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Review of Metribuzin Pollution and Its Impact on Oxidative Stress in Cardiovascular Diseases

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Abstract

Metribuzin is an herbicide belonging to the triazinone group, which is incorporated as a weed killer in wheat, potatoes, tomatoes, etc. The aim of this study was to evaluate the effect of metribuzin as a cause of cardiovascular disease. Human exposure to Metribuzin occurs through inhalation and ingestion, usually in agricultural settings. However, few studies have evaluated population exposure to this herbicide. Metribuzin can accumulate in soil and water and cause damage to plants and animals. Furthermore, the herbicide metribuzin has a highly variable toxicity, in the short term it can cause acute poisoning that can cause difficulty in breathing and drowsiness but high exposures can cause various cardiovascular pathologies including coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism. Some organophosphate compounds, such as diazinon, can trigger oxidative stress in the cardiovascular system. Accordingly, it is necessary for farmers to avoid its use and replace it with biological fertilizers that are less harmful to human and animal health.

Keywords: Pesticides; Metribuzin; Oxidative Stress; Cardiovascular Diseases

Abbreviations

CVD: Cardiovascular Disease; WHO: World Health Organization; ROS: Reactive Oxygen Species; CHD: Coronary Heart Disease; $O_2^{\bullet-}$: Superoxide Radical; H_2O_2: Hydrogen Peroxide; $HO^{\bullet}$: Hydroxyl Free Radical; GSH: Glutathione; CAT: Catalase; GST: Glutothione Transferase; SOD: Superoxide Dismutase; GPx: Glutothione Peroxidase; GR: Glutathione Reductase; MDA: Malondialdehyde; GOT: Glutamyl Oxaloacetic Transaminase; LDH: Lactate Dehydrogenase; CPK: Creatine Phosphokinase.

Introduction

In agriculture, pesticides are chemical compounds utilized to eliminate or manage pest populations, including those that act as disease vectors for humans or animals [1]. These substances are widely recognized as significant contributors to environmental pollution in contemporary society. While designed to be fatal to pests, pesticides can also have detrimental effects on non-target organisms, including humans, upon ingestion [2]. The application of agricultural pesticides has seen an upward trend in recent years [3]. The

Algerian Association for the Protection of the Environment reports that Algeria is one of the highest consumers of pesticides, using approximately 30,000 tons annually [4]. The discovery of pesticide residues in food has generated concern regarding their potential negative impact on human health. Several pesticides have been associated with a range of health issues, such as developmental abnormalities, endocrine disruption, neurological impairment, and certain forms of cancer. Consequently, substances intended to enhance and protect food production may inadvertently jeopardize human well-being [5].

Metribuzin, a compound categorized as an asymmetric triazine characterized by the chemical formula 4-amino-6-(1,1-dimethyl)-3-(methylthio)-1,2,4-triazin 5(4H)-one, received regulatory approval for herbicidal application in the United States in the year 1973 [6]. This compound operates by obstructing electron transport mechanisms that are critical for photosynthesis, thereby efficiently controlling broadleaf weeds and grasses across a diverse array of crops, turfgrasses, and non-agricultural environments [7]. Metribuzin finds extensive use in the agricultural sector, particularly for crops like potatoes, soybeans, peas, tomatoes, and lentils [8]. This herbicide's versatility allows for application both pre- and post-emergence to effectively manage annual grasses and broadleaf weeds [9]. The recommended dosage fluctuates based on soil characteristics and regional factors [10]. Despite its efficacy, concerns have been raised regarding metribuzin's potential adverse impacts on human health, aquatic ecosystems, and domesticated animals [11].

The human body's circulatory system is often viewed as its primary means of transportation. This vital system ensures the continuous flow of life throughout the body. To provide safe and effective care, it is crucial to comprehend the circulatory system's roles and its intricate network of veins, arteries, and capillaries [12]. Cardiovascular disease (CVD) encompasses a broad spectrum of conditions affecting the heart and blood vessels [13]. The World Health Organization (WHO) reports that CVDs claim the lives of roughly 17.9 million individuals annually, representing one-third of all deaths worldwide [14]. Research indicates a possible connection between exposure to pesticides and chronic health conditions, particularly those affecting the cardiovascular system [15]. The primary objective of the research endeavor articulated herein is to conduct an in-depth examination of the implications and consequences associated with oxidative stress that is induced by metribuzin, particularly focusing on its intricate effects on the underlying mechanisms that contribute to the development and progression of various cardiovascular diseases.

Metribuzin

The compound 4-amino-6-tert-butyl-4,5-dihydro-3-methyltio-1,2,4-triazin-5-one, commonly known as metribuzin, is categorized as a systemic herbicide [16], and falls under the triazinone chemical group [9]. Its mode of action involves interfering with photosynthesis by blocking the electron transport chain in this process [17]. This herbicide is applied both pre- and post-emergence to control annual grasses and broadleaf weeds. It is extensively employed in agricultural settings to curb the proliferation of broad-leaved weeds and grasses, particularly in crops like potatoes, carrots, soybeans, and various grain species [17]. Metribuzin received official approval for use as a herbicide in the United States in 1973 [6]. Given its toxicity even at low levels, the European Commission has identified it as a potential candidate for substitution under directive 540/2011 [17]. The toxicity mechanisms typical of most xenobiotics, including herbicides and environmental pollutants, are exemplified by metribuzin, a foreign chemical compound. These mechanisms involve compromising the body's overall antioxidant defense system and encouraging lipid peroxidation through enhanced free radical generation [1]. The harmful effects of metribuzin are primarily facilitated by reactive oxygen species (ROS), which interact with various biological molecules [18]. Research has demonstrated that metribuzin induces intracellular oxidative stress [4]. Studies examining the toxic impact of Metribuzin (Figure 1) have observed increased oxidative stress and changes in antioxidant levels in both experimental settings and living organisms [11]. Oxidative stress arises when an imbalance occurs between the production and accumulation of ROS in cells and tissues, and the biological system's ability to detoxify these reactive products [19]. This phenomenon plays a crucial role in contributing to physiological and metabolic alterations, as well as various bodily diseases [20].

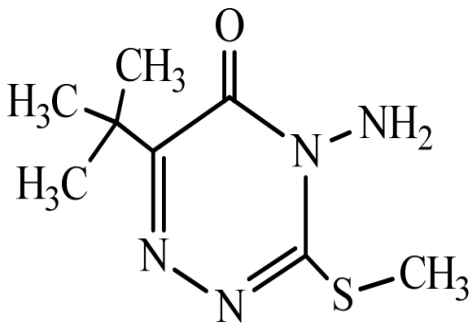

Figure 1: Chemical structure of metribuzin [21].

Table 1 provides a detailed and systematic presentation of the extensive physical and chemical characteristics associated with the herbicide metribuzin.

Characteristics	Metribuzin	Reference
Chemical name	4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one	[22]
Type of pesticide	Herbicide	[23]
Chemical family	Triazinone	[24]
Chemical group	Triazine	[25]
Chemical formula	$C_8H_{14}N_4OS$	[26]
Molecular weight	214.3	[27]
Mode of action	PSII inhibition	[28]
Appearance	White crystalline solid	[29]
Odour	Slight sulphur odour	[30]
Half-life	Between 5-50 days	[31]
Melting point	125-126 °C	[32]
Solubility in water	1.05 g/L	[33]
Absorbance wavelength λ (nm)	294 ± 1.0 nm	[34]
Vapor pressure	4×10^7 mmHg	[35]

Table 1: Physicochemical properties of metribuzin.

Cardiovascular Diseases

Cardiovascular disease (CVD) encompasses a broad spectrum of conditions affecting the heart and blood vessels [13]. The impact of CVD is particularly severe in developing nations, where it contributes significantly to increased mortality and morbidity rates, posing a global health challenge [36]. In the United States, CVD claims a life every 39 seconds, surpassing cancer as the leading cause of death [12]. The term CVD covers various interconnected pathologies, including coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism [37]. Cardiovascular diseases (CVD) are multifaceted conditions with diverse pathophysiological mechanisms, and elevated oxidative stress is considered a potential common underlying cause [38]. The primary types of cardiotoxic reactive oxygen species (ROS) include superoxide radical (O2•-), hydrogen peroxide (H_2O_2), and hydroxyl free radical (HO•) [39] and [40]. In the cardiovascular system, oxidative stress can trigger various disorders such as atherosclerosis, ischemic heart disease, hypertension, congestive heart failure, cardiac hypertrophy, and cardiomyopathies by inflicting damage on cardiovascular tissues (Figure 2). This stress alters cell membrane permeability and disrupts cardiovascular cell function, particularly the uptake of Ca+ ions, which is crucial in both healthy and diseased states [41]. Additionally, hypercholesterolemia and hypertriglyceridemia are well-established risk factors for cardiovascular disease [42].

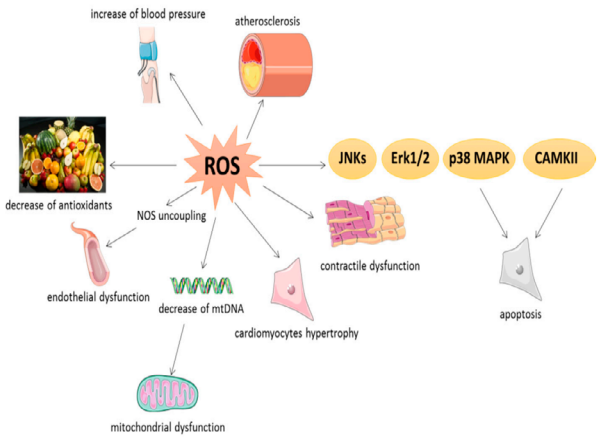

Figure 2: Pathological effects of oxidative stress on cardiovascular systems [43].

Discussion

An imbalance between antioxidants and pro-oxidants, favoring the latter, results in oxidative stress [12] and [44]. This phenomenon is integral to various physiological and metabolic changes, as well as numerous health issues [45]. The introduction of foreign substances can compromise antioxidant defense mechanisms, such as glutathione (GSH), catalase (CAT), glutothione transferase (GST), and superoxide dismutase (SOD), and leading to premature and excessive free radical production. This process ultimately damages macromolecules, including DNA [1]. Pesticides can trigger oxidative stress by generating free radicals and modifying antioxidant or oxygen free-radical scavenging enzymes, including superoxide dismutase (SOD), catalase (CAT), glutothione peroxidase (GPx), glutathione reductase (GR), and glutothione transferase (GST) [46]. Studies have indicated that specific pesticides can stimulate the production of reactive oxygen species (ROS), inducing oxidative stress in organisms that are not the intended targets [11]. Furthermore, metribuzin exposure has been correlated with the occurrence of oxidative stress within cellular environments [4]. The creation of oxygen-free radicals is regarded as the principal mechanism underlying pesticide toxicity, fostering an increased generation of reactive oxygen and nitrogen species. This process leads to elevated lipid peroxidation across diverse tissues and a subsequent decrease in antioxidant defenses [47]. As a result, scientists have suggested that lipid peroxidation plays a key role in the toxic effects of pesticides [48]. This biochemical process, which can impair the integrity and functionality of cellular membranes, is initiated when free radicals attack lipids and is typically evaluated by measuring malondialdehyde (MDA) concentrations [2]. Pesticides and other foreign substances can trigger acute inflammation, which in turn enhances their harmful effects on various physiological systems [20]. Animal studies have shown that metribuzin exposure may lead to negative health outcomes, including changes in the histological structure of tissues [49]. Certain pesticides are known to cause cellular toxicity through mechanisms involving oxidative responses, which can lead to various detrimental effects. These include both programmed and unplanned cell death, harm to lipids in cell membranes, disruption of metabolic processes, changes in various signaling pathways, or alterations to tight junctions [50]. Research indicates a possible connection between exposure to pesticides and chronic health conditions, particularly those affecting the cardiovascular system [15]. For instance, some organophosphate compounds, such as diazinon, can trigger oxidative stress in the cardiovascular system. This stress can cause significant changes in proteins, including their accelerated breakdown, potentially resulting in arrhythmias (Figure 3). These arrhythmias may occur due to imbalances in electrolytes or disruptions in the mechanisms responsible for repairing and healing damaged heart muscle tissue [51]. The primary myocardial enzymes measured are glutamyl oxaloacetic transaminase (GOT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK). When cardiomyocytes undergo inflammation (myocarditis) or necrosis (myocardial infarction) due to various causes, these enzymes from heart cells can enter the bloodstream, leading to an increase in their activity (concentration) [52]. The heart is particularly vulnerable to oxidative stress from free radicals because it contains a greater concentration of mitochondria and lower levels of antioxidant enzymes compared to other organs [40].

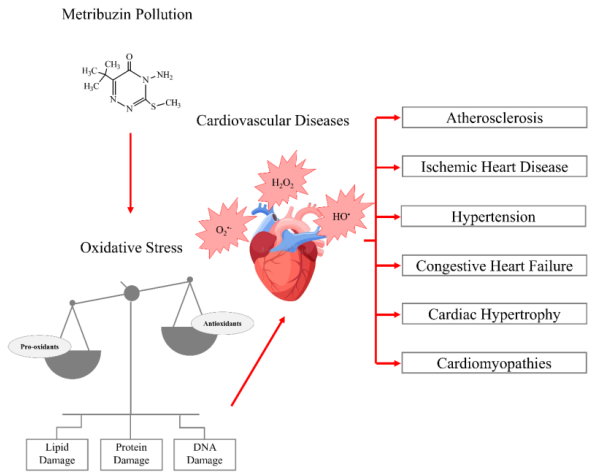

Figure 3: Effects of metribuzin pollution on oxidative stress in cardiovascular diseases.

Conclusion

This comprehensive information provides a substantial understanding regarding the deleterious effects associated with the exposure to metribuzin, thereby enabling us to unequivocally establish the significant contribution of these particular pesticides to the development of cardiovascular diseases, even when administered in minimal dosages, which is particularly concerning not only in the context of individuals who have experienced occupational exposure, but also extends to the broader general population who may inadvertently consume food products or water that has been contaminated with these harmful pesticides, thus posing a serious threat to public health at large.

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