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Open Access Journal of Agricultural Research
ISSN: 2474-8846

Pesticides Exposure in Relevance to Cancer Risk

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Mini Review

Volume 2 Issue 2

Received Date: January 23, 2017

Published Date: February 20, 2017

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Abstract

Pesticides are widely used throughout the world because of their benefits to maintain high agricultural products quality and quantity. There is growing epidemiological evidence that exposure of humans to pesticides correlate with an increased incidence of cancer. Agricultural health studies often established a positive correlation between occupational exposure to pesticides and different types of cancer; however data on non-occupational exposures are scarce to draw any conclusion. The frequency of cancer diagnosis has increased dramatically among adults population, and there are no studies addressing the impact of pesticides or their residues on cancer development among high risk groups of adults' population. Cancer is the second leading cause of chronic diseases-related death among adults, yet there is no enough information to link pesticides exposure and cancer incidence. The biological link between pesticides use and increasing cancer incidence needs to be addressed, in particular the biochemical and epigenetic modifications that might be associated with continuous pesticides exposure. Lack of evidence in this regard has promoted us to write this mini-review as an attempt to evaluate the mechanisms by which pesticides develop cancer, and we hypothesized that long-term exposure to pesticides induce cellular oxidative stress, epigenetic modifications, and alterations of DNA methylation in multiple human organ systems leading to cancer development among high risk groups.

Keywords: Pesticides Exposure; Oxidative Stress; Cancer

Introduction

The presence of a detectible pesticide residue in an edible food should be at levels far lower than those that are considered health risks as indicated by USDA's Pesticide Data Program. Western epidemiological and agricultural health studies reported the effect for pesticides-associated carcinogenesis in multiple human organ systems such as breast cancer, prostate cancer, lung cancer, brain cancer, testicular cancer, colorectal cancer, pancreatic cancer, esophageal cancer, stomach cancer, brain cancer, skin cancer, and non-Hodgkin lymphoma. There is mounting evidence on the link of pesticide's exposure with the incidence of cancer at higher rates among pesticides manufacturing workers, applicators, farmers, and farms inhabitants. In many countries, agricultural workers and farmers as compared to the general population have higher rates of cancer incidence, for example, farming communities in the United States have higher rates of leukemia, non-Hodgkin lymphoma, multiple myeloma, and soft tissue sarcoma, as well as cancers of the skin, lip, stomach, colorectal, brain, and prostate [1]. Even though no one set of risk factors explains these higher cancer rates, the range of environmental exposures in the farming community is of concern; where farmers, farm workers, and farm family members are exposed to substances such as pesticides, engine exhausts, solvents, dusts, animal viruses, fertilizers, fuels, and specific microbes that may account

for these elevated cancer rates. There is growing epidemiological evidence on the putative positive association between long-term exposure to pesticides in occupational settings and an elevated rate of cancer, but data on biological links are scarce to draw any conclusion. Risk factors that are often related to the risk for cancer incidence are generally classified as non-modifiable or modifiable factors. Non-modifiable factors that are often related to cancer incidence rates are age, gender, family history, and genetic predisposition. Modifiable risk factors that are often discussed with increased cancer risk are smoking, low intake of dietary antioxidants, B-vitamins deficiency and Obesity [2]. Cancer may also be linked to modifiable risk factors that are classified as environmental; these environmental risk factors can be altered or changed as they relate to personal behaviors, dietary intake, lifestyle and occupation [3]. Pesticides exposure among general population represents an environmental risk factor in relation to cancer development, and represents a missing component of the present knowledge as there is a lack of evidence in the current available literature. Pesticides are unique, intrinsically toxic chemicals designed to be deliberately spread into the environment to kill off pests. They are comprised of many different categories of chemicals and approximately 5.2 billion pounds were used worldwide in 2006 and a similar amount in 2007, but only 1% of this amount reaches the target pests at lethal doses [4,5].

Herbicides account for the largest portion of that amount, followed by other pesticides, insecticides and fungicides. Exposure to pesticides can occur through multiple pathways (e.g. food, drinking water, residential, occupational) and routes (oral, inhalation, dermal). Although the contribution of a given route or pathway to overall exposure depends on the pesticide, it is the totality of exposure, by multiple routes and multiple pathways, what determines the risk [6]. The type and severity of adverse health effects of pesticides are determined by the individual chemical category, the dose and the duration of exposure and the exposure route [5,6]. Given that humans are much larger than the target species for pesticides, they are expected to be unaffected by small amounts of these compounds. However, pesticides are indeed toxic to humans not only at high doses, responsible for acute poisonings, but even in low doses, as there are mixtures of pesticides that might synergize through the long-term exposures and lead to an array of health effects (respiratory, reproductive and developmental toxicity) and human chronic diseases, including cancer. Pesticides are often applied in mixtures to crops, their residues can be found in foods, drinking water, and aquatic environment, including surface waters that support aquatic life [7].

Assessment of pesticide exposure to humans is generally based on measurement of non-specific metabolites in urine and hair samples, which enables the assessment of the type of exposure and to associate this exposure to relevant health issues. In the European Union and the United States, legislation has been laid down regulating the presence of pesticides residues in food products by setting maximum residue levels (MRL) of individual pesticides. As long as the individual residues do not exceed the MRLs, the presence of multiple residues in one sample as such is not a reason to be considered as not compliant with the MRL legislation. The international agency for research on cancer (IARC), United States national toxicology program (US NTP), United States environmental protection agency (US-EPA), and toxic release inventory (TRI) have indicated that in humans, the carcinogenic properties of pesticides can be influenced by a series of complex factors including age, sex, individual susceptibility, amount and duration of exposure, and simultaneous contacts with other cancer causing chemicals. In experimental animals' models, the carcinogenic mechanisms of pesticides were explored in their potential to affect genetic material either directly via induction of structural or functional damage to chromosomes, DNA, and Histone proteins, or indirectly via disrupting the profile of gene expression through impairment of cellular organelles like mitochondria and endoplasmic reticulum, nuclear receptors [8,9].

Human exposure to low-dose pesticide mixtures may occur from environmental or nutritional sources (foods and drinking water) and may have a long-lasting and negative health impact in the long-term, some being connected with the increase of cancer in humans as evidenced in Western countries [10]. Despite many articles describe the carcinogenic effects of exposure to pesticides and their mixtures, relatively little information is available on the nature of metabolic interactions (independent, dose addition or interaction) that may occur between the constituents of a pesticide mixture, and results in biological events favoring cancer incidence via inhibition of detoxifying enzymes, increasing the cytotoxicity, and stimulating or activating oncogenes [11].

Based on rising evidence given by epidemiological and agricultural health studies associated with exposure to pesticides and carcinogenesis, the International Agency

for Research on Cancer (IARC) has considered chronic low-dose exposure to pesticides as one of the important risk factors for cancer incidence. Therefore, carcinogenicity tests are now applied to detect carcinogenic potential of pesticides before allowing them to be marketed. These carcinogenicity testing is conducted by the Environmental Protection Agency (US-EPA), and it is a long-term (around two years) rodent bioassay using two species of both sexes, and according to a new list of chemicals evaluated for carcinogenic potential by EPA's pesticide program published in 2010, more than 70 pesticides have been classified as a probable or possible carcinogen [12]. This classification has been accomplished based on the information extracted from animal genotoxicity and mutagenicity-based studies, and there is a need for human-based clinical trials to address these issues.

Evidences for the Link between Pesticide Exposure and Incidence of Cancer

Based on rising evidence given by epidemiological and agricultural health studies associated with exposure to pesticides, different types of neoplasm have been reported such as breast cancer, prostate cancer, lung cancer, brain cancer, colorectal cancer, testicular cancer, pancreatic cancer, esophageal cancer, stomach cancer, skin cancer and non-Hodgkin lymphoma [13]. It has been pointed out that exposure to pesticides was a risk factor for prostate cancer and leukemia by a meta-analysis of risk estimates in pesticide manufacturing workers [14]. Series of agricultural health studies consistently provided an association between exposure to pesticides and cancer incidence, particularly lymphohematopoietic cancers for alachlor, lung cancer for chlorpyrifos, and colorectal cancer for aldicarb [15]. Nowadays, chronic low-dose exposure to pesticides is considered as one of the important risk factors for cancer expansion. Therefore, carcinogenicity tests are now applied to detect carcinogenic potential of pesticides before allowing them to be marketed. Carcinogenicity testing is a long-term (around two years) rodent bioassay using two species of both sexes.

According to a new list of Chemicals Evaluated for Carcinogenic Potential by EPA's Pesticide Program published in 2010, more than 70 pesticides have been classified as a possible carcinogen. This classification has been accomplished based on the information extracted from animal studies, metabolism studies, structural relationship with other carcinogens, and if available, epidemiologic findings in human. Carcinogenic properties of pesticides can be influenced by a series of complex factors including age, sex, individual susceptibility, amount and duration of exposure, and simultaneous contacts with other cancer causing chemicals. However, carcinogenic mechanisms of pesticides can be explored in their potential to affect genetic material directly via induction of structural or functional damage to chromosomes, DNA, and Histone proteins, or indirectly disrupting the profile of gene expression through impairment of cellular organelles like mitochondria and endoplasmic reticulum, nuclear receptors, endocrine network, and the other factors involved in maintenance of cell homeostasis [16].

Molecular Mechanisms Linking Pesticide Exposure to Cancer

A) Genetic Damages

Genetic damages are caused by direct interaction with genetic material resulting in DNA damage or chromosomal aberrations and considered as a primary mechanism for chronic diseases within the context of carcinogenesis and teratogenesis. Growing body of data concerning genetic toxicity of pesticides have been collected from epidemiological and experimental studies using different types of examinations, including chromosomal aberrations, micronucleus, sister chromatid exchanges and comet assay [17]. Genetic damages are classified into three groups as follows: 1. Premutagenic damages like DNA strand breaks, DNA adducts or unscheduled DNA synthesis; 2. Gene's mutation which means insertion or deletion of a couple of base pairs; 3. Chromosomal aberrations, including loss or gain of whole chromosome, deletion or breaks, and chromosomal segments or rearrangements [18].

Micronucleus has been recognized as the most reliable and successful test for genetic damage [19]. A micronucleus is referred to the third nucleus formed during the metaphase/anaphase transition of mitosis. The group of these cytoplasmic bodies is called micronuclei having a portion of acentric chromosome or whole chromosome, which does not integrate in the opposite poles during the anaphase. This results in the formation of daughter cells without a part or all of a chromosome. Regarding sensitivity, reliability, and cost-effectiveness of this test, it has been proposed as a biomarker for genotoxicity calculations, and has been used in different studies on pesticide-exposed populations. Most of these surveys implied on the increased level of micronucleus formation in people dealing with pesticides for a long time [20]. Genotoxicity assays are among necessary tests

applying for pesticides prior to introducing to the market, and it is done only in animal studies. Therefore, further studies focusing on genotoxicity of pesticides, of course in appropriate models like human exposure to pesticides residues, are required to understand the carcinogenic and tumorigenic mechanisms of pesticides.

B) Epigenetic Modifications

Epigenetic is referred to the heritable changes in gene expression or cellular phenotype without any alterations in the DNA sequence, and its mechanisms include DNA methylation, histone modifications and expression of non-coding RNAs. A growing body of evidence has implicated on the role of environmental exposures, particularly in early development, in the induction of epigenetic changes (alterations of DNA methylation and their regulatory role in gene expression) that may be transmitted to subsequent generations or may serve as a basis of diseases developed later in life. Furthermore, it has become so likely that epigenetics contribute to the causes or transmission of chronic disorders from one generation to another. Cancer is now considered as an epigenetic disease the same as a genetic disease. There is tremendous evidence on the contribution of epigenetic events in the initiation, promotion and progression of different types of cancers, mainly through silencing of tumor suppressor genes and/or activation of proto-oncogenes. These modifications have allocated such a fundamental role in cancer development that epigenetic therapy of cancer is rapidly growing in medical sciences [21]. In addition, epigenetic changes currently have been a powerful tool for studying the carcinogenesis mechanisms of occupational and environmental exposures [22]. The first note on pesticide-induced carcinogenesis through epigenetic mechanisms was reported in relation to hepatocarcinogenesis of organochlorine pesticides with no genotoxic effects in hepatocytes and suspected to epigenetic modifications disrupting intracellular communications [23]. Later, reports presented about epigenetic actions of vinclozolin, a fungicide known to be an environmental endocrine disruptor, in association with adult-onset diseases, particularly tumor development [23]. Pesticides were introduced as carcinogens acting through epigenetic or non-genotoxic mechanisms [24].

Evidences for the Link between Pesticide Exposure, Oxidative Stress and Cancer Risk

Increased production of reactive oxygen species (ROS) and/or decreased capacity of antioxidant defense can disrupt oxidative balance and result in damaging all components of the cell, including lipids, proteins, and DNA. Further, oxidative stress can disrupt various parts of cellular signaling because ROS are considered as one of the main messengers in redox signaling. There is a huge body of literature on induction of oxidative stress by pesticides, and it has been implicated in development of health problems mediated by exposure to pesticides [25]. It has been revealed that pesticides can disturb oxidative homeostasis through direct or indirect pathways, including mitochondrial or extra mitochondrial production of free radicals, thiol oxidation, and depletion of cellular antioxidant reservoirs [26]. Considering the oxidative stress as a powerful promoter of other cellular pathways involved in cancer development, it has been put in the spotlight of the most mechanistic studies regarding the association of pesticides exposure with cancer risk.

Conclusion

Taken together, pesticides-associated carcinogenesis as discussed above is considered as the major disorder affecting public health in the 21st century. The relationship between cancer risk and environmental exposures, particularly pesticides increasingly continues to strengthen. Near to all studies carried out in the area of pesticides, and cancer are categorized in the field of epidemiologic evidence or experimental animal investigation with no mechanistic insight into the cancer development. It should not be forgotten that these mechanisms work alongside or sequentially rather than singly, or they even can potentiate genetically susceptible individuals.

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