

## Impact of Pesticides Present in Food on Public Health

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### Abstract

Pesticides are the only chemicals that are intentionally released to the environment with the purpose of killing living things. Therefore, all classes of pesticides are toxic by definition, at least for some forms of life, and have the potential of causing harm to non-target organisms. It has been demonstrated that humans are continuously exposed to a cocktail of pesticides, mainly through the daily food, and it has been estimated that a given consumer could be exposed to as much as 1 mg/day of a mixture of these toxic chemicals. Studies demonstrate that this exposure begins even before conception and is continued during the uterine period, and afterwards throughout the entire life. We can now say that pesticide exposure may be a risk factor for many chronic diseases of complex etiology as it has been demonstrated they may induce alterations in: a) the endocrine system (reproductive and developmental disorders, increased risk of hormone-dependent tumors such as breast or testis, and alterations in the thyroid function or growth hormone levels); b) cardiovascular System (altering blood pressure and/or heart function); c) metabolism (some pesticides are obesogenic and diabetogenic compounds); d) central nervous system (relating pesticide exposure in children with neurocognitive disorders, or neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, in adults, or autism in children); or e) cancer. In this short review we briefly describe the main proven adverse effects to human's health, which are attributable to the exposure to pesticides.

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### Introduction

Currently food production in the developed world is based on an industrial model that enhances production by minimizing losses caused by pests through the use of pesticides. There is an extensive legislation which regulates how these pesticides should be used. To protect the consumers' health, the maximum amounts of residues that the food can contain have been set worldwide, although there are Global differences in pesticide legislation act as a technical barrier to trade. International parties such as the European Union (EU), Codex Alimentarius Commission (Codex), and North American Free Trade Agreement (NAFTA) have attempted to harmonize pesticide legislation by providing maximum residue limits (MRLs), but globally these limits remain variable (Handford, et al., 2015). However, literature demonstrates that these measures are not fully effective, probably in part due to this lack of harmonization (Handford, et al., 2015; Tago, et al., 2014). Thus, we could say that this type of intensive method of producing food many times prioritizes the economic aspects of production rather than its impact on the environment and population. The use (and abuse) of pesticides has resulted in the contamination of soil and aquifers, which adds to the residual amount of the products that are directly applied to foodstuff (Antunes, et al., 2010; Vieira, et al., 2016). Thus the residues of pesticides easily reach the population through the



daily meals, and it has been demonstrated that diet is the main source of the non-occupational exposure to pesticides (Oates, et al., 2011). Our research group demonstrated that in the Canary Islands 99% of the population has some pesticide residues, and that most of canaries have between 5 and 7 different pesticides in blood (Burillo-Putze, et al., 2014). Pregnant women of these islands have pesticide residues in amniotic fluid, indicating the existence of a prenatal exposure to these substances (Luzardo, et al., 2009). Therefore, we are able to ensure that the human exposure to these toxic pollutants begins before birth and continued throughout our entire lives (Colborn, T., 2004).

A pesticide is a chemical that is capable of killing a pest, and accordingly it can be derived that pesticides are toxic substances by definition. The question then could be whether the continued exposure to these toxic substances, even at low concentrations, can affect the health of the population. Based on the scientific evidences we can now say that pesticide exposure of general population may be a risk factor for many chronic diseases of complex etiology (Casals-Casas, et al., 2011). In this short review we briefly describe the main proven adverse effects to human's health, which are attributable to the exposure to pesticides.

### **Non-Occupational Exposure to Pesticides and Adverse Effects on Health**

**Endocrine system:** Many pesticides belong to the so-called endocrine-disrupting chemicals (EDCs), which are compounds that may disrupt hormonal balance resulting in developmental abnormalities, reproductive disorders, alterations in thyroid function, or increased incidence of hormone-dependent tumors such as breast or testicular cancers, among others (Casals-Casas, et al., 2011). About 105 pesticides can be listed as EDCs (Mnif, et al., 2011). Endocrine disrupting pesticide mixtures (EDPs) would mimic hormones, activating or inhibiting the same mechanisms than them (Mnif, et al., 2011), and contributing to modify gene expression in an abnormal manner (McLachlan, et al., 2016). More recently a growing body of research proposed that exposure to EDPs during in-utero and/or neonatal development is even more important than exposure throughout adult life, as this early exposure can cause long-term health problems via mechanisms of epigenetic memory. A major criticism to the linking of EDPs with the development of certain endocrine diseases is that this linkage in humans is usually presumed without solid experimental evidence, based only in increasing trends of suspected diseases in ecological studies of populations, or in findings from traditional epidemiological studies of individuals. However, the most plausible scenario in humans is that exposure to EDPs leads to subtle modifications of genomic and epigenomic responses, which contribute to an increasing risk of related diseases at the ecological level, but inconsistent associations, would be expected in traditional epidemiological studies, and even more *in vitro* experiments (Lee, et al., 2015). Thus, it has been shown that the increasing internal body concentrations of endocrine disrupting pesticides have an associated increased risk of endocrine alterations, such as subfertility in men and women, or alterations in child development (fetal growth, early reproductive tract development, pubertal development, or neurodevelopment) (Casals-Casas, et al., 2011).

**Metabolism:** Besides effects on the endocrine system, recently the term "metabolic disrupters" has been coined for some chemicals, including pesticides, as it has also been shown that continuous exposure to low doses of some pesticides has the ability to increase the risk of certain metabolic diseases such as diabetes, obesity, or metabolic syndrome. The prevalence of type 2 diabetes (T2D) has dramatically increased worldwide during the last few decades. There are well-known lifestyle factors, such as decreased physical activity and energy-dense diets, together with genetic predisposition, which definitely influence this increase, but the role of environmental chemicals including pesticides have been demonstrated to increase the risk of developing insulin resistance and/or disruption of pancreatic  $\beta$ -cell function, as well as disorders of glucose homeostasis (Chevalier, et al., 2015). Recent experimental studies in animals have also suggested that perinatal exposures to certain pesticides may be associated with early onset obesity. The clearest findings suggest an influence of maternal Dichloro diphenyl dichloro ethylene (DDE) exposure on offspring can cause overweight and obesity, but extensive research indicate that many other pesticides, such as organophosphate insecticides or fipronil, may be involved in the development of obesity. The evidence is even higher when exposure occurs in the perinatal period, which would result in higher adolescent body fat content, including android fat deposition, independent of puberty (Tinggaard, et al., 2016). Given the importance of these new findings, the U.S. Environmental Protection Agency has commissioned the screening of 320 pesticides, herbicides, fungicides and other chemicals in a series of high throughput assays (ToxCast™ PPAR $\gamma$  and RXR $\alpha$  assays). The preliminary results of these assays indicate some degree of PPAR $\gamma$  and RXR $\alpha$  activation and adipogenesis for many of the targeted pesticides, and conclude that it is likely that many obesogenic chemicals remain to be identified (Janesick, et al., 2016; Janesick, et al., 2016).

**Cardiovascular System:** Exposure to pesticides (especially prenatal or early exposure) has also been associated with various cardiovascular disorders, such as congenital malformations, or abnormalities of blood pressure or cardiac function. It has been reported that in most cases the causes of congenital heart defects (CHD) remain unknown, while a growing number of studies have indicated the potential role of environmental agents as risk factors in CHD occurrence. Specific classes of pesticides, such as organochlorine pesticides, some organophosphate insecticides, or some herbicides have been identified as potential risk factors for CHD (Gorini, et al., 2014). On the other hand, epidemiological studies have also reported significant associations between exposure to pesticides and increased blood pressure (BP), especially during pregnancy (gestational hypertension). The strongest associations have been reported for organochlorine pesticides (Henriquez-Hernandez, et al., 2014). Besides, experimental research in animals has demonstrated that many other pesticides, such as fipronil or organophosphorus compounds, may produce hypertension by reducing antioxidant capacity, and lowering the levels of circulating matrix metalloproteinase 2 (MMP-2) and nitric oxide (NO) metabolites (Chaguri, et al., 2016).

**Nervous system:** Along with the wide use of pesticides in the world, a parallel increase in the incidence of neurodegenera-

tive disorders like Parkinson, Alzheimer, or amyotrophic lateral sclerosis (ALS) has occurred, and research indicates that this association is not casual (Saeedi Saravi, et al., 2016). Once again, prenatal exposure to pesticides seems to be especially worrying, as may result in impaired motor and cognitive development in newborns and infants. As described for other chronic pathologies, the best studied pesticides are the persistent and bioaccumulative organochlorine compounds, which have been described to contribute to neurodegenerative and neurocognitive diseases (Saeedi Saravi, et al., 2016). However, other classes of pesticides, such as pyrethroids, organophosphates, carbamates, and some types of herbicides have been associated to the development of pathologies such as Parkinson's disease (PD), leading to  $\alpha$ -synuclein accumulation, which is which is a key constituent of Lewy bodies, a crucial factor in PD pathogenesis, and to the depletion of dopaminergic neurons. On the other hand, some of these pesticides have been involved in Alzheimer's disease due to their ability to increase beta-amyloid (A $\beta$ ) peptide and the phosphorylation of Tau protein (P-Tau), causing senile/amyloid plaques and neurofibrillary tangles (NFTs) characteristic of this disease (Chin-Chan, et al., 2015). Finally, numerous studies have suggested a strong relationship between organophosphate and organochlorine pesticides and autism spectrum disorder, whose rapid increase in prevalence also parallels the increase in the use of pesticides and other chemicals (Fujiwara, et al., 2016).

**Cancer:** The highest amount of evidence about the adverse health effects of environmental exposure to pesticides has been cancers. Obviously not all pesticides have been linked to cancer, but among several hundreds of active ingredients evaluated for carcinogenicity by the US Environmental Protection Agency (EPA), 25 pesticides were classified as likely to be carcinogenic (probable) to humans, and 52 had suggestive evidence of carcinogenic potential (suspected) to humans ([http://npic.orst.edu/chemicals\\_evaluated.pdf](http://npic.orst.edu/chemicals_evaluated.pdf)). The molecular mechanisms underlying such effects are supposed to be very complex, and remain unclear in most cases, and therefore deserve tremendous efforts of investigation. It is probable that the effects of environmental concentrations of pesticides producing increased risk of cancer are more related to subtle epigenetic mechanisms than to direct mutagenesis or genomic damage (Collotta, et al., 2013). Several epigenetic mechanisms related to cancer development, including DNA methylation, histone modifications and microRNA expression, can be triggered by environmental factors, such as pesticides. *In vitro*, animal, and human investigations have identified several classes of pesticides that modify both genetic and epigenetic marks<sup>[23]</sup>. Regardless the mechanism by which pesticides increases the risk of cancer, many epidemiological studies link malignancies to pesticides, including leukemia, neuroblastoma, Wilms' tumor, soft-tissue sarcoma, Ewing's sarcoma, non-Hodgkin's lymphoma, and cancers of the brain, colorectum, prostate, testes, and all classes of gynecological cancers. Of special concern are children as they are especially vulnerable and are exposed to pesticides from use in homes, schools, other buildings, lawns and gardens, through food and contaminated drinking water, from agricultural application drift, overspray, or off-gassing, and from carry-home exposure of parents occupationally exposed to pesticides (Zahm, et al., 1998). As previously described for other chronic diseases prenatal exposure to pesticides seems to be determinant for the development of both childhood and adulthood cancers (Collotta, et al., 2013).

## Conclusion

In short, it can be said that the uncontrolled chemical pollution of our environment, to which the pesticide use contributes greatly, have a direct effect in the human populations and their health. Pesticide use and the inherent environmental contamination that produces can be considered a significant risk factor in chronic and increasingly prevalent pathologies worldwide. Being a 'preventable' factor, it seems reasonable to conclude that it is urgent to articulate measures directed to reduce population exposure to pesticides, and especially in those most susceptible population subgroups (women of childbearing age and children).

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