



Could Endocrine Disruptor Pesticides be Responsible for the Increasing Prevalence of some Endocrine Diseases in Cameroon? A Review

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Abstract

Pesticides have a variety of uses as they are used in crop protection, at home and in public health for vector control. Although useful, the general public is becoming increasingly concerned about the possible impact on the health of humans and the environment. Some of these pesticides have been identified as endocrine disruptor chemicals (EDC) that interfere with human and animal hormone systems and are capable of altering hormone balance and embryo development with the risk of adverse effects on the health of organisms and their offspring. Our reviews reveal that EDC exposure show that the general population is in fact exposed to a mixture of EDCs. A majority of the studies show that there is an association between exposure to endocrine disruptor chemicals and the disorders affecting the endocrine system. Exposure of humans to pesticides could either be due to their occupations or through dietary or the environment via water, air and soil. Our discussion of some endocrine diseases emphasizes the need to focus on the high prevalence of cancer as an endocrine disease and stress on further research to explore the cause of the increasing prevalence of cancer in Cameroon.

Keywords: Endocrine disruptors; Pesticides; Human effects; Endocrine system; Endocrine diseases; Cameroon

Introduction

Pesticide

A pesticide is a chemical used for killing pests which are living organisms that interfere with the growth, development and yield of a crop. There are many different types of pesticides to kill different types of pests. The common ones being herbicides, fungicides, insecticides and rodenticides, which kill weeds, fungi, insects (may also control ticks, mites, etc.) and rodents respectively. The toxicity of pesticides varies, so some are very hazardous to use while others are

less hazardous. Safety is one of the most important considerations when working with pesticides which include safety to the user, to other people, to domestic animals and to the environment generally. They are three possible routes by which a pesticide can enter the body; through the skin (dermal absorption), through the mouth (oral ingestion) and through breathing (inhalation - lungs). Unfortunately, the poor use of pesticides and spray application of crops has led to rural workers, their family and the environment exposed to the chemicals being used for crop protection, with the risk of affecting their health. The safe and efficient use of agrochemical and bio-products is important to minimize the risks.

Pesticides use in agriculture

With reference to the Population Reference Bureau [1], the world population is expected to increase from its current level to around 8.5 billion in the year 2035. About 80% of this population will be living in the developing world where arable land per person is shrinking – from 0.38 ha per person by 2050 [2]. The ability of the world's farmers to produce food has increased greatly in recent years, which has indicated to the Food and Agriculture of the United Nations that by 2030, the estimated global food production in developing countries will be 70% higher than in 1995/1997 [2]. With land pressure already high on productive cropping areas, these increases will have to come from improved crop varieties (including genetically modified strains), improved production practices, more attention to soil fertility and water management, and reduced crop losses to serious pests (including diseases and weeds), which can otherwise cause losses estimated at 50% of harvestable produce [3]. Pesticides have become regarded by many farmers as the principal tool for combating these pests in agriculture. Although organic production is increasing, it currently only represents a small proportion of world food production and with lower yields per hectare is likely to remain a niche market. Integrated pest management (IPM) production systems are expected to become more widely adopted to reduce external inputs, even though pesticides can be used more judiciously with IPM. In the year 2018, the global market for pesticides was estimated to reach a value of USD 90 billion by the year 2023 [4].

The general public is becoming increasingly concerned about the possible impact of these pesticides on human and environmental health. Hazards may arise for consumers and the environment due to poor regulation of pesticides, lack of information and training of farmers so their choice of chemical and method of application of pesticides may be poor. Furthermore a lack of Personal Protective Equipment (PPE) increases the risk of exposure thus affecting their health.

Methodology

In the developed world, various regulatory actions have been taken to limit the impact of pesticides, by refusing to register the most highly hazardous pesticides. Within the European Union (EU) harmonized legislation of pesticides has resulted in the removal of many of the older pesticide products, which are still available in many other parts of the world due to porous borders. Within the EU there are now regulations requiring compulsory testing of sprayers and the mandatory certification of sprayer operators.

Fears are growing in developing countries about pesticide hazards, but the facilities, systems and legislation that exist to monitor and

mitigate them are very limited at present. Similarly the support for research and extension services has limited the evaluation of control methods so farmers do not get adequate information on crop protection. This is being made more noticeable as crops grown in developing countries and exported to the EU may have pesticide residues that exceed the EU maximum residue level (MRL).

It is clear that strenuous efforts must be made to deal with pesticide safety problems for producers, consumers and the environment wherever they occur in the world. Specifically there is a need to quantify their magnitude, to identify their causes and to develop ways to reduce them without compromising agricultural sectors or geographic regions. In Africa; successive governments have not supported either agricultural research or extension services adequately. There is also another constraint being the health of farmers in the rural areas. Residues in harvested crops where pre harvest intervals are not respected continue to add to the consequences borne by the consumer.

Pesticides use in public health

Africa remains affected by many diseases transmitted by insects, as well as HIV/AIDS and TB. Malaria is still a major cause of mortality especially of young children and morbidity, and it has been implicated in increased susceptibility to HIV infections; even those that gain some immunity to malaria and survive to become adults often have periods of recurring sickness. A lot of mosquito genera are involved in the transmission of other diseases such as zika virus, mansoniasis, lymphatic filariasis, yellow fever, and West Nile fever. Tsetse flies transmit Human African trypanosomiasis (HAT); black flies (*Simulium damnosum*) breed in rapids along rivers and transmit the filarial worm (*Onchocerca volvulus*) that causes river blindness. To control these vector borne diseases, pesticides are used. The World Health Organisation (WHO) successfully carried out a 20-year programme to stop the transmission of *Onchocerca volvulus* in many West African countries involving aerial application of larvicides into rivers. Although successful in its aim of interrupting disease transmission [5] the adult biting flies are still present and in areas not treated, the large numbers of black flies that occur along the river valleys cause endless irritation to the inhabitants. To continue in fighting this very vector, other techniques such as ground larviciding in rivers and dams are being employed, alongside the use of a drug that has an impact on the parasite. The use of DDT as a residual spray inside houses in the 1950-60s has been replaced by other insecticides, but also by treating bed nets with an insecticide, better overall control of mosquitoes entering houses has been achieved. Mortality of young children has been significantly reduced, yet malaria remains a problem in many areas [6, 7]. The paradox is how then we handle these seeing how beneficially they are in both crop protections, environmental and human health without jeopardising human health. They are many pesticides that have bioaccumulation properties and high toxicity such as aldrin, chlordane, DDT, hexachlorobenzene, endrin, heptachlor, mirex, toxaphene [8]. Focusing on the benefits without looking at their bioaccumulation in humans is where the problem lies.

Health hazards of pesticides

There is no doubt that pesticides, used judiciously, are beneficial to humans but [9] at the same time there is the risk of harm to both humans and wildlife [10]. Studies have shown that many pesticides are harmful to the environment. The first person to have drawn attention to the hazards of pesticides use for the environment and human health was Rachel Carson in 1962 [11]. Some pesticides have

been known to persist in soils and aquatic sediments while others bio concentrate in the tissues of invertebrates and vertebrates moving up to trophic chains and affecting top predators [12].

A report of the World Health Organization Commission on Health and Environment shows that annually, about 3 million pesticides poisonings occur causing 220,000 deaths worldwide [13]. According to Mesnage and Séralini [14], different studies on the harmful effects of pesticides have revealed that the toxicity of pesticides is generally underestimated. Some diseases such as cancer, allergies, neurological disorders and reproductive disorders have been thought to be linked to pesticide exposure. Other disorders associated with pesticide exposure include Parkinson's disease, Alzheimer's disease and Attention Deficit-Hyperactivity Disorder (ADHD) [15]. This article therefore aims to focus on the harmful effects of pesticides that are endocrine disruptor chemicals (EDCs). It reviews the existing literature on the exposure and adverse effects of the pesticides that affect the endocrine system.

The endocrine system

The endocrine system is a network of glands that produce hormones, which are chemicals that regulate metabolism, growth and development, tissue function, sexual function, reproduction, sleep and mood, among other things [16]. The hormone or endocrine system functions as a communication system as this is essential between cells and is based on chemical signals. Neighboring cells communicate through surface molecules and special junctions, whereas communication between distant cells is carried out through the release of chemical signals, hormones that target cells and interact with specific receptors. Chemical signals travel through the bloodstream (circulatory system) to reach target cells. The endocrine cells are cells responsible for signal or hormone releases.

Literature Review

The glands of the endocrine system produce different types of hormones (chemical messengers) that evoke a specific response in other cells, tissues and/or organs located throughout the body. The hormones that are secreted by these glands travel through the bloodstream to various target organs and tissues which have receptors in the body where they tell these organs and tissues what to do or how to function when there is a hormonal imbalance. This could be that there is either too much or too little of a certain hormone thus causing serious effects throughout the whole body as even tiny changes can cause this. Although some hormones levels fluctuate throughout one's lifetime as a result of natural aging, other changes occur when the endocrine glands get disrupted by other factors. When these glands produce an incorrect amount of hormones, endocrine diseases occur. Among these are diabetes, high blood pressure, high cholesterol, heart disease, obesity, neuropathy, tumors (benign or cancerous), stress, and eating disorders. There are common hormonal conditions that affect both men and women that could cause weight gain, fatigue, depression, anxiety, decreased sex drive, infertility among others. Hormonal imbalance in women causes polycystic ovary syndrome (PCOS) which is the most common. And in men (adult males), they will experience erectile dysfunction, infertility, osteoporosis, loss of muscle mass among others. Children are not left out of hormonal imbalance as they can suffer from delayed puberty and some have a condition called hypogonadism in both boys and girls.

Endocrine disruptor chemicals

Endocrine disruptors are chemicals that interfere with human and animal hormone systems and are capable of altering hormone balance and embryo development with the risk of adverse effects on the health of organisms and their offspring. The term is broadly defined as “an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and regulation of developmental processes” [17, 18, and 19]. Amongst the many chemicals that have been identified as endocrine disruptors are pesticides. About 105 pesticides have been listed as EDCs with 46% being insecticides, 31% fungicides and 21% herbicides [20, 21-24]. Because of their disrupting effects some such as DDT and atrazine were withdrawn from general use many years ago but are still found in the environment [12]. EDCs are known to interfere with natural hormones. They have an antagonistic effect as they have a strong potential to bind to estrogen or androgen receptors [25]. EDCs can bind to various hormone receptors activating or not activating them and thus mimicking the natural hormone’s action thereby blocking the receptors and inhibiting their action. Another mode of action of EDCs is that they may also interfere with the synthesis, transport, metabolism and elimination of hormones causing hormonal imbalance by decreasing the concentration of natural hormones. Some EDC pesticides such as cyhalothrin, maneb, mancozeb, fipronil, pentachloronitrobenzene can inhibit the production of the thyroid hormone [26, 27, 28].

Exposure to EDCs

The results of published studies on EDC exposure show that the general population is in fact exposed to a mixture of EDCs [29, 30]. EDCs are found at different levels in individuals depending on factors like sex, age, educational level and social status, but they exceed, both on an individual and collective scale, the concentration levels known to cause endocrine disruption. Pregnant women and infants are the most vulnerable population groups due to high EDC concentrations they are exposed to. Exposure to EDCs could either be by ingestion, occupation or biocides [17, 31]. Research suggests that food is an important source of EDC exposure in the human population [32, 33, and 34]. This type of exposure affects children in particular, whose ingestion of some pollutants (PCBs and dioxins) might exceed the recommended levels of exposure established for other categories. Epidemiological studies relate some infant health disorders with parental occupation [15, 35-38]. Additionally, studies on male fertility in industrial sectors (pharmaceutical, plastics and particularly agriculture) associate reproductive disorders and prostate cancer with pesticide exposure [39]. There are no available data with which to establish occupational exposure to EDCs, however the existing information, although fragmented, could help outline significant traits in this field. Despite a lack of specific data, it is reasonable to assert that endocrine disruptors affect a vast array of occupation [40]. Exposure to organ chlorine biocides is associated with disabling neuroimmune disorders such as myalgic encephalopathy/chronic fatigue syndrome/post-viral fatigue syndrome, fibromyalgia and multiple sclerosis [41]. It is hypothesized that repeated exposure to these chemicals causes damage to the hypothalamus-hypophysis axis through physical or chemical micro traumas.

Doses of exposure

EDCs may cause harm at very low doses [42]. There is a nonlinear dose-effect relationship i.e. damage can occur at very low doses whereas high or intermediate doses might have no effect at all. Timing of exposure may be even more significant than level. Effects may pass to future generations as they may affect gene expression. Latency plays a great role as adverse effects may occur many years after exposure and so effects of prenatal exposure become evident mostly during adulthood. There is also ubiquity of exposure as studies that monitor the effects of EDC exposure show effects on all age groups in the population. EDCs have been detected in umbilical cord blood, hair and urine of infants and children as well as in adult blood and fat tissue. So no safe threshold can be established for EDC exposure.

Periods of particular vulnerability and time of exposure

Knowing the specific time of exposure in developing organism is essential in assessing the nature, gravity and subsequent evolution in EDC effects as they are different in embryos, fetuses, newborns and adults. If EDC exposure takes place during critical periods (like early developmental stages characterised by rapid cellular differentiation and organogenesis) damage is irreversible [43]. The latency period (the time between exposure and manifestation of the first symptoms) can be lengthy [44]. Exposure to biologically active chemicals in concentrations that affect hormones can lead to a series of effects that vary progressively through different developmental stages of the organism. Similarly, these effects might differ from the response observed during exposure to high doses of the same chemical or from responses in fully developed individuals [45]. While hormonal effects are mostly associated with signal activation and are reversible in adults, untimely exposure to hormones during foetal organ development primarily affects the structure and function of organs, causing irreversible damage [46]. The effects of in utero exposure to EDCs are not necessarily evident at birth; they may remain latent for years or become apparent in the offspring of exposed individuals, so that the consequences of exposure occur more frequently in the offspring than in the exposed parents. The genetic mechanisms by which the effects of exposure pass to future generations are known as epigenetic changes [44]. Some hormone-related cancers (breast, prostate, testicular, ovarian, and endometrial) may originate during either foetal development or puberty as there is high level sensitivity to chemical exposure during these periods.

Effects on human health and wildlife

A significant body of scientific evidence shows that many EDCs studied to date have a wide range of effects on human health as well as on wildlife. A report issued by the European Commission [47] showed the effects of EDCs on human health and wildlife. Invertebrates such as birds [48, 49-52], fish [53, 54] and reptiles [55, 56, and 57] are particularly vulnerable to the endocrine disrupting effects of pesticides [56, 57, and 58]. Studies show that their exposure to organochlorine pesticides affects their reproductive function [59, 60, and 61]. Several studies have also shown that endocrine disruptor pesticides have adverse effects on the reproductive and sexual development of humans [62, 12]. The effects on humans seem to depend on factors like age, diet, gender and occupation [12]. Age has been noted to be a sensitive factor as human fetuses, infants and children are more susceptible to EDCs than adults [63, 64, 65] as much of the damage occurs during gametogenesis and the early development of the foetus [66, 67, 68] although the effects may also be dormant till adulthood.

Epidemiological studies have shown that residential proximity to agricultural activity is a factor often described to explain developmental abnormalities such as low birth weight, foetal death and childhood cancers [69, 70, and 71]. EDCs cause damages to reproductive health both in males and females. In males, exposure to EDCs is associated with the reduction of reproductive capacity manifested by infertility [72] and decrease of sperm quality, changes in foetal development resulting in congenital deformity of the male genital tract such as chryptorchidism (failure of testicular descent) and hypospadias (abnormal placement of the male external urethra orifice) and the presence of testicular germ-cell tumors. A higher prevalence of chryptorchidism and hypospadias has been reported in areas where there is extensive farming and the use of pesticides and in sons of women working as gardeners [73, 74, and 75]. Recent studies also show a relationship between chryptorchidism and persistent pesticide concentration in maternal breast milk [67, 76, and 77]. In females, exposure to EDCs, particularly during in utero developmental stages is associated with precocious puberty, reduced fecundity pregnancy complications, endometriosis, uterine fibroids (non-cancerous tumors), as well as breast and ovarian cancer.

Uterine fibroids have been associated with exposure to organochlorine pesticides. They affect 25 to 50% of women [29] and given their hormone-dependent nature, the role of EDC exposure in their development is a topic of medical interest. The incidence of breast cancer has grown, causing great concern in both industrialised and developing countries. Risk factors include reproductive determinants, genetic predisposition and exposure to environmental pollutants. Research has shown that breast cancer is hormone-dependent and is associated with exposure to estrogenic EDCs such as polychlorinated biphenyls, polycyclic aromatic hydrocarbons (PAHs), dioxins, chlorinated furans and organic solvents [78]. It has also been reported that the risk of breast cancer is said to be four times greater in women with increased blood levels of DDE [79]. Several studies conducted on women have shown an increased risk of breast cancer caused by combined exposure to estrogenic pollutants, measured as a total load of xenoestrogens in serum and fat tissue [80]. Research conducted on Spanish women showed a relationship between breast cancer and the total load of estrogenic chemicals they were exposed to [81]. Still similar studies have revealed correlations between damage to the immune system and increased amounts of organochlorine residues in certain cancerous tissues [82]. A lot of other studies support the hypothesis that pesticide exposure influences the risk of breast cancer [83]. Another type of cancer of concern is prostate cancer where androgenic hormones play a key role in its etiology. Research has shown that high level of testosterone and its metabolite DHT increase prostate cancer risk. Prostate cancer incidence is related with exposure to EDCs, particularly organochlorine and organophosphate pesticides during their manufacture and application, as well as to PBCs, cadmium and arsenic [84]. According to some studies [85, 86] agricultural populations exposed to pesticides have consistently demonstrated a higher risk of prostate cancer than the general population. An example is DDT, an organochloride pesticide where farmer exposed to it were associated with a statistically significant higher rate of prostate cancer in a multi-site case-control study carried out in five rural areas between 1990 and 1992 in Italy [87]. Similar studies carried out in the USA and Sweden showed similar results as farmers and commercial pesticide applicators had a slightly and/or significantly higher rate of prostate cancer than the general population [88, 86, 89]. Several organochlorine EDCs are associated with testicular cancer among the p,p-DDT, PCBs and other

organochlorine pesticides. As with breast cancer, the additive effect of exposure to a combination of estrogenic EDCs is considered a risk factor. Thyroid cancer is among the most prevalent diseases in young women. It is three times more frequent in women, affecting mostly those between ages 15 and 44 [29]. Genetics play a key role as a risk factor but does not explain the sharp increase of this type of cancer in recent years. Pesticides and biocides and other environmental and occupational pollutants such as diesel exhaust are EDCs that may influence the development of such conditions.

Some Endocrine diseases in Cameroon

Some endocrine diseases in Cameroon include diabetes, cancer, hypertension, neuropathy, obesity, heart disease, high cholesterol, osteoporosis among others. Diabetes and cancer are public health issues worldwide. Here, the focus will be on cancer only. The most common cancer in the world is cervical cancer ranking the 7th position and the third leading cause of cancer deaths among females in less developed countries [90]. It is also the second most commonly diagnosed cancer after breast cancer with highest incident rates in countries with low income [91] and causing about 90% deaths in the world [92]. Saslow and collaborators [93] have estimated the prevalence of 12% worldwide. Cervical cancer is slow growing and can take over a period of 10-20 years [94]. An incidence of 80 000 and a 75% mortality rate have been reported annually with most of the cases found in sub-Saharan Africa [91]. Cancer has been recognized as a public health problem in Cameroon. The epidemiology of cancer in the whole country is not known as there is no available data. However, some studies have been carried out in selected areas with some useful data showing new cases which are diagnosed annually with related prevalence [95, 96]. The WHO Global Cancer Observatory [97] reported the number of new cases in 2018, both sexes and all ages. The top 5 most frequent excluding non-melanoma skin cancer and ranked by cases include breast (20.8%), cervix uteri (14.9%), prostate (14%), liver (6.1%), colorectum (5.5%) and other cancers (38.7%). The prevalence of cervical cancer was 7.9% in 2000. There seems to be an alarming increase in the prevalence of cervical cancer as the years go by. In 2012, EnowRock and collaborators [98] reported a 13.8% in Yaounde-Cameroon and in 2013; a study by Bhatla colleagues [99] recorded a 29.9% still in Yaounde-Cameroon. A study carried out by Nkfusai and collaborator in 2019 [90] shows that the predominant type of cancer in the Bamenda Regional Hospital was cervical with a 52.2%. A study carried out in the capital city Yaounde alone showed that cervical cancer prevalence was up to 13.8%. According to, [100] over 6 million Cameroonian females aged 15 and above are at risk of developing cervical cancer with 1993 new cases resulting to 1120 deaths yearly. Studies have shown that rural women are at high risk of developing cervical cancer [101].

Discussion

The use of endocrine disruptor pesticides continue to pose a serious threat to human and environmental health [102]. Although they remain as an indispensable tool for combating pests in agriculture, disease vectors in public health, homes, municipality and medical purposes worldwide, their effects on human and environmental health cannot be undermined. Strenuous efforts have been made to deal with pesticide safety problems for producers, consumers and the environment but more has to be done to curb their hazardous effects. Endocrine disruptor pesticides act as antagonists to the hormonal system of humans who are exposed to these compounds as they have a strong

potential to bind to estrogen or androgen receptors [25]. Exposure to EDCs could either be by ingestion, occupation or biocides [17, 31] and research suggests food to be an important source in humans. Exposure to just a single compound is hazardous as reported by most risk assessment epidemiological studies implying that the combined action of pesticides may cause higher toxic effects [103]. Factors like age, gender, diet and occupation are key in EDCs exposure. Pregnant women and infants are the most vulnerable population group to have been noted with high concentrations of EDCs as some infant health disorders have been related with parental occupation. Studies on male fertility in industrial sectors (pharmaceutical, plastics and particularly agriculture) have associated reproductive disorders and prostate cancer with pesticides exposure. Various other factors have been suggested to explain the increase in prostate cancer in agricultural or rural populations, such as dietary issues, contact with infectious agent via livestock, dust, tobacco and chemical products [104]. Additionally, exposure to organochlorine biocides is associated with disabling neuroimmune disorders. Dosage is not a factor in EDC exposure as they may cause harm at very low doses [42]. Damage can occur at very low doses whereas high or intermediate doses might have no effect at all thus no safe threshold can be established for EDC exposure. Studies have shown that if EDCs exposure takes place during critical periods like early developmental stages characterized by rapid cellular differentiation and organogenesis damage is irreversible [43, 46].

Some hormone-related cancers (breast, prostate, testicular, ovarian and endometrial) may originate during either foetal development or puberty as there is high sensitivity to chemical exposure during these periods. Endocrine disruptor pesticides affect the reproductive and sexual development of humans [62, 12]. Age has been noted as a sensitive factor as human foetuses, infants and children are more susceptible to EDCs than adults [63, 64, 65] although the effects may also be dormant till adulthood. Residential proximity to agricultural activity is a factor often described to explain developmental abnormalities such as low birth weight, foetal death and childhood cancers [69, 70, 71]. EDCs cause damages to reproductive health both in males and females [76, 67, 77]. In females, exposure to EDCs particularly during in utero developmental stages is associated with uterine fibroids (non-cancerous tumors) as well as breast cancer [83, 81, 80]. In males, prostate cancer [85, 88, 86, 87, 89]. From scientific literature on endocrine disruptor pesticides, it is evident that they cause endocrine diseases such as cancer and diabetes which are public health issues worldwide. This discussion focuses on cancer in Cameroon. Cervical cancer is the most common cancer in the world ranking the 7th position and 3rd leading cause of cancer deaths among females in less developed countries like Cameroon. It is also the 2nd most commonly diagnosed cancer after breast cancer. The epidemiology of cancer in Cameroon is not known as there is no available data but some studies carried out in selected areas show alarming prevalence. The top five most frequent excluding non-melanoma skin cancer and ranked by cases include breast (20.8%), cervix uteri (14.9%), prostate (14%), liver (6.1%), colorectum (5.5%) and other cancers (38.7%). For example, the prevalence of cervical cancer was 7.9% in the year 2000 but recent studies show an alarming increase in prevalence. This is in collaboration with a study by Coste et al [100] who reported that over 6 million Cameroonian females aged 15 and above were at risk of developing cervical cancer yearly. Another study by Tufon and colleagues showed that rural women are at high risk of developing cervical cancer [101]. Although literature has reviewed that age, gender, diet and occupation [12] are key factors

in EDC exposure, further research is required to explore the cause of the high prevalence of cancer in Cameroon.

Recommendations

On the basis of the above review, the following recommendations can be made studies should be carried out on exposure to EDC that should lead to public health measures to reduce the level of population exposure. It may be necessary that cancer patients be tested for some pesticides disruptors to roll out their presence as many cancers involve hormones such as prostate, breast and other reproductive tissues. It is important that decisions about regulation of chemicals be based on the most modern scientific understanding of how hormones act, and how EDCs perturb these actions. Since EDCs and other chemicals may act in an additive, synergistic or antagonistic manner, research also needs to consider the simultaneous co-exposures to EDCs and other chemicals. Risk assessment studies should consider the combine actions of pesticides as a mixture of these substances may cause high toxic effects than those expected from single compounds.

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