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Chemical Pesticides and Human Health: The Urgent Need for a New Concept in Agriculture

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The industrialization of the agricultural sector has increased the chemical burden on natural ecosystems. Pesticides are agrochemicals used in agricultural lands, public health programs, and urban green areas in order to protect plants and humans from various diseases. However, due to their known ability to cause a large number of negative health and environmental effects, their side effects can be an important environmental health risk factor. The urgent need for a more sustainable and ecological approach has produced many innovative ideas, among them agriculture reforms and food production implementing sustainable practice evolving to food sovereignty. It is more obvious than ever that the society needs the implementation of a new agricultural concept regarding food production, which is safer for man and the environment, and to this end, steps such as the declaration of Nyéléni have been taken.

Keywords: pesticides, agrochemicals, environmental health, endocrine disruptors, food sovereignty

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INTRODUCTION

Pesticides are substances or mixtures of substances that are mainly used in agriculture or in public health protection programs in order to protect plants from pests, weeds or diseases, and humans from vector-borne diseases, such as malaria, dengue fever, and schistosomiasis. Insecticides, fungicides, herbicides, rodenticides, and plant growth regulators are typical examples (1–3). These products are also used for other purposes, such as the improvement and maintenance of non-agricultural areas like public urban green areas and sport fields (4, 5). Furthermore, there are other less known applications of these chemical substances, such as in pet shampoos (4), building materials, and boat bottoms in order to eliminate or prevent the presence of unwanted species (6).

Many of the pesticides have been associated with health and environmental issues (1, 2, 7–12), and the agricultural use of certain pesticides has been abandoned (2). Exposure to pesticides can be through contact with the skin, ingestion, or inhalation. The type of pesticide, the duration and route of exposure, and the individual health status (e.g., nutritional deficiencies and healthy/damaged skin) are determining factors in the possible health outcome. Within a human or animal body, pesticides may be metabolized, excreted, stored, or bioaccumulated in body fat (1, 2, 13). The numerous negative health effects that have been associated with chemical pesticides include, among other effects, dermatological, gastrointestinal, neurological, carcinogenic, respiratory, reproductive, and endocrine effects (1, 2, 8, 10, 14–30). Furthermore, high occupational, accidental, or intentional exposure to pesticides can result in hospitalization and death (1, 31).

Residues of pesticides can be found in a great variety of everyday foods and beverages, including for instance cooked meals, water, wine, fruit juices, refreshments, and animal feeds (32–39). Furthermore, it should be noted that washing and peeling cannot completely remove the residues

(40). In the majority of cases, the concentrations do not exceed the legislatively determined safe levels (36, 39, 41, 42). However, these "safe limits" may underestimate the real health risk as in the case of simultaneous exposure to two or more chemical substances, which occurs in real-life conditions and may have synergistic effects (1, 43). Pesticides residues have also been detected in human breast milk samples, and there are concerns about prenatal exposure and health effects in children (13, 44–46).

This current review aims at highlighting the urgent need for a new concept in agriculture involving a drastic reduction in the use of chemical pesticides. Given the fact that the health effects have been extensively discussed in the current literature, this paper focuses on the major chronic health effects and recent findings regarding health effects that have been associated with exposure to common classes of chemical pesticides, i.e., organochlorines, organophosphates, carbamates, pyrethroids, triazines, and neonicotinoids. More emphasis is given to the widely used herbicide "glyphosate," which is an organophosphate pesticide very closely related to current agriculture (47). The important health effects, as discussed below, reveal the urgent need for implementing alternative solutions.

ORGANOCHLORINE PESTICIDES

The most widely known organochlorine pesticide is dichlorodiphenyltrichloroethane, i.e., the insecticide DDT, the uncontrolled use of which raised many environmental and human health issues (2, 48, 49). Dieldrin, endosulfan, heptachlor, dicofol, and methoxychlor are some other organochlorines used as pesticides.

There are a few countries that still use DDT or plan to reintroduce it for public health purposes (13, 48, 49). Furthermore, DDT is also used as a solution in certain solvents (2). It is a ubiquitous chemical substance, and it is believed that every living organism on Earth has a DDT body burden, mainly stored in the fat (48, 50). There is also evidence that DDT and its metabolite p,p-dichlorodiphenyldichloroethylene (DDE) may have endocrine-disrupting potential and carcinogenic action (48). *In utero* exposure to both DDT and DDE has been associated with neurodevelopmental effects in children (51). Moreover, a recent study related DDE to hepatic lipid dysfunction in rats (50).

The general class of organochlorine pesticides has been associated with health effects, such as endocrine disorders (10, 52), effects on embryonic development (53), lipid metabolism (54), and hematological and hepatic alterations (55). Their carcinogenic potential is questioned, but concerns about possible carcinogenic action should not be underestimated (38, 39, 56, 57).

ORGANOPHOSPHORUS PESTICIDES

Organophosphates, which were promoted as a more ecological alternative to organochlorines (58), include a great variety of pesticides, the most common of which is glyphosate. This class also includes other known pesticides, such as malathion, parathion, and dimethoate; some are known for their endocrine-disrupting potential (10, 59, 60). This class of pesticides has been associated with effects on the function of cholinesterase enzymes (58), decrease in insulin secretion, disruption of normal cellular metabolism of proteins, carbohydrates and fats (54), and also with genotoxic effects (61) and effects on mitochondrial function, causing cellular oxidative stress and problems to the nervous and endocrine systems (54).

Population-based studies have revealed possible relations between the exposure to organophosphorus pesticides and serious health effects including cardiovascular diseases (62), negative effects on the male reproductive system (63) and on the nervous system (58, 64–66), dementia (67), and also a possible increased risk for non-Hodgkin's lymphoma (68). Furthermore, prenatal exposure to organophosphates has been correlated with decreased gestational duration (69) and neurological problems occurring in children (70).

Regarding glyphosate, the safety of which is the subject of an ongoing scientific controversy (60, 71–76), it is the most widely used herbicide in current agriculture (47, 75), especially since the introduction of glyphosate-tolerant genetically modified crops, such as certain types of soybean and maize (60, 77–80). Its extensive use in genetically modified soybean cultivation has raised concerns about possible synergistic estrogenic effects due to the simultaneous exposure to glyphosate and to the phytoestrogen "genistein," which is a common isoflavone present in soybeans and soybean products (80, 81).

Glyphosate can display endocrine-disrupting activity (80, 82), affect human erythrocytes *in vitro* (83), and promote carcinogenicity in mouse skin (84). Furthermore, it is considered to cause extreme disruption in shikimate pathway, which is a pathway found in plants and bacteria as well as in human gut bacteria. This disruption may affect the supply of human organism with essential amino acids (85). Commercial glyphosate formulations are considered to be more toxic than the active substance alone (80, 83, 86, 87). Glyphosate-based herbicides, such as the well-known "Roundup," can cause DNA damages and act as endocrine disruptors in human cell lines (60) and in rat testicular cells (88), cause damages to cultured human cutaneous cells (89), and promote cell death in the testicular cells of experimental animals (88, 90). There is evidence also for their possible ability to affect cytoskeleton and intracellular transport (91).

A recent study examined the possible relation between glyphosate, genetically modified crops, and health deterioration in the USA. Correlation analyses raised concerns about possible connections between glyphosate use and various health effects and diseases, such as hypertension, diabetes, strokes, autism, kidney failure, Parkinson's and Alzheimer's diseases, and cancer (82). Furthermore, there are concerns about the possible ability of glyphosate to cause gluten intolerance, a health problem associated with deficiencies in essential trace metals, reproductive issues, and increased risk to develop non-Hodgkin's lymphoma (92).

CARBAMATE PESTICIDES

Carbamate pesticides, such as aldicarb, carbofuran, and ziram, are another class of chemical pesticides that have been associated with endocrine-disrupting activity (10, 93), possible reproductive disorders (63, 93), and effects on cellular metabolic mechanisms and mitochondrial function (54). Moreover, *in vitro* studies have revealed the ability of carbamate pesticides to cause cytotoxic and genotoxic effects in hamster ovarian cells (94) and to induce apoptosis and necrosis in human immune cells (95), natural killer cells (96, 97), and also apoptosis in T lymphocytes (98).

Furthermore, it has been confirmed that carbaryl, which belongs to the category of carbamate pesticides, can act as a ligand for the hepatic aryl hydrocarbon receptor, a transcription factor involved in the mechanism of dioxin toxicity (99). There is also evidence for the ability of carbamate pesticides to cause neurobehavioral effects (65, 100), increased risk for dementia (67), and non-Hodgkin's lymphoma (101).

OTHER CLASSES OF CHEMICAL PESTICIDES

Triazines, such as atrazine, simazine, and ametryn, are another class of chemical pesticides that have been related to endocrine-disrupting effects and reproductive toxicity (10, 102, 103). Moreover, it was found that there is a possible statistical relationship between triazine herbicides and breast cancer incidence (104). Atrazine is the most known of the triazines, and it is a very widely used herbicide that has been associated with oxidative stress (103), cytotoxicity (105, 106), and dopaminergic effects (107, 108). Furthermore, the exposure of experimental animals to atrazine has been associated with reproductive toxicity (109) and delays in sexual maturation (110).

Synthetic pyrethroids, such as fenvalerate, permethrin, and sumithrin, are considered to be among the safer insecticides currently available for agricultural and public health purposes (111, 112). However, there is evidence for their ability to display endocrine-disrupting activity (10, 113–115), and to affect reproductive parameters in experimental animals including reproductive behavior (114, 116). Furthermore, a recent study related more than one pyrethroid metabolite to DNA damages in human sperm, raising concerns about possible negative effects on human reproductive health (117). It should also be mentioned that there are also concerns about their possible ability to display developmental neurotoxicity (25, 118, 119).

Neonicotinoid pesticides, such as imidacloprid, thiacloprid, and guadipyr, are relatively new and also the most extensively used insecticides (120) that were promoted for their low risk for non-target organisms (121). However, there is plenty of evidence to the contrary (115, 122–125); their effect on bees is a common example (124, 125). There is also evidence for possible effects on the endocrine and reproductive systems of animals (115, 126, 127). Moreover, a recent study demonstrated that neonicotinoids are able to increase the expression of the enzyme aromatase, which is engaged in breast cancer and also plays an important role during developmental periods (128).

URGENT NEED TOWARD CLEANER AND SAFER AGRICULTURAL PRACTICES

Current agricultural practices include the wide production and extensive use of chemicals known for their ability to cause negative health effects in humans and wildlife and to degrade the natural environment. Therefore, an urgent strategic approach is needed for a reduction in the use of agrochemicals and for the implementation of sustainable practices. Furthermore, current agriculture has to implement environmentally friendlier practices that pose fewer public health risks. Reforming agricultural practices aligned to fulfill these criteria is a step toward the sustainability of the agricultural sector in contrast to precision agriculture (129–134).

However, the reduction in the use of agrochemicals by applying them only when and where they are necessary, the spatiotemporal variability of all the soil and crop factors of a given field must be taken into consideration. This variability includes yield, field, soil, and crop variability but also factors, such as wind damage or flooding. Technological systems, such as geographical information systems, global positioning systems, and various sensors, can be useful (130–132, 135). These technological systems are developed by precision agriculture which of course we do not endorse, but we consider that selected technological tools can be used to decrease risks for environmental pollution and water pollution and to enhance economic benefits stemming from the reduction in the use of chemical products (130, 132).

It should be clear that the reform into an aggregate of machine-centered procedures and losing a human-centered character are not the desired. In contrast, the reduction in the use of pesticides assisted by innovative technological methods we strongly believe that may reduce the use of chemical substances or maybe it can lead to a total abandonment in many cases, such as in the case of urban green areas. The decision of the Italian village of Mals near the Austrian and Swiss borders to ban the use of pesticides and produce pesticide-free foods can be considered as a pioneer example across Europe. In 2014, more than 70% of the inhabitants of Mals who participated in a referendum voted against the use of pesticides (136). This historical decision apart that is consistent with the food sovereignty concept, which is discussed in the following section, also declares the need for disseminating information for raising awareness of the public in order to develop informed consents.

An innovative idea developed by the international movement "Via Campesina," was the democratic concept of food sovereignty that has accompanied the progress toward sustainability for more than 20 years. It acquired a strong basis in 2007 in the African village Nyéléni in Mali, where representatives from more than eighty countries adopted the "Declaration of Nyéléni." According to its principles, all the people of the world have the right to choose their own national and local policies to eliminate poverty, malnutrition, and hunger, to protect their traditions and also the natural environment (137–141).

The industrialization of agriculture has brought a series of problems including economic, social, and environmental impacts that local populations cannot manage. Furthermore, the overproduction of food, export-oriented monocultures, the demand for cheap labor, and the other characteristics of industrialization have clearly failed to solve the problems of hunger and malnutrition. On the contrary, inequitable food distribution, overexploitation of land and water sources, the overuse of agrochemicals, and the degradation of the natural environment are some of the results of the dominant agricultural model (138, 142–144). Food sovereignty promotes social, economic, and environmental sustainability, for instance, through the protection of the indigenous population and the production of food for distribution in local markets, and there is an ongoing effort for its recognition as a basic human right (138–140, 142, 145).

The dominant agricultural model has increased the chemical burden on natural environment (140, 142). Moreover, international agrochemical companies absorb traditional agricultural companies, leading to an industrialized agriculture model and leaving the local farmers and small producers to face the consequences (138, 143). In many cases, these people are obliged to adopt environmentally unfriendly techniques to increase their production in order to survive in the market, causing more environmental degradation (138). However, due to the fact that food sovereignty does not necessarily mean pesticide-free, organic food production, and because it does not determine pesticide use levels, for this reason, international eco-friendly standards should be implemented. People must be free to decide the method of production of their own food, and an important component of this decision concerns agrochemical products. The decision of the people of Mals to reject pesticides can be considered a step in this direction.

DISCUSSION

The need for protection against pests is a given and has its roots in antiquity, when both organic and chemical substances were applied as pesticides (146). Since then, numerous chemical pesticides have been produced, and now multinational agrochemical companies, which mostly control global food production, apply new chemical substances with pesticide properties and implement biotechnological advances, thus diverging from traditional agricultural methods. Furthermore, current agricultural practices are based on the wide use of chemical pesticides that have been associated with negative impacts on human health, wildlife, and natural environment (9, 11, 120, 147, 148).

Current agriculture has to deal with important factors, such as population growth, food security, health risks from chemical pesticides, pesticide resistance, degradation of the natural environment, and climate change (149–155). In recent years, some new concepts regarding agriculture and food production have appeared. A concept as such is climate-smart agriculture that seeks solutions in the new context of climate change (152, 153). Another major ongoing controversy exists between the advocates and the opponents of genetically engineered pesticide-resistant plants, regarding not only their safety (29, 156, 157) but also their impact on pesticide use (158–160).

Furthermore, the real-life chronic exposure to mixture of pesticides with possible additive or synergistic effects requires an in depth research. The underlying scientific uncertainty, the exposure of vulnerable groups and the fact that there are numerous possible mixtures reveal the real complex character of the problem (161–163). The combination of substances with probably carcinogenic or endocrine-disrupting effects may produce unknown adverse health effects. Therefore, the determination of "safe" levels of exposure to single pesticides may underestimate the real health effects, ignoring also the chronic exposure to multiple chemical substances.

Taking into consideration the health and environmental effects of chemical pesticides, it is clear that the need for a new concept in agriculture is urgent. This new concept must be based on a drastic reduction in the application of chemical pesticides, and can result in health, environmental, and economic benefits (164) as it is also envisaged in European Common Agricultural Policy (CAP) (165).

We believe in developing pesticide-free zones by implementing a total ban at local level and in urban green spaces is easily achievable. Furthermore, alternative procedures to the current model of food production should be implemented in new agricultural policies targeting sustainable development and protection of the consumers' health. Despite the difficulties of establishing an innovative concept, the transition to a new cleaner and safer agricultural model is necessary.

AUTHOR CONTRIBUTIONS

Professor PN-S and Professor LH are the principal authors. Mr. SM contributed with proof reading, literature review, and editing. Mrs. CK and Mr. PS contributed with literature review and editing.

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