poisoning, which is characterized by disruptions in the balance between oxidants and antioxidants, hormonal imbalances, and potential carcinogenic effects. Computational approaches such as molecular modeling, QSAR, and bioinformatics provide cost-effective insights into metribuzin's mechanisms of toxicity, health risks, and risk assessment.

Keywords: Metribuzin, Oxidative Stress, Endocrine System Alteration, Cancer, Computational Approaches.

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Introduction

Agents designed to eliminate pest organisms are known as pesticides. The word's etymology stems from the Latin suffix "cida," meaning "killer" [1]. In agriculture, these chemical substances are employed to destroy or fight against pests, including those that transmit diseases to humans or animals [2]. Agricultural productivity benefits from pesticides, as they help increase crop yields, make food more accessible and affordable, and reduce the prevalence of pests, weeds, and plant diseases [3].
Fungicides, insecticides, and herbicides are the most frequently utilized pesticides, primarily used to manage weeds and pests in agricultural areas [4]. In the present day, pesticides are widely acknowledged as major contributors to environmental contamination [5].
Over the last ten years, there has been a rise in the agricultural use of pesticides [6]. Asian countries account for more than half of the world's pesticide application, followed by the Americas and Europe [7]. Globally, over a thousand different pesticide compounds are employed [8]. The Food and Agriculture Organization (FAO) reports that approximately four million tons of pesticides are utilized worldwide each year [4]. According to the Algerian Association for the Protection of the Environment, Algeria is among the nations with the highest pesticide consumption. Yearly, about 30,000 tons of pesticides are applied in Algeria [9].
The classification of pesticides typically involves several factors, including their chemical nature [10], target pests [11], and mode of action [4]. From a chemical standpoint, pesticides are grouped into various categories, such as organiochlorine, organic phosphorous, carbamate, pyrethrin, and

pyrethroid compounds [10]. Another classification method is based on the pests they target; for example, fungicides are designed to combat fungi, insecticides are used against insects, herbicides target weeds, and rodenticides are employed to control rodents [11]. Furthermore, pesticides are categorized according to their mode of action, which encompasses acetylcholine esterases, chloride channel antagonists and GABA gated channels, sodium channel modulators, juvenile hormone mimics, and mitochondrial complex I electron transport inhibitors [4].
While pesticides are effective in controlling or eradicating target organisms, they are commonly thought to cause substantial unintended damage to humans and non-target species [12]. The presence of pesticide residues in food has sparked concerns about their potential negative effects on human health [13]. Exposure to chemical pesticides has been linked to various harmful health outcomes, including toxic reactions, cancer, skin problems, digestive issues, neurological disorders, respiratory complications, reproductive difficulties, and endocrine disruptions [14]. Consequently, compounds designed to enhance and safeguard food production may unintentionally endanger human well-being [13]. The World Health Organization (WHO) categorizes pesticides into four groups based on their toxicity: extremely hazardous, highly hazardous, moderately hazardous, and slightly hazardous [15].

Metribuzin

Difinition of Metribuzin

Metribuzin, a compound with the chemical name 4-amino-6-tert-butyl-4,5-dihydro-3-methyltio-1,2,4-triazin-5-one, is classified as a systemic herbicide [16], belonging to the triazinone chemical group [17]. Its effectiveness stems from its ability to disrupt photosynthesis by impeding the electron transport chain during this process [18]. This herbicide is utilized both before and after plant emergence to suppress annual grasses and broadleaf weeds [17]. It is widely used in agriculture to manage the growth and spread of broad-leaved weeds and grasses, particularly in crops such as potatoes, carrots, soybeans, and various grains [18]. In 1973, metribuzin was officially sanctioned for use as a herbicide in the United States [19]. Due to its toxicity even at low concentrations, the European Commission has designated it as a potential substitute under directive 540/2011 [18].

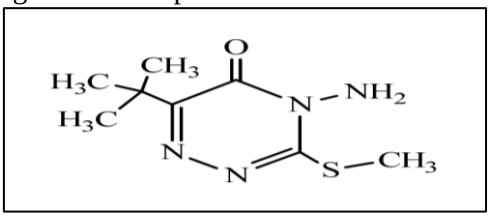

Figure 04: Chemical structure of metribuzin [20]

Physical and Chemical Characteristics of Metribuzin

The extensive physical and chemical characteristics associated with the herbicide identified as metribuzin have been meticulously articulated and are systematically displayed within the framework of **Table 01**.

Table 01: Physical and chemical characteristics of metribuzin

Characteristics	Metribuzin	Reference
Chemical name	4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one	[21]
Type of pesticide	Herbicide	[22]
Chemical family	Triazinone	[23]
Chemical group	Triazine	[24]
Chemical formula	$C_8H_{14}N_4OS$	[25]
Molecular weight	214.3	[26]
Mode of action	PSII inhibition	[27]
Appearance	White crystalline solid	[28]
Odour	Slight sulphur odour	[29]
Half-life	Between 5-50 days	[30]
Melting point	125-126 °C	[31]
Solubility in water	1.05 g/L	[32]

Absorbance wavelength λ (nm]	294 ± 1.0 nm	[33]
Vapor pressure	4×10^{7} mmHg	[34]

Metribuzin Exposure Routes in Humans

Humans can be exposed to pesticides through both direct and indirect means. Direct exposure occurs via agricultural activities, household use, and professional applications, while indirect exposure happens through the food chain [35]. Significant dietary exposure begins early in life through breast milk, as evidenced by high levels of organochlorine pesticides found in human breast milk samples [36]. The main routes of human pesticide exposure include food consumption, air, water, soil, and contact with plants and animals [37]. People who are exposed to pesticides, either directly or indirectly, may suffer from acute toxic effects and long-term health problems [38]. According to Simões et al., more extensive research is needed to examine the health impacts of (non-occupational) pesticide exposure on humans, especially vulnerable groups such as expectant mothers and their babies [39].

There are four primary pathways through which pesticides can infiltrate the human body: dermal, oral, ocular, and respiratory routes [37]. Dermal exposure constitutes a considerable risk for individuals engaged in the application of pesticides [40]. Oral exposure may also occur when individuals fail to observe proper hand hygiene prior to the ingestion of food or the engagement in smoking activities [41]. Respiratory exposure, which takes place through inhalation or respiration, results from the volatile components of pesticides and presents significant health hazards to workers, particularly impacting the nasal, pharyngeal, and pulmonary tissues when substantial amounts of pesticides are inhaled from environmental matrices such as air, water, and soil [38]. The exposure of unprotected ocular tissues to pesticides may arise from accidental splashes of these agents, leading to their penetration into ocular structures and potentially resulting in severe ocular toxicity [42]. **Table 02** illustrates the pathways through which humans encounter pesticide exposure [35].

Table 02: Human routes of pesticide exposure [35]

Routes	**Mechanism of exposure**
Dermal exposure	Pesticide absorption can occur through accidental contact, such as splashing, spillage, or spray mist, especially during the handling phases of mixing, loading, disposal, and equipment cleaning.
Oral exposure	Pesticides may inadvertently be transferred when pouring from a labeled container into an unmarked one, particularly if soft drink or drinking water bottles have been previously contaminated with these chemicals.
Respiratory exposure	Spraying pesticides typically produces finer droplets, especially when traditional application methods are employed.
Eye exposure	Certain agrochemicals have been substantiated to be taken up via the ocular area, resulting in significant and potentially lethal health repercussions.

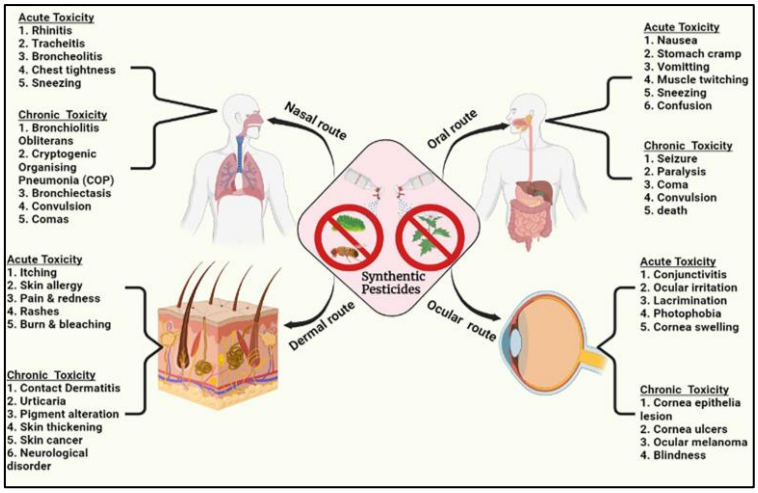

Figure 03: Human pesticide exposure pathways [43]

Effects of Metribuzin on Human Health

Metribuzin-Induced Oxidative Stress

An imbalance between antioxidants and pro-oxidants, favoring the latter, defines oxidative stress [44], which leads to various metabolic and physiological changes, as well as numerous diseases [45]. A wide range of health issues, including cancer, diabetes, heart diseases, neurodegenerative disorders, inflammatory conditions, and aging, are closely associated with oxidative stress [46]. Pesticides are known to induce oxidative stress by generating free radicals and altering the body's antioxidant or oxygen-free radical scavenging enzyme systems [47]. Studies have demonstrated that different types of pesticides share a common ability to cause oxidative stress in various cell types and animal models [48]. Some pesticides can directly produce reactive oxygen species (ROS), such as superoxide anion ($O^{2\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$) [13]. When ROS levels become excessive, they can damage lipids, proteins, and DNA, resulting in mitochondrial stress, followed by apoptosis and cell death [49]. Living cells contain scavenging mechanisms that include superoxide dismutase (SOD), catalase (CAT), peroxidases, other antioxidant enzymes, and low-molecular weight antioxidants [50]. Studies have shown that exposure to pesticides, either singly or in combination, can inhibit antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [51]. The fatty acid composition of organisms may be affected by pesticide exposure through increased lipid peroxidation [52]. Oxidative cellular damage is indicated by lipid peroxidation (LPO), a major factor in cell function loss, as well as DNA damage, enzyme inactivation, and hormone oxidation [53]. Intracellular oxidative stress has been found to be induced by metribuzin [9]. Studies on the toxic effects of metribuzin have shown increased oxidative stress and alterations in antioxidant levels in both laboratory settings and living organisms [54]. The oxidative stress effects of metribuzin across various species were illustrated in **Table 03**.

Table 03: Oxidative stress effects of metribuzin across various species

Species	Dose	Experimental period	Organs	Parameters	Reference
Rabbits	3.22 and 6.44 mg/kg	60 days	Kidneys	MDA, GSH and GST	[6]
Rabbits	3.22 and 6.44 mg/kg	60 days	Liver	MDA, GSH and GST	[9]
Rats	133.33 mg/kg	21 days	Liver, kidney, brain and testis	MDA, GSH and GPx	[5]
Rats	1.3 and 13 mg/kg	90 days	Liver, adipose tissue, muscle and intestine	MDA, carbonyl proteins and GSH	[55]

Metribuzin-Induced Endocrine System Alteration

Pesticides are known to function as endocrine disrupting chemicals (EDCs), interfering with the regular operation of natural hormones [56]. The origin of endocrine disorders can be traced to the hormone-mimicking effects of pesticides at low doses, which lead to changes in the production and breakdown of the body's innate hormones [57]. These substances primarily impact hormonal signaling pathways and the neuroendocrine system, while also generating oxidative stress that contributes to various metabolic conditions [58]. Besides causing toxic effects in the pancreas, pesticides alter hormone release, triggering metabolic disorders [59]. By acting as antagonists to sex hormone functions, pesticides can cause abnormal sexual development and interfere with other vital physiological processes [60]. Many studies have identified triazine herbicides as potential endocrine disruptors [61]. Moreover, findings from animal research suggest that metribuzin may cause harmful health effects, including endocrine disturbances [9]. Jyoti et al. also reported that long-term exposure to metribuzin is associated with a higher occurrence of endocrine abnormalities [62].

Metribuzin-Induced Cancer

Cancer constitutes a significant public health dilemma globally [63] and serves as the foremost source of mortality [64]. Research has shown that some pesticides may increase cancer risk [13]. Epidemiological studies, primarily focused on agricultural workers, have revealed links between pesticide exposure and higher incidence of various cancers, including prostate, lung, ovarian, rectal, testicular, skin, and breast cancers, as well as Non-Hodgkin Lymphoma (NHL), multiple myelomas, and leukemia [65]. According to Cavalier et al., recent evidence suggests causal relationships between pesticide exposure and cancer, with the strongest support for connections to acute myeloid leukemia (AML) and colorectal cancer (CRC), as these associations were consistently observed across multiple studies [66]. In 1998, the Environmental Protection Agency (EPA) classified metribuzin as group D, meaning there was insufficient evidence to determine its human carcinogenicity [67]. However, research by Delancey et al. suggested a potential association between metribuzin use and certain lymphohematopoietic cancers in males [68].

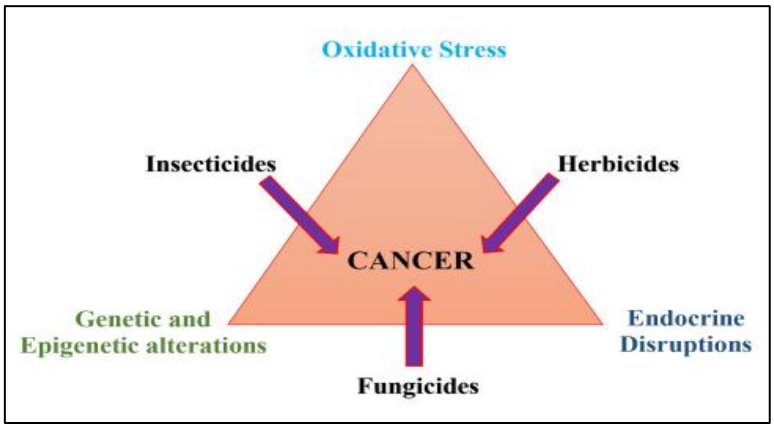

Figure 02: Key molecular mechanisms involved in the cancer-causing effects of pesticides [69]

Computational Approaches in Assessing Metribuzin Toxicity and Health Risks

Recent advances in computational toxicology have provided valuable tools for understanding and predicting the health risks associated with pesticide exposure, including metribuzin. In silico methods such as molecular docking, quantitative structure–activity relationship (QSAR) modeling, and molecular dynamics simulations enable researchers to explore the interaction of metribuzin with key biomolecules involved in oxidative stress pathways, endocrine regulation, and carcinogenesis. Bioinformatics and systems biology approaches further allow the integration of large-scale omics data to identify potential biomarkers and disrupted signaling networks. Additionally, predictive software platforms support the evaluation of metribuzin’s environmental fate, bioaccumulation, and long-term human health risks. By complementing experimental studies, these computer applications offer cost-effective, rapid, and mechanistic insights that enhance risk assessment and guide the development of safer agricultural practices. Computational approaches such as molecular modeling, QSAR, and

bioinformatics provide cost-effective insights into metribuzin's mechanisms of toxicity, health risks, and risk assessment.

Conclusion

Metribuzin, a pesticide commonly employed to manage broadleaf and grassy weeds in vegetable crops, has been found to pose significant health risks to humans and animals. People can be exposed to this pesticide through various routes, including direct contact during agricultural work, household usage, and professional applications, as well as indirectly through the food supply chain. The toxicity of metribuzin varies, but it can cause acute poisoning, which is characterized by disruptions in the balance between oxidants and antioxidants, hormonal imbalances, and potential carcinogenic effects.

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