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The Possible Role of Organophosphorus Pesticides in Augmentation of Food Allergenicity: A Putative Hypothesis

^{1,2}R. Falak, ²M. Sankian and ³A.R. Varasteh

¹Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

²Immunobiochemistry Laboratory, Immunology Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

³Allergy Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding Author: Abdol Reza Varasteh, Allergy Research Center, Department of Allergy and Immunology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, 9196773117, Iran Tel: 985117112410 Fax: 985117112596

ABSTRACT

During the last few decades, the prevalence of food allergies has been increased dramatically. Concurrently organophosphate pesticides have been increasingly used in agriculture and in select industries. It seems that these organic agents might perpetuate the clinical severity of allergic manifestations in atopic patients, or even modify the epigenetic control of allergen expression in plants. In addition to altered allergen expression, these tiny molecules may directly bind to non-allergenic proteins and potentially modify their epitopes-now rendering these proteins allergenic. This type of change would be along the lines of how certain metal pollutants (like chromium) can modify proteins in the skin after dermal contact and give rise to 'allergic' reactions in the exposed host. Lastly, the organophosphate pesticides might also lead to increases in the production of polyamines in fruits and cause pseudo-allergic reactions. This review analyzes some evidence regarding possible mechanisms of pesticide-induced allergenicity of plant proteins.

Key words: Allergenicity, organophosphates, pesticides, dermal contact, pseudo-allergic reactions

INTRODUCTION

Although, there is not enough scientific evidence to confirm that organic foods are safer than conventional foods, people commonly find them more desirable. Recently, there was an increased demand of these types of foods, despite of their higher prices (Magkos *et al.*, 2003, 2006; Crinnion, 2010). Moreover, since introduction of genetically modified foods, a general drawback due to fear of allergic side effects of these products has been publicized (Helm, 2002; Meredith, 2005; Cantani, 2006; Selgrade *et al.*, 2009). The other type of fear comes from canned and processed foods due to having preservatives. Although, application of green houses helped in production of fruits and vegetables at any time of the year and in different climates; it should be considered that they have a different maintenance and pesticide spraying systems. Moreover, introduction of new pesticides have increased the possibility of their uncontrolled applications. Unfortunately, there are not suitable checkpoints for amount and time of pesticide spraying in traditional systems, especially in developing countries.

In fact, the claim of improved safety of organic foods largely goes back on their minimal pesticide contamination. Obviously, organically grown fruits and vegetables contain significantly lower levels of pesticide residues; however, agriculturists believe that the amount of pesticide residues in conventional foods is usually below the established toxicity levels. Taking together, although inappropriate use of pesticides in developing countries may lead to excessive direct exposure of the inhabitants to these compounds and consequently raise the prevalence of their undesired adverse effects; there is scarce data available about indirect effect of these chemicals on human health, especially alterations in the allergic status of plant proteins.

We hypothesize that there could be an association between the increased application of pesticides and increments in allergic disease-especially food allergies in recent decades. Since, these pesticides are categorized into different types with various mechanisms of actions, a singular evaluation of their impact on allergenicity could be a complicated procedure. In this article, we discuss the possible impact of Organophosphate Pesticides (OPs), as common pollutants, on the augmentation of food protein allergenicity. Still, it is important to note that the potential involvement of other types of widely-used classes of pesticides in these toxic processes should not be neglected.

HYPOTHESIS

It was previously shown that environmental pollutants could affect expression levels of allergens or alter their allergenicity. Most of such studies were focused on alteration of atmospheric conditions. So, the impact of industrial air pollution (Behrendt *et al.*, 1997; Armentia *et al.*, 2002; Diaz-Sanchez *et al.*, 2003; Proietti *et al.*, 2003; Chehregani *et al.*, 2004; Bartra *et al.*, 2007), ultraviolet irradiation and increment of global temperature (Ziska *et al.*, 2003; D'Amato and Cecchi, 2008), carbon dioxide (Caulfield and Ziska, 2000; Mohan *et al.*, 2006) and ozone contents on aeroallergens (Ziska, 2002; D'Amato *et al.*, 2005; Jang *et al.*, 2005) were investigated.

Since the 1950s, the use of pesticides has doubled every decade. Interestingly, in parallel, the incidence of allergic disease has also increased in concert with increased industrialization and application of pesticides in agriculture. However, this increment could be partly due to better surveillance and more sensitive allergy detection methods, as well as pseudo-allergic reactions caused by food-borne toxicants, preservatives, and/or additives. Several studies have already confirmed the potential cytotoxic and genotoxic side effects of pesticides on occupationally-exposed populations (Al-Saleh, 1994). Moreover, an association was found between application of a number of OPs and development of allergic contact dermatitis (Rycroft, 1977; Matsushita *et al.*, 1985; Sharma and Kaur, 1990; Sato *et al.*, 1998) as well as exacerbation of asthma (manifestations) in antigen-sensitized patients after inhalation of OP, via bronchoconstriction and airway hyper-reactivity mechanisms (Bryant, 1985; Deschamps *et al.*, 1994; Dong *et al.*, 1998; Fryer *et al.*, 2004; Gaspari and Paydarfar, 2007; Proskocil *et al.*, 2008).

Still, however, it remains unclear whether these widely-used chemicals affect protein allergenicity and thereby contribute to the observed increases in allergic diseases. It is clear that stressors such as heat, cold, winter, drought, pollution, reduced light level, pH variations and lack of nutrients could affect cell protein expression patterns via epigenetic mechanisms. Some OP (such as chlorpyrifos) may up-regulate expression of proteins-including those involved in inflammatory pathways-via phosphorylation of tyrosine residues (Mense *et al.*, 2006; Ghelis, 2011; Mithoe and Menke, 2011). Moreover, OPs may activate extracellular signal-regulated kinase (ERK), most probably via accumulation of diacylglycerol molecules. The elevation of this secondary

messenger molecule occurs as a result of inhibition of the activity of the OP-sensitive diacylglycerol lipase (Bomser and Casida, 2000; Bomser *et al.*, 2002). As a result, these types of pesticides should also be considered potential stressor agents capable of affecting the expression of Pathogenesis-Related (PR) proteins (Graham, 2005).

The epigenetic control of allergic disease has recently been studied in humans (Renz *et al.*, 2011). However, the epigenetic control of plant allergens has not yet received similar detailed scrutiny (Steimer *et al.*, 2004; Rapp and Wendel, 2005; Boyko and Kovalchuk, 2008). Some recent studies revealed the epigenetic control of allergen expression in peanut embryos (Li *et al.*, 2009, Guohua *et al.*, 2010). It is our belief that there should be an association between allergenic potentials of plants and the impact of environmental factors on epigenetic modification and control of genes responsible for production of allergens such as profilin and lipid-transfer proteins.

As is already known, auto-degradation of OPs may result in production of active organic phosphorous molecules that could directly attach to plant (or animal) proteins through serine, lysine, threonine, tyrosine and histidine amino acids and affect their function/integrity. These could be reflected in several ways. (1) In the case of enzymes such as esterases that have a serine-bearing active site, OP conjugation may lead to alteration of the active site structure and, ultimately, enzyme inactivation. In another scenario, tyrosine-usually implicated in signaling pathways-phosphorylation might lead to up-regulation of gene expression (Ghelis, 2011; Mithoe and Menke, 2011) and increased risk of expression of allergy-inducing antigens. (2) Phosphorylation may cause a mild change in nascent protein structures and so result in presentation of some new epitopes (i.e., phosphorylated/non-phosphorylated peptides) with newly-modified immunoreactivity potentials (Nishimura *et al.*, 1998; Mohammed *et al.*, 2008; Weiskopf *et al.*, 2010). These changes in epitopes could be monitored by phosphorylation detection methods, as well as by comparison of immunoblots of pesticide-treated and untreated plant extracts using sera from allergic patients (Noorbakhsh *et al.*, 2010). (3) Alterations in the phosphorylation of signaling pathway molecules might result in activation of transcription factors and, again, altered allergen expression levels (Niijima *et al.*, 1999; Bomser and Casida, 2000; Mense *et al.*, 2006). Here, evaluation of PR protein (stressor-sensitive family of proteins) expression levels could be used to monitor pesticide-induced changes (Midoro-Horiuti *et al.*, 2001; Graham, 2005).

In an alternative mechanism (i.e., one not dependent on the above-noted complex formations), plants that are grown under stress conditions (such as drought, cold, altered soil pH) often contain higher level of polyamines and other biogenic amines (such as histamine) that upon consumption can trigger the same types of allergy-like symptoms outlined above (Di-Tomaso *et al.*, 1988; Kiss *et al.*, 2006). Biogenic amines are also produced in response to abiotic and biotic stress conditions (Moret *et al.*, 2005; Alcazar *et al.*, 2006; Groppa and Benavides, 2008; Gill and Tuteja, 2010; Hussain *et al.*, 2011). It is plausible to assume that some pesticides and/or herbicides possess some abiotic stressor characteristics (for example, in the case of excessive [overdosing] application) that could increase the production of such biogenic amines in plants (Sprecher *et al.*, 1993; Saladin *et al.*, 2003; Graham, 2005; Yin *et al.*, 2008; Toni *et al.*, 2010). Oxidative stress could also lead to enhanced bioamine formation; unfortunately, while it is clear that OP agents can cause oxidative stress in animal cells (Banerjee *et al.*, 2001; Shadnia *et al.*, 2005; Soltaninejad and Abdollahi, 2009; Moore *et al.*, 2010), there is scarce data about such effects in plant cells. Alternatively, even without inducing bioamine synthesis, some pesticides (especially OP) on the plants-when consumed-might directly activate mast cells and cause histamine release

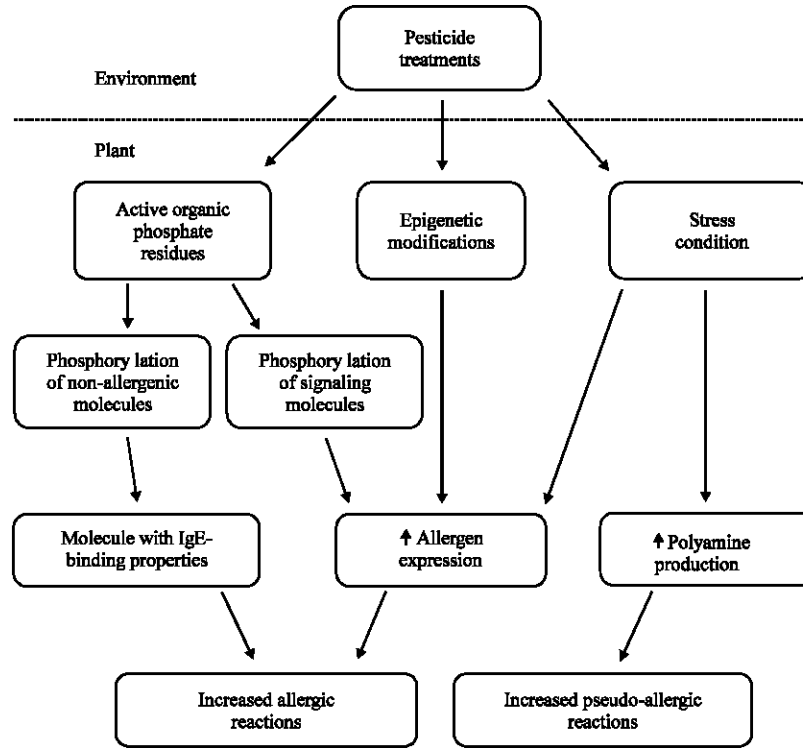


Fig. 1: Schematic view of the hypothesis. Pesticides may affect plant allergen expression level through different mechanisms

(Gietzen *et al.*, 1996; Xiong and Rodgers, 1997). This would be readily obviated in histamine-intolerant hosts who might consume recently-sprayed raw fruits and vegetables that are rich in pesticide remnants (Maintz and Novak, 2007).

Taken together, it seems that pesticides may affect the potential of allergenicity of plants through different mechanisms (Fig. 1). However, we have not yet found any specialized study in the literature that specifically has addressed this concept. Although, the side effects of these types of chemicals have been studied in human and animal cells, there is a paucity of information on effect of optimized (or even overdose) amounts of these compounds on domestic plant cells, in particular with regard to the issue of allergenicity.

ENVIRONMENTAL FACTORS AND ALLERGY

As mentioned above, some environmental pollutants can affect protein allergenicity. With regard to allergen sources, most studies have focused on the impact of air pollution on pollen allergens (Koren, 1997; D'Amato *et al.*, 2000; D'Amato, 2002). Due to continuous damage, pollens from polluted urban sources show increased allergenicity relative to those from more rural areas (D'Amato, 2000; Armentia *et al.*, 2002). Although this is mostly due, in part, to increased bioavailability of pollen allergens, some experiments indicates that allergen over-expression might also be occurring (Behrendt *et al.*, 1997; D'Amato, 2000; Behrendt and Becker, 2001; Armentia *et al.*, 2002; D'Amato *et al.*, 2010). Electron microscopic analyses of pollen grains have revealed that pollutants appear to induce changes in pollen shape and tectum, causing increased allergen exposure (Chehregani *et al.*, 2004). Moreover, exposure of non-allergic pollens

to air pollutants may result in expression of new IgE binding proteins as well as variations in electrophoretic patterns of pollen extracts (Chehregani and Kouhkan, 2008). Bryce *et al.* (2010) recently reported 26 differences in protein spot intensities between pollen from urban and rural areas following two-dimensional electrophoresis.

Regarding allergenic molecules, much effort has been exerted by investigators into determining expression levels of PR proteins. This family of allergens is constitutively expressed in some plant tissues, such as pollens or ripe fruits; however, their expression levels may be increased in response to stress conditions such as exposure to certain chemicals (Ebner *et al.*, 2001; Midoro-Horiuti *et al.*, 2001; Bjorksten, 2005).

PESTICIDES

Pesticides constitute a heterogeneous category of chemicals and are specifically designed to control plant diseases. Nowadays industrial horticulture without these chemicals seems impossible. However, appropriate application of these potentially toxic chemicals should be well considered in production of safe foods and increment of public health. During the last few decades, a considerable increase in food allergies has occurred; this was in concert with increases in industrialization and application of pesticides in agriculture. However, the impact of these widely-used chemicals on allergy has not been well studied. Food allergies have a number of socio-economical disadvantages and recently “hypo-allergenic” labels have become an attractive lure for consumers (Crevel, 2005).

Interestingly, the prevalence and pattern of food allergies varies in different countries (Shek and Lee, 2006; Gelincik *et al.*, 2008; Shek *et al.*, 2010). Furthermore, allergies are more common in urbanized and industrialized populations rather than people from rural regions (Bibi *et al.*, 2002; Dagoye *et al.*, 2003; Majkowska-Wojciechowska *et al.*, 2007; Hamid *et al.*, 2011). Although, several explanations including hygiene hypothesis and genetic dissimilarities were proposed; the influence of epigenetic factors resulting from environmental conditions have been more anticipated. So, far, the effect of air pollution; life style, probiotics and nutritional habits on maturation of immune system have been studied and their possible roles in leading of the immune system toward an atopic status was discussed. Pesticides are generally small molecules and do not directly elicit immediate type allergic reactions. However, these haptenic molecules may bind to some tissue proteins and contribute to delayed type hypersensitivity reactions.

Plants up-regulate the expression of PR proteins in stress conditions, such as exposure to physical or chemical agents (Ebner *et al.*, 2001; Belhadj *et al.*, 2008; Petit *et al.*, 2009). It is not clear if exposure to pesticides, as common stressors, could result in over-expression of PR proteins. Some recent effort of horticulturists to produce fruits with high resistance to pathogens is partly based on over-expression of PR proteins. Moreover, there is scarce data about the capability of chemicals such as pesticides on alteration of allergenic status of non-allergic plant proteins. Beil *et al.* (2001) studied binding of pesticides to apple extract proteins and showed a 13% binding of chlorpropham to apple proteins. These authors also showed that chlorpropham binding decreased reactivity of the specific IgE to apple allergens that seems to be due to steric hindrance. Moreover, they showed a direct histamine liberation from basophils that was induced by pesticides. Surely, these types of effects depend on the amount and type of the investigated chemicals. Usually, there is an enough period between pesticides spraying and fruits marketing time which helps in degradation of toxic pesticides. However, some pesticides such as OPs may activate transcription factors and consequently change the expression levels of allergens.

ORGANOPHOSPHATE PESTICIDES

Organophosphate Pesticides (OPs) are commonly used all over the world for different applications. So far, several clinical cases of contact dermatitis (Rycroft, 1977; Matsushita *et al.*, 1985; Sharma and Kaur, 1990) and asthma following inhalation of these chemicals were reported (Bryant, 1985; Deschamps *et al.*, 1994). Usually it is considered that these types of asthmatic symptoms occur due to direct activation of mast cells and basophiles and release of active mediators; however, they may be due to activation or over-expression of some enzymes. Niijima *et al.* (1999, 2000) confirmed that intravenous injection of OPs could augment the tyrosine phosphorylation and activation of several kinases. Application of high-dose forms of such pesticides could probably cause similar effects in plants.

In the past, risk assessment of pesticides was limited to evaluation of their toxic effects on human health but nowadays other pathological risks are taken into account too. Several studies evaluated the side effect of OPs on laboratory animals as well as human physiology. Most of these studies focused on evaluation of cytotoxic effects of these compounds on nervous, respiratory and immune systems, especially due to accidental swallowing of them by children. The high level exposure of these compounds is associated with poorer neurodevelopment (Abou-Donia, 2003; Colosio *et al.*, 2003; Bajgar, 2005; Kanthasamy *et al.*, 2005; Jameson *et al.*, 2007; Keifer and Firestone, 2007; Moser, 2007; Slotkin and Seidler, 2007; Eskenazi *et al.*, 2008; Rosas and Eskenazi, 2008).

Although, OPs can clearly cause toxic effects after acute exposure(s), their more chronic adverse effects should not be neglected. The most prominent side effect of OPs in animals is cholinergic disorders due to phosphorylation of cholinesterases (Shankar, 1978; O'Malley, 1997; Bajgar, 2005; Goel and Aggarwal, 2007). Mechanistically, they are reactive compounds and exert inhibition on esterase activity by irreversibly binding to the catalytic site of these enzymes, causing acute and chronic neurotoxic effects (Emmett *et al.*, 1985; Maurissen, 1997; Garg *et al.*, 2004a, b). However, these effects could initiate other neurologic problems such as Parkinson disease (Kanthasamy *et al.*, 2005). Serine hydrolases which play a vital role in complement and coagulation systems, are also non-reversibly inhibited by OPs. Other adverse effects of OPs, namely, phosphorylation of proteins, imposition of oxidative stress and modulation of signal transduction pathways could lead to disruption or damage of the immunocytes (Rodgers *et al.*, 1986; Botham, 1990; Banerjee, 1999; Galloway and Handy, 2003; Neishabouri *et al.*, 2004; Colosio *et al.*, 2005; Li, 2007). However, the outstanding adverse effect of OPs on human immune system is suppression of cell-mediated immunity and development of contact dermatitis and autoimmune diseases (Galloway and Handy, 2003; Neishabouri *et al.*, 2004; Li and Kawada, 2006; Alluwaimi and Hussein, 2007; Li, 2007).

Pesticides have been considered as potential genotoxic and mutagenic chemicals, too. There is an association between occupational exposure to pesticides and chromosomal aberrations (Garrett *et al.*, 1986; Joksic *et al.*, 1997; Bolognesi, 2003; Sanchez-Pena *et al.*, 2004; Pina-Guzman *et al.*, 2006; Hreljac *et al.*, 2008; Salazar-Arredondo *et al.*, 2008). It was shown that OPs could phosphorylate protamines and lead to alterations in sperm chromatin condensation and DNA damage during late spermatid differentiation (Pina-Guzman *et al.*, 2005).

CONCLUSION

It appears that organophosphate pesticides which form a major bulk of commonly used insecticides, should be more closely examined for their possible role in establishment or augmentations of allergic disease. The degradation of OPs may result in production of active

organic phosphorous molecule that could directly attach to proteins and affect their function. These modifications could also lead to 'up-regulation' of allergen expression and/or an alteration of the protein's allergenic status. At a 'global' level, such changes might possibly affect the allergenicity potential of foods, fruits and pollen proteins.

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