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Review on Toxicity, Mechanisms and Health Effects of Herbicides and Prevention Mechanisms

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Review Article

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Abstract

In agricultural crop production, herbicides are typically used to prevent or control weeds and other plant pathogens by reducing crop losses and maintaining high product quality. This brief overview sheds light on the level of toxicity, mechanisms of toxicity, health effects and prevention strategies. Three main levels of toxicity have been identified in herbicides: acute (short-term exposure), sub-chronic (medium-term exposure), and chronic (long-term exposure). These levels of toxicity have detrimental effects on humans, animals, and the environment. Herbicides must be handled and administered appropriately to minimize or completely prevent their negative side effects. It is recommended to manage herbicide to its minimum residue level while using them in agriculture. On the hand, certain mechanisms of action must be followed including contact, absorption, movement, toxicity, and death in order to be effective in management of weed by herbicides. This mechanism of actions of herbicides are also applied to humans and animals too. Improper usage of herbicides has adverse health effects on humans such as carcinogenic, cardiovascular, respiratory, hormonal, metabolic, cellular and neurological effects. In order to eliminate or minimize their effect the preventive safety mechanisms/strategies such as employing alternative and less herbicide-dependent cropping systems, properly using all certified personal protective equipment (PPE), proper packaging and package leaflet, proper labeling and giving general awareness about the use or handle of herbicide for farmers or any others who are not familiar with the use of herbicides must applied before or after handling of herbicides. In order to minimize or totally avoid the negative impacts of herbicides on humans, animals, and the environment, it is not just the responsibility of farmers but also of other stakeholders (agricultural experts, policymakers, etc.).

Keywords: Acute; Chronic; Exposure; Herbicide; Preventive

Introduction

Agriculture must be intensified in order to meet local and global food demand [1-3]. It is strongly linked to dietary changes, instability in society, population growth, and climate change, all of which have a negative impact on food security and the environment and have a significant effect on both human health and the environment [4,5]. The sustainable development goal number two (SDG2), a goal that calls for the eradication of hunger and malnutrition by 2030, is severely hampered by food insecurity in developing nations, particularly in Africa [6]. As a result of unsustainable agricultural practices like the uncontrolled expansion of arable land, low agricultural productivity in regions that are developing like Africa fails to meet the continent's growing food demand. This leads to additional environmental issues like soil erosion, marine pollution, greenhouse gas emissions, and biodiversity loss [7]. Studies reveal that

future population growth is expected to be highest in areas with low agricultural productivity [8]. One strategy for address low productivity and food quality in order to meet the demand for food imposed by population growth and changing dietary patterns is the appropriate application of herbicides. Agriculture and livestock production are two methods of producing food. The extent to which other plant, animal, microbial, and parasitic biological systems compete with the species of interest for production for resources found within the environment has a significant impact on the yield of food production [9].

Weeds are a serious concern in agricultural systems across the world, causing huge economic losses through decreasing crop yields and quality of the harvest if they are not managed in proper manner [10,11]. For this reason, variety of plant protection chemicals such as herbicides have been used in agriculture; their potential to improve crop quality and productivity by eliminating weeds has grown significantly in recent decades [12]. Herbicides are phytotoxic compounds that are used to kill or inhibit the growth of weeds. They account for over 48% of total use of pesticides worldwide and their utilization showed to be the quickest and cheapest approach by avoiding by hand weeding, which was slower and needed more human resources, as well as lowering fuel expenses for machines [13].

They vary in their specificity. Herbicides that are either selective or non-selective are the two main categories of weed control [14]. Herbicides that are highly specific and best suited for eliminating one particular type of plant without destroying the others are known as selective herbicides (e.g., 2,4-D, mecoprop, dicamba, etc.), which is an efficient way to manage weeds in fields or crops. However, these herbicides are ineffective against turf grasses. On the other hand, non-selective herbicides, such as glyphosate, glufosinate, paraquate etc., destroy every plant they come into contact with [14]. They serve in the clearance of railroad embankments, waste grounds, and industrial areas. Many factors, including plant physiology, soil topography, environment, application technique and timing of administration, influence how selective or non-selective herbicides are Varshney, et al. [15]. A successful weed removal and control strategy must take into account a number of factors, including site of action, detoxification, translocation, metabolism, and absorption [16,17]. Herbicides must pass through the following stages in order for their mode of action to be effective in killing weeds, as shown in the Figure 1 [18]. Herbicides' mode of actions includes inhibiting, halting, disrupting, or mitigating normal plant growth [19,20].

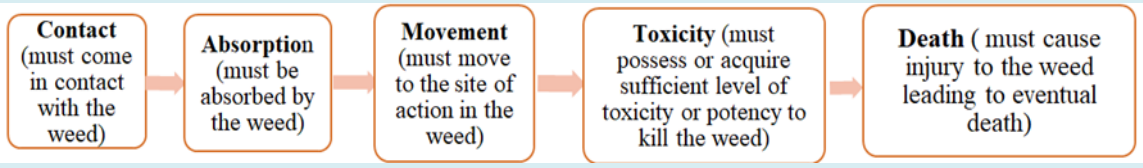

Figure 1: Mechanism of actions of herbicides on weeds.

Herbicides, like other pesticides, can be classified into several classes based on their mode of action (i.e., selective herbicides that inhibit the growth of a specific type of weed and nonselective herbicides that control the growth of both wanted and unwanted plants), activity (i.e., control, suppression, crop safety, and defoliant), timing of application (e.g., preplant, preemergence, and postemergence), method of application (e.g., soil or foliar applied), mechanism of action (e.g., lipid synthesis inhibitors, amino acid synthesis inhibitors, growth regulators, photosynthesis inhibitors, pigment inhibitors, cell membrane disrupters, seedling root/shoot growth inhibitors, nitrogen metabolism inhibitors), chemical structure (e.g., phenoxyacids, bipyridinium, dinitroaniline, chloroacetamide, carbamate, phenyl acetic acid, benzonitrile, urea, uracil, glyphosate, triazine, and phthalic acid) [21,22]. Herbicides can be administered before or after planting in agricultural fields. They are most often used in row-crop farming, where they are applied before or during planting to increase crop yield while reducing other vegetation. Although herbicides boost food production, there is a need to use them correctly in order to safeguard humans as well as the environment. Farmers' understanding of herbicide application procedures, timing, and dose is frequently poor [23].

Herbicide exposure is regular, particularly among applicators who use these chemicals on daily basis [23]. Farmers in developing countries face enormous exposure risks due to the use of toxic chemicals that are banned or restricted in other countries, incorrect application techniques, poorly maintained or completely inappropriate spraying equipment, inadequate storage practices, and the reuse of old pesticide containers for food and water storage [24,25]. Toxic chemicals have serious adverse effects on humans, animals, and the environment. This is particularly the case of chemicals used in agriculture, such pesticides (herbicides, fungicides, insecticides, rodenticides) which have either been banned or severely restricted. Several agricultural food products were found to contain highly toxic pesticides, including anthraquinone, carbendazim,

malathion, omethoate, and chlorates. Pesticides that is extremely hazardous and persistent like DDT, HCB, and chlordecone, are mostly found in products that originate from animals [26]. In Europe, over 74 percent pesticides that were marketed in various regions of the world were banned from usage due to health and environmental concerns [26]. The residues were detected in 5811 food samples, which accounted for 6.2% of all the samples analysed. The bulk of these samples (75.2%) were plant-based items. Brazil, Malaysia, Morocco, Vietnam, India, Iran, and China are among the top 15 countries importing pesticides that are prohibited (severely restricted chemicals) in Europe. The countries of origin of the products are those where the highest frequency of banned pesticides (30-47% range) were found [26]. Herbicides enter the body by three major routes: dermal (via the skin or eyes), respiratory (via inhalation into the lungs), and oral (via eating) [23]. Certain precautions should be taken before, during, and after herbicide treatment. Most herbicides are very hazardous by nature since they are designed to kill specific organisms and hence pose a risk of damage. Herbicides and other pesticides continue to persist in our environment as a result of careless or intentional use, and the use of pesticides has raised serious concerns not only about actual effects on human health, but also about impacts on wildlife and sensitive ecosystems, as well as non-target organisms [27,28]. This review article covers toxicity, mechanisms of toxicity, health effects, and some preventative strategies that we can use to minimize or avoid exposure as well as adverse health effects from the herbicides.

Toxicity and Hazard of Herbicides

Herbicides must be toxic or poisonous in order to be effective against the pests they are designed to control. They are poisonous and may negatively impact humans, animals, other organisms, and the environment. As a result, people who use pesticides or come into regular contact with them must understand the relative toxicity and actual adverse health effects of each product they utilize. There is a difference between the words "toxicity" and "risk" in terms of herbicide safety. Toxicity is defined as a material's inherent toxic ability [29]. Toxicological studies assess a compound's toxicity, which is expressed in quantitative terms such as LD50 or LC50 (lethal dose or concentration 50%, i.e., the dosage or concentration at which a material will kill 50% of a reference organism). The risk (or hazard) of a material is determined not only by its toxicity, but also by its possibility of exposure when applied.

Toxicity is the ability of a substance to cause illness or even death, whereas risk (hazard) is the combination of toxicity and exposure (Figure 2). As therefore, the risk (hazard) associated with a certain pesticide is determined by its toxicity as well as the amount and type of exposure experienced. To estimate risk (hazard), information on both toxicity and exposure is needed. Normally, the actual for detrimental effects on humans caused by extremely toxic herbicide is greater than that of less toxic herbicide [29]. Other factors, such as the concentration of the herbicide in a formulation, the period of exposure to the herbicides, and the route of entry into the human body, are important in the potential for poisoning [30]. Clearly, a pesticides applicator has limited influence over an herbicide's toxicity, but considerable influence over risks associated with its usage might be expected. For example, a sealed container of a highly toxic herbicide poses little risk before the seal is broken. Even if the container is opened, the risk is low, unless the end user is not wearing protective gear. The risk, however, can be severe if the container is damaged or leaking, or if suitable protective equipment is not used,

Figure 2: Risk is a combination of toxicity and exposure.

Classification of Toxicity Based on The Type of Exposure

Herbicides toxicity in humans may be classified into three groups based on the length of time exposed to the pesticide and the rate at which toxic symptoms appear [31]. As thus, workplace or environmental exposure may be classified as acute, sub-chronic, or chronic (Table 1). When a farmer is exposed to a single dosage of a pesticide, this is known as acute exposure, and the impact is known as acute toxicity. Acute toxicity describes how poisonous a pesticide is to an organism following a single short-term exposure.

Type	Meaning
Acute toxicity	Occurring from a single incident of exposure (single short-term exposure)
Sub-chronic toxicity	Occurring from repeated incidents of exposure over several weeks or months (intermediate exposure, normally less than the lifetime of the exposed organism)
Chronic toxicity	Occurring from repeated incidents of exposure for many months or years (repeated long-term exposure, sometimes lasting for the entire life of the exposed organism).

Table 1: Types of toxicity based on the extent of exposure to herbicides.
Source: Damalas, et al. [32]

The signal words on the product label are selected based on the herbicide's acute toxicity. Sub-chronic toxicity refers to a chemical compound's actual to create hazardous health consequences for more than a year but less than the lifetime of the exposed organism. Chronic exposure occurs when an individual is regularly exposed to herbicide. This impact can be categorized as chronic dermal, chronic oral or chronic inhalation toxicity (Table 2).

Categories	Signal word	Oral (mg/kg)	Dermal (mg/kg)	Inhalation (mg/L)
I-Highly toxic	Poison	0 to 50	0 to 200	0 to 0.2
II-Moderately toxic	Warning	50 to 500	200 to 2000	0.2 to 2.0
III-Slightly toxic	Caution	500 to 5000	2000 to 20000	2.0 to 20.0
IV-relatively non-toxic	Caution	5000+	20000+	20+

Table 2: Types of acute toxicity measures and warnings.
Source: Damalas, et al. [32]

Chronic toxicity is the capacity of herbicide to cause unfavourable health effects over an extended period of time, generally following repeated or continuous exposure, which may last for the entire lifespan of the exposed organism. This sort of pesticide toxicity is of concern not only to the general public, but also to individuals who work directly with pesticides, because to the possible exposure to pesticides found on/in food, water, and the air. It is often assessed in experimental the conditions after three months of either continuous or occasional exposure. A chemical with high acute toxicity may not always have high chronic toxicity. Chronic toxicity is an herbicide's tendency for causing adverse health effects over an extended period of time. Continuous absorption of the same small dose every day can cause major chronic sickness or even death. Acute and chronic toxicity have dose-dependent effects, the higher the dose, the greater adverse effects. When characterizing herbicide toxicity, it is obvious that information for single-dose (acute) and long-term (chronic) effects, as well as information for intermediate length exposure, is required. Chronic exposure is referred to as continuous exposure to low levels of a toxicant, whereas delayed toxicity might be caused by a single dosage or a brief exposure event, resulting in a prolonging effect [33]. As a result, issues related to dose, duration, and exposure for delayed toxicity are not identical to those concerning chronic exposure. Indeed, epidemiological studies are critical for detecting additional cases of delayed toxicity.

Mechanisms of Herbicides Toxicity

Herbicide and other related chemical toxicity to non-target organisms is still a serious concern across the world. Because herbicides may cause several physiological and biochemical changes when enter the body, search for mechanisms of their toxicity can be considerably more difficult than expected. Perhaps the mode of action of herbicides is one of the most dependable techniques for researching the mechanisms of their toxicity. Herbicides may adversely affect the body by interfering with hormones or messengers [34], affecting the nervous system (e.g., Organochlorine herbicides) [35], or directly or indirectly altering the activities of specific enzymes [36,37]. Due to their autoxidation by molecular oxygen, a variety of pesticides could directly enhance ROS (Reactive Oxygen Species) levels in living organisms [35]. Mostafalou, et al. [38] have conducted a significant amount of time systematically catalog the molecular mechanisms of herbicide toxicity. The studies they conducted yielded a theoretical understanding of the causal links between pesticide exposure and human chronic illnesses caused by DNA damage [38].

Herbicide misuse has caused human health issues, and the mechanisms of toxicity of many herbicides to non-target species are still unknown. Understanding the mechanism of action of herbicides might be a useful tool for

improving their effectiveness; application ways in various agricultural practices, dealing with weed resistance issues, and investigating hazardous qualities [39]. Most herbicides kill plants in different ways since they are designed to target specific plant metabolic pathways (e.g., photosynthesis, plant hormone action, cell division regulation, etc.) [35,40]. However, before killing the target, the herbicide must make contact with the site of action in the weed; otherwise, its actions become useless. Cellular mechanisms that contribute to the manifestation of toxicity. A series of events that begins with exposure and involves several interactions between the toxicant and the organism. The toxicant is the substance that eventually interacts with the endogenous target molecule and/or alters the biological environment. The severity of the toxic effects depends on both concentration at the target site and persistence (time of exposure) at the target site. There are four main steps in toxicity mechanisms. Delivery; site of exposure to the target (1); reaction of the ultimate toxicant with the target molecule (2); cellular dysfunction and resultant toxicity (3) and repair or disrepair (4) (Figure 3).

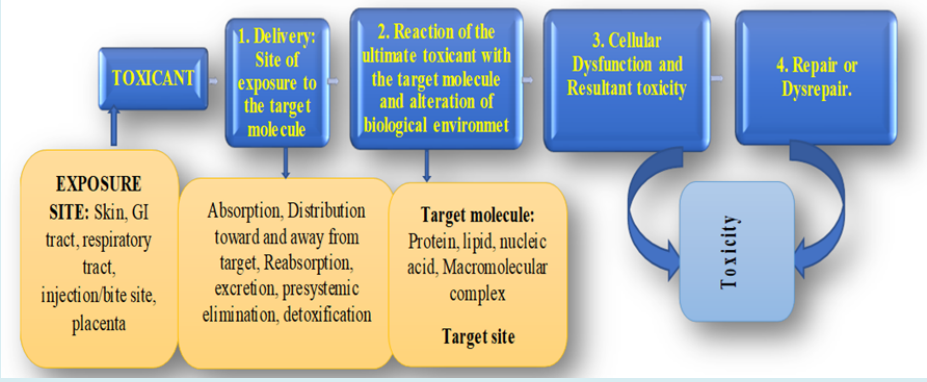

Figure 3: General scheme for mechanisms of pesticides (herbicides) toxicity.

Health Effects of Herbicides on Humans

Herbicides are used extensively across the world. Herbicides exposure through food intake is estimated to be five times greater in size than other exposures such as air and water [41]. According to the World Health Organization, fruits and vegetables are the most widely eaten food group, accounting for 30% of total food intake. Furthermore, because fruit and vegetables are primarily consumed raw or semi-processed, it is expected that they contain higher levels of pesticide residue than other plant-based food groups, such as bread and other cereal-based foods [42,43]. Herbicides can enter the body by skin contact, ingestion, or inhalation. Pesticides can be metabolized, excreted, stored, or bio accumulated in body fat in humans and animals [44,45]. Herbicide misuse has been linked to diabetes, reproductive disorders, neurological dysfunction, cancer, respiratory disorders, dermatological, gastrointestinal, and endocrine effects [38,44,46]. Herbicides account for the largest share of pesticides used globally [47,48].

Herbicides' adverse effects on human health are determined by a number of factors, including the chemical class of those compounds, dose, duration, and route of exposure. Herbicides can be toxic to people at both high and low concentrations [49]. Herbicide exposure can cause a variety of human health effects, including cancer, reproductive, developmental toxicity, acute toxicity [48,50], neurodegenerative [51], and respiratory effects [52], some of which, such as glyphosate, are highly controversial [53,54]. Furthermore, excessive levels of occupational, accidental, or intentional chemical exposure, such as herbicides, can lead to hospitalization and death [55].

Many herbicides are banned in various countries each year owing to their negative effects on human health; however this is done after tonnes of herbicides have been applied and distributed across the environment. Several herbicides had to be banned because they caused major health problems. This is not to say that the herbicides allowed for use are without risk, because their direct and indirect effects are difficult to assess, difficult, and costly. Some banned herbicides, such as paraquat, can cause diseases and even death [56]. The World Health Organization reported that poisoning cases caused by pesticide are approximately three million people each year [57]. Herbicides have two major types toxicity: acute and chronic. In terms of their toxicity, the herbicides 2,4- dichlorophenoxyacetic acid (2,4-D) and 3,6-dichloro-2-methoxy benzoic acid (Dicamba) belong to the Auxinic group and are categorized as class II members (moderately dangerous) by Syguda, et al. [58]. Dicamba and 2,4-D have been shown to generate Sister chromatid exchanges (SCEs) in mammalian cells and to be clastogenic [59]. The US EPA has classified dicamba (2-Methoxy-3,6-dichlorobenzoic acid)

as a highly toxic toxin has a negative reproductive impact and a cholinesterase inhibitor [60].

In cancer risk studies, dioxin pollution and exposure to 2,4-D in combination with other pesticides produced a wide variety of the effects [59]. Hernández, et al. [52] found that Organochlorine herbicides can cause endocrine disruption via many mechanisms, including agonist or antagonist actions on various receptors. Triazines, such as atrazine, simazine, and ametryn, are another class of herbicides associated with endocrine disruption and reproductive toxicity [61,62]. Furthermore, Kettles, et al. [63] discovered a probable statistical link between triazine herbicides and breast cancer incidence. Atrazine is the most well-known triazine, and it is a commonly used herbicide that has been linked to oxidative stress [62], cytotoxicity [64], and dopaminergic effects [65]. Furthermore, atrazine has been linked to reproductive toxicity [66] and sexual maturation delays [67].

Organophosphates, which were advanced as a more ecological alternative to organochlorines [68], incorporate an extraordinary variety of herbicides, the most common of which is glyphosate. Glyphosate is the chemical substance that's the best-selling herbicide in human history and the world and constitutes 60% of the broad-spectrum herbicide sales [56]. Glyphosate-based herbicides, such as the well-known "Roundup," can cause DNA harms and act as endocrine disruptors in human cell lines [69] and in rat testicular cells [70], cause harms to cultured human cutaneous cells [71], and advance cell passing within the testicular cells of test animals [70,72]. There is also evidence for the ability to affect cytoskeleton and their intracellular transport [73]. Correlation analyses have raised concerns about a possible link between glyphosate use and various health and disease effects, such as hypertension, diabetes, stroke, autism, kidney failure, Parkinson's and Alzheimer's disease and cancer [74].

In addition, there are concerns about the possibility that glyphosate may cause gluten intolerance, health conditions associated with essential trace metal deficiencies, reproductive problems, and an increased risk of developing diabetes. Non-Hodgkin lymphoma [75]. Population-based studies have linked exposure to organophosphate herbicides to serious health effects, including cardiovascular disease [64], male reproductive system effects [76], nervous system effects [68,77], dementia effect [78], and possible increased risk of non-Hodgkin's lymphoma [79]. In addition, prenatal exposure to organophosphates is associated with shortened gestational age [79] and neurological problems in children [80].

Paraquat (PQ, 1,1'-dimethyl-4,4'-bipyridinium dichloride) is a highly toxic quaternary ammonium herbicide widely used in agriculture. Mortality from PQ poisoning reaches 60-80%, mainly due to acute lung injury and progressive pulmonary fibrosis [81,82]. PQ cannot be excreted normally and continues to accumulate in the body. As a result, other organs such as the liver, heart, and lungs are also affected, leading to multiple organ failure [82]. According to He, et al. [83], paraquat, the second most widely used herbicide in the world, selectively accumulates in human lungs by causing oxidative damage and fibrosis, resulting several individuals to death. Chronic exposure to this herbicide has also been associated with hepatic lesions, kidney failure, and Parkinson's disease [84]. He, et al. [83] studied the toxicity of paraquat to normal His BEAS-2B cells (human bronchial epithelial cells) and found that it was dose-dependent, leading to mitochondrial damage, oxidative stress, death of exposed lung cells, cytokine production, cause transformation of profibrogenic growth factors and my fibroblasts. Herbicides must be properly managed while handling them, unless otherwise, there will be the higher tendency to contaminate the environment and toxic to humans, animals or non-targeted organisms and even they effects can lead to death as well. The major health effects of herbicides can be summarized in Figure 4.

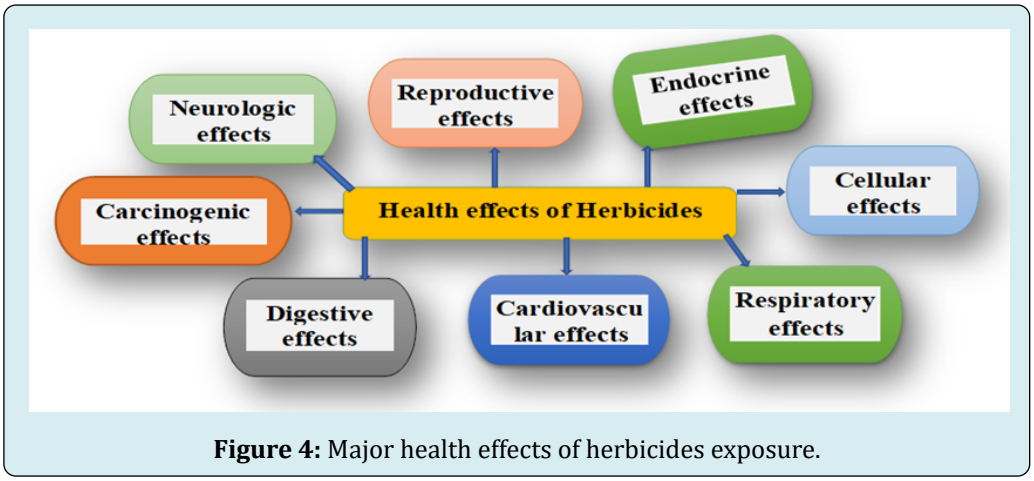

Figure 4: Major health effects of herbicides exposure.

Prevention Mechanisms of Herbicides Exposure and Health Effects

The preventive safety measures can be applied early in the planning of agricultural activities, during the steps of anticipating, identifying and recognizing the risks previously described. Preventive safety measures are aimed at the risk factors and can be divided into two groups: to eliminate and reduce the risk of poisoning. Preventive measures aim to ensure a safe working environment and to ensure that workers are qualified, motivated and in good health. The preventive safety strategies must be also applied for the people who have tendency to be exposed by herbicide (i.e., people who are near farm areas or herbicides production areas). When planning agricultural activities using herbicides, preventive measures will act on risk factors in order to reduce the toxicity of the herbicide and/or the exposure.

Alternative and Emerging Cultivation Systems Less Dependent on Herbicides

Among all pesticide classes, herbicides rank highest in terms of application rate. They are classified as emerging contaminants or pollutants which have adverse effects on humans, animals and the environment as well. Therefore, it is very important to shift to alternative and emerging farming systems that are less dependent or totally independent on herbicides to minimize or avoid the risks associated with the use of herbicides. Biological controls (insects, pathogens, grazing animals, agronomic practices, etc.) [85-87], Nano composite-based herbicides [88] and artificial intelligence and robotics application [89,90] are the sum of alternative and emerging trends that are used in controlling the weed. The advent of robotic devices presents a promising future for weed management. These cutting-edge systems will be able to precisely remove weeds through robotic deployment, store and analyse data on weed presence, help with decision-making regarding the timing and location of weed control efforts, and then collect data on treatment effectiveness to enable post-treatment evaluation.

Most of the alternative trends of weed management are concentrated on ecological approaches to plant protection based on available ecological knowledge. The goal of this approach is to increase the ability of agricultural systems to direct the natural process of pest control, contributing to improved agricultural production, sustainable pest control system, Disease and weed control should include three basic elements: prevention, decision-making and control [32]. Prevention is optimized by maximizing the use of natural processes in cultivation systems, suppressing harmful microbes by facilitating the development of antagonists, optimizing system diversity and stimulating recycling of internal resources [91]. Tools to accomplish this include: (i) farm hygiene, including the key elements of using clean seeds or planting material and maintaining temporal and spatial segregation between crops of the same species (e.g., volunteer management); (ii) cultivation systems; synergistic and antagonistic effects that occur in, for example, disease and pest control through engineered systems of non-chemical prevention methods such as growing cover crops and using soil amendments to increase populations of antagonists, (iii) cultural practices that support ecological processes; Delaying planting to reduce weed growth and even prevent seed set, removal of crop residues and plant debris, management of soil organic matter and cultivation strategies; Other input optimizations for attack by pathogens, or increased damage threshold; (v) breeding for resistance, e.g. by selecting certain plant types that are more competitive or more tolerant to weeds; e.g., Against powdery mildew.

Use of Personal Protective Equipment (PPE)

Various types of personal protective equipment (PPE) can be used to limit skin exposure when working with herbicides. Gloves, boots, hats, long sleeve shirts, and chemical resistant coveralls are the most common types of his PPE. The toxicity of the pesticides used, exposure conditions, and a worker's personal preferences will ultimately influence the type of PPE. Gloves and boots are the minimum PPE for most herbicides' products. As a general rule, highly toxic herbicides require the use of multiple types of PPE to reduce exposure. Various types of PPE provide complementary personal protection against dermal exposure. Wearing gloves proved to be the most effective way to protect against pesticide exposure. The protection provided by PPE depends on the protective properties of each type of PPE itself, how the herbicide is applied, and the level of correct application and maintenance by the farmer. Common protective clothing provides protection against exposure depending on the type of fabric, such as thickness and weight. Clothing made from barrier and non-barrier fabrics has been shown to reduce dermal exposure [92]. However, waterproof polypropylene fabrics have been found to provide better protection when compared to cotton garments [93].

Penetration in cotton garments ranged from 11.2% to 26.8%, whereas penetration in synthetic fabrics was found to be less than 2.4% [94]. However, a study of US citrus growers found little difference between synthetic and woven fabrics [95]. The effectiveness of PPE in terms of herbicide penetration through clothing has been reported to be affected by the application method [96]. However, results concerning this issue have been inconsistent. For example, while low-pressure backpack spraying was associated with greater herbicide penetration through the clothing than high-pressure spraying [97], according to other research [94], a low-pressure backpack application resulted in lower

penetration than high-pressure hand lance spraying. An important but often neglected factor in PPE effectiveness is how each piece of PPE is actually used. Farmer movement during herbicide application promotes movement and further diffusion of dust and liquids across PPE fabrics, and farmer perspiration, especially in hot environments, often also affects penetration resistance of PPE fabrics [95]. Given that farmers' movements can cause friction, some polyethylene coveralls showed greater penetration [98]. Of course, the protective effectiveness of PPE depends on its correct use. For example, farmers who frequently roll up their sleeves or remove gloves when working with herbicides are at increased risk of dermal exposure [94].

Improper, improperly worn, improperly maintained, and improperly used PPE can provide inadequate personal protection. Therefore, the theoretical maximum level of protection is rarely achieved in everyday use of PPE, and the actual level of personal protection is difficult to assess. As herbicides continue to be tools of modern agriculture, it is important to develop strategies to reduce their impact [99]. This includes accurate diagnosis and advanced knowledge of pest problems, optimized timing of interventions to maximize long-term effects, selection of agrochemical products with minimal impact on non-target organisms and workers, and through improved application methods, with minimal pesticide use. Amount of product selected for maximal dose delivery to biological targets [100]. Overall optimization of herbicide handling processes, strict compliance with regulations, and addressing public concerns about herbicide residues in food and drinking water are essential. To this end, when using herbicides, functional and well-maintained sprayers, and the necessary precautions at all stages of herbicides handling, are essential and can reduce farmers' exposure to herbicides.

Appropriate Selection of Persons Who Have Knowledge and Skill About The Herbicides Use

To be able to engage in hazardous activities, employees must have physical and psychological profiles suitable for working conditions. Personality traits can be strong and prominent, positive or negative, and indicate strengths and weaknesses such as irresponsibility, stubbornness, and irritability [101]. A worker`s personality, positive or otherwise, can influence the work environment and lead to unsafe behavior and unsafe working conditions. Negative traits can cause employees to ignore safety regulations, behave unsafely, or make mistakes in the performance of their duties, which can lead to work-related injuries. Accidents can be prevented by taking into account the physical and psychological profiles of workers required to perform dangerous tasks [101].

Psychological Measures

As employees interact throughout the workplace (physical or abstract space), they are positively or negatively impacted, altering their physical, mental and social states. On the other hand, it is natural for employees to bring personal issues into the workplace [102]. In work activities, a personal anxiety factor arises when a worker is unwilling to work under an abnormal physical condition (disease, physical or mental disability) without the experience, knowledge and proper training. Due to personal insecurities, employees may cause accidents or occupational diseases through negligence, recklessness, or misconduct [102]. Companies should take steps to evaluate their employees by promoting their professional and personal development to control the impact of the human factor on the risk of pesticide poisoning. Such measures increase employee self-esteem, improve performance and commitment, and create a more welcoming work environment. Other positive actions include employee dynamics, recognition campaigns, and willingness to listen to suggestions for workplace improvement. More than ever, companies are looking for professionals who work in groups, are proactive and have leadership qualities.

Proper Herbicides Packaging

Herbicide containers shall be designed and constructed to prevent leakage, evaporation, loss or alteration of the contents and to facilitate cleaning, sorting, reuse, recycling and proper disposal. Rigid packages containing water-miscible or water-dispersible formulations should be applied by the user with her triple wash or equivalent technique as directed on the label, package insert, or brochure package insert. Users must return empty containers of water-miscible pesticides and lids that have been washed three times to the place of purchase within one year from the date of purchases. The user must provide the control authority with a store, collection point, or empty container return slip provided by the collection point for at least one year after the return of the package. Packaging containing unusable or unused product should be disposed of according to the guidelines in the package insert [102].

Proper Herbicides Labels and Package Leaflets

Warnings about the hazards of herbicides regarding labels and package leaflets must be clearly displayed. The underside of the herbicide label must have a distinct colored stripe with a height equal to 15% of the height of the label/package, separate from the rest of the label. The colours of the ribbon correspond to the different toxicological classes of herbicides [102]. It is prohibited to work on newly treated surfaces before the re-entry interval indicated on the label has passed unless recommended protective equipment

is used. Also, during aerial spraying, no one is allowed to enter or remain in the treatment area. If access is required during this period, the personal protective equipment (PPE) recommended for the application must also be used. Recommended PPE should be worn in the following order: Boots, aprons, respirators, goggles, hoods and gloves.

Giving Awareness about The Use of Herbicides

Employers, on the other hand, should select the least toxic products and create conditions for mechanization and automation of work to minimize worker exposure to pesticides. Training in the handling and use of pesticides under field conditions is essential to reduce risk and prevent poisoning [103]. Awareness of the use or handling of herbicides must be provided by technical people who have background knowledge and skills about the herbicides or other materials that are to be used [104].

Conclusion

The use of herbicides in agricultural production brings important benefits such as: rapid onset of action and the control of some weed species that contribute significantly to yield reduction. Despite these advantages of herbicides, it is known that widespread and improper use has serious consequences for the structure, pollution and the entire biological system, often endangering human health. Improper use of herbicides has a significant impact on health, particularly in humans and animals, in the form of both short- and long-term damage. The degree of their damage or poisoning depends on the dose (concentration), exposure time and route of entry into the human body. Exposure to herbicides can cause a variety of adverse health effects, including carcinogenic, cardiovascular, reproductive, neurological, respiratory, cellular, digestive, or hormonal/endocrine effects. It is very important to understand and consider the level of toxicity and toxicity mechanisms of herbicides before using herbicides for various purposes in order to minimize their adverse effects. Employing alternative, less herbicide-dependent cropping systems, properly using all certified personal protective equipment (PPE) when handling herbicides, appropriate selection personnel who have knowledge and skill about the pesticides (i.e., especially for occupational purpose), applying suitable psychological measures (i.e., particularly for occupational purpose), proper packaging and package leaflet, proper labelling and giving general awareness about the use or handle of pesticide for farmers or any others who are not familiar with the use of pesticides are the major prevention strategies to minimize or avoid exposure and its health effects. Not only farmers but also others stakeholders (researchers, agricultural experts, policymakers, etc.) involvement are needed to reduce or totally avoid the risks associated with the improper use of herbicides in agriculture.

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