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Health and Insecticides

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1. Introduction

Pyrethroids are synthetic chemicals similar to pyrethrins in the pyrethrum extract which is obtained from Chrysanthemum plant. Historically, pyrethroids have been classified into two classes that differ in their chemical structure and symptoms of exposure:
Type I pyrethroids include allethrin, tetramethrin, d-phenothrin, permethrin, and bioresmethrin.
Type II pyrethroids include cypermethrin, cyphenothrin, deltamethrin, cyfluthrin, fenvalerate , (Klaassen *et al*, 1996; Ray, 1991).
Pyrethroid kills the insects that eat or come in contact with it by quickly affecting the insect's central nervous system (Tomlin, 1994; Costa, 1997).
Cypermethrin is one of the most widely used type II pyrethroid insecticide, first synthesized in 1974 (WHO, 1989; Patel *et al*, 2006).

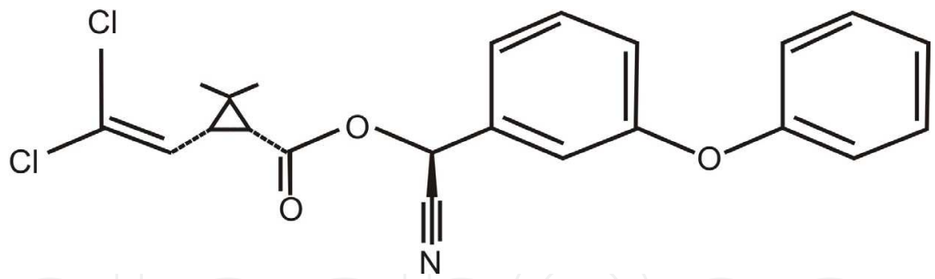

Fig. 1. Structural Formula of Cypermethrin; Molecular formula: $C_{22}H_{19}Cl_2NO_3$, Molecular weight: 416.3

It is considered to be environmentally safe and widely used in agriculture and veterinary medicine (Shukla *et al*, 2002). It is classified by the World Health Organization (WHO) as "moderately hazardous" *(WHO Recommended Classification of Pesticides by Hazard 1994-95, WHO, Geneva)*. It is a fast-acting neurotoxin and is known to cause free radical-mediated tissue damage (Patel *et al*, 2006). Like other pyrethroids, cypermethrin kills the insects by interacting with the sodium channels in nerve cells through which sodium enters the cell in order to transmit a nerve signal. These channels can remain open for up to seconds instead of the normal period of a few milliseconds, after a signal has been transmitted. Cypermethrin also interferes with other receptors in the nervous system. The effect is that of long-lasting trains of repetitive impulses in sense organs. (Rodriguez *et al*, 2008; Tomlin, 1994; Costa, 1997).

Cypermethrin may become an air pollutant and its toxic effects in humans include abnormal facial sensations, coughing, dizziness, tingling, burning, itching, headache, nausea, anorexia and fatigue, vomiting and increased stomach secretion. It is also a skin and eye irritant (Klaassen *et al*, 1996; Sitting, 1991). Patients with severe exposure to cypermethrin may suffer from muscular twitching, coma and convulsive attacks. Mice on exposure to cypermethrin display symptoms including writhing, convolutions, salivation, etc (Lawrence *et al*, 1982). Chronic symptoms after exposure to cypermethrin include brain and locomotory disorders, polyneuropathy and immuno-suppression, and resemble the multiple chemical sensitivity syndromes (Müller-Mohnssen, 1995).

Cypermethrin is classified by the US EPA as a weak category C oncogen, a possible human carcinogen with evidences of carcinogenesis in animals but no evidence of carcinogenicity in humans (US EPA, 1989; US EPA, 1997). It possesses complete carcinogenic and co-carcinogenic potential (tumor initiating and promoting potential) in both the sexes of Swiss albino mice and male as well as female mice develop benign tumors in skin upon exposure to cypermethrin (Shukla *et al*, 2002).

Cypermethrin is genotoxic in mouse spleen and bone marrow cells where it induces the chromosomal aberration and sister chromatid exchange (Amer *et al*, 1993; Giri *et al*, 2003). It induces systemic genotoxicity in mammals by causing DNA damage in vital organs like brain, liver, kidney, apart from that in the hematopoietic system (Patel *et al*, 2006). It possesses mutagenic activity inducing dominant lethal mutations in male germ cells of mice (Shukla *et al*, 2002). It induces chromosomal aberrations and single stranded breaks in DNA in the cultured human lymphocytes. Moreover, it also affects the cell cycle causing a decrease in the proliferative rate index (Puig *et al*, 1989).

Lungs are an important entry point for airborne contaminants (e.g., toxic gases, particulates, aerosols, volatile organic solvents etc). Toxicants present in the breathing zone may be absorbed in the nasopharyngeal, tracheobronchial, or pulmonary exchange surfaces of the lung, depending upon the physical and chemical properties of the toxicant. But the lung alveoli and the terminal bronchioles are one of the most effective surfaces in the body for absorption and are responsible for most of the resultant toxicity that occurs during respiratory exposure. Materials that remain within the respiratory system may produce local toxicity that may take form of lung cancer (Richards, 2008).

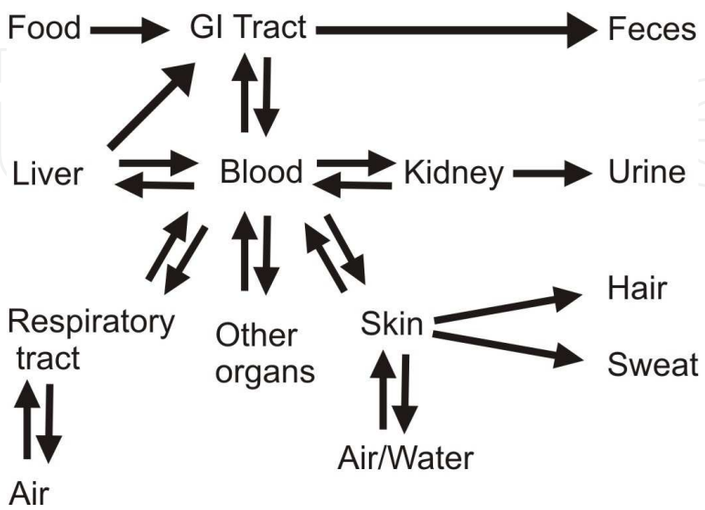

Fig. 2. Absorption & distribution of chemicals in animals (Apostoli, 2002).

Toxicants may also pass into the systemic circulation from the lungs and affect the other body parts especially the liver because the hepatocytes directly receive the chemicals from the blood (Richards, 2008).

The process of oncogenesis is a progression of events that lead to the formation of a tumor. Of the known carcinogenic agents (viruses, ultraviolet and ionizing radiations, and chemicals), chemicals appear to be of major importance in the induction of human cancers (Richards, 2008; Miller & Miller, 1981). Chemical carcinogenesis is a multistage process which involves initiation, promotion & progression (Simons, 1995; Pitot, 2001; Luch, 2005; Richards, 2008; Miller & Miller, 1981; Lyman, 1992). Initiation requires an irreversible change in the cellular genome within the portions of genome that are involved in regulating process of cellular growth and differentiation, whereas promotion moves initiated cells further along their transformation, commonly associated with prolonged and reversible exposure. Tumor progression results in genotypic and phenotypic changes associated with tumor growth, invasion, and metastasis (Richards, 2008; Miller & Miller, 1981; Lyman, 1992).

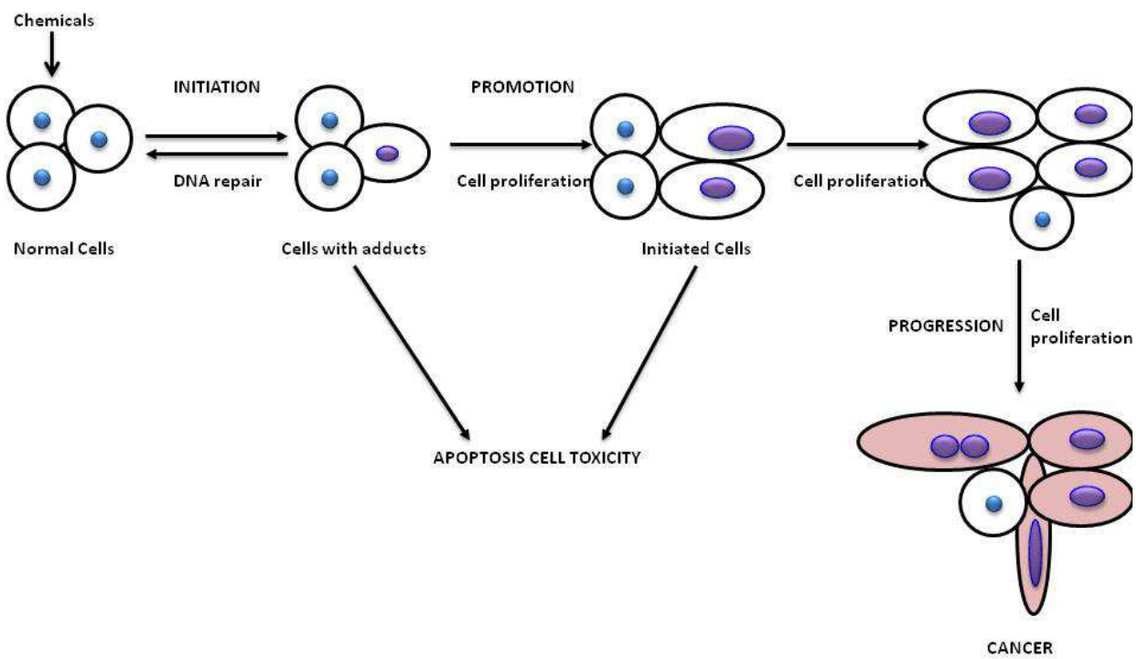

Fig. 3. Malignant cell characteristics (Adapted Oliveira et al. An Acad Bras Cienc (2007), vol. 79(4): 595).

The process of oncogenesis requires several changes in the normal properties of a cell. Typically the malignant cell properties include acquisition of self-sufficiency in growth signals and loss of sensitivity to anti-growth signals (leading to uncontrolled growth), loss of capacity for apoptosis, acquisition of sustained angiogenesis, acquisition of ability to invade neighbouring tissues, acquisition of ability to build metastasis at distant sites and loss of capacity to repair genetic errors (Hanahan and Weinberg, 2000).

Lung cancer is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells

(Ashley, 1980). The major causes of lung cancer are chemical carcinogens such as those in tobacco smoke and air pollutants, ionizing radiation as radon gas, and viral infection (Lombard, 2006; Kotin & Falk,1959; Stock & Campbell,1955).

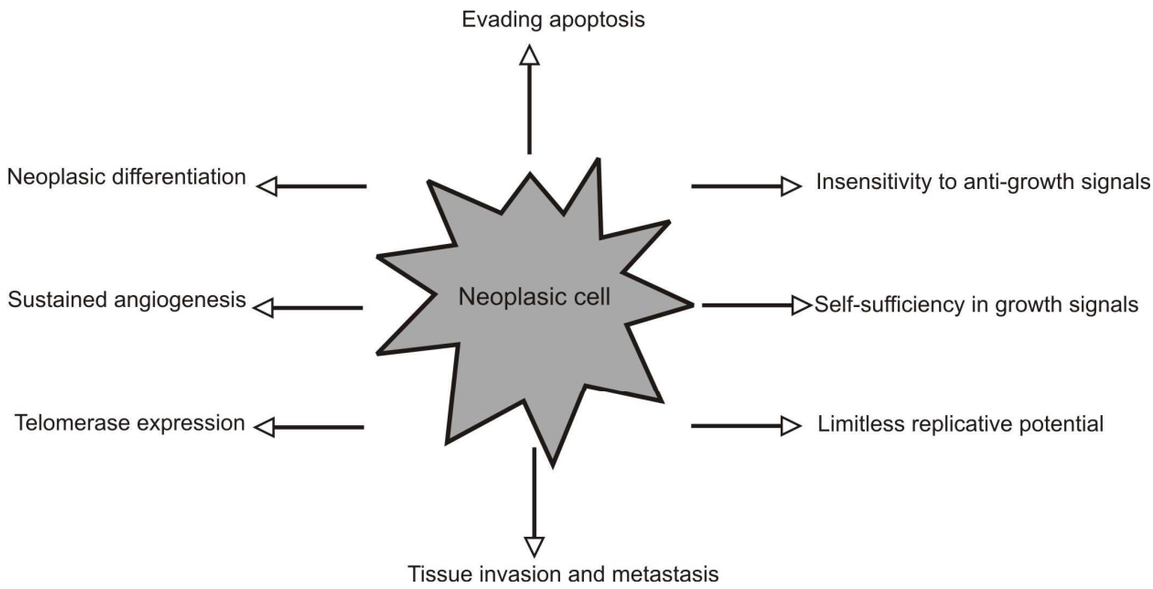

Fig. 4. Chemical carcinogenesis stages and the occurrences involved in each one. (Adapted Oliveira et al. An Acad Bras Cienc (2007), Fig. 2, , vol. 79(4): 597).

There are many histopathologic types of lung cancer and World Health Organization (WHO) classification, recommended originally in 1977 is usually accepted as the definitive classification of this cancer. Major types of lung cancer are adenocarcinoma, squamous cell carcinoma and large cell carcinoma collectively known as non-small-cell lung cancer (NSCLC) accounting for 75-80% of all lung cancers and small-cell lung cancer (SCLC) comprises the remaining 20-25% of lung cancer cases (Colby *et al*, 1995).

Adenocarcinoma is the most common form of lung cancer originating in the peripheral glandular tissues of lung (Guillan *et al*, 1967). These tumors predominantly consists of mucin-secreting or non-mucinous columnar cells arranged as regular or irregular tubular and papillary elements supported by a well or poorly developed fibrous stroma (Ashley & Davies, 1967).

Squamous cell carcinoma also called epidermoid carcinoma usually appears as central tumors consisting mainly of clearly defined flattened or polygonal cells of pavement type arranged in keratinizing whorls, irregular masses and narrow or wide anatomizing or branching columns dispersed haphazardly through a fibrous stroma (Smith & Dexter, 1963).

Large cell or bronchiolar carcinoma is the least common of all NSCLCs. It is composed of large cells with prominent nucleoli, and no mucin production or intercellular bridging is identified. A variant of large cell carcinoma has been identified; it contains neuroendocrine features and is called large cell neuroendocrine carcinoma (Zhiyong *et al*, 2006).

Small cell lung carcinomas (SCLC) typically are centrally located, arising in peribronchial locations. These are richly cellular neoplasms consisting of more or less regular, darkly staining cells with characteristic nuclei, which because of their shape have been linked to oat grains. These nuclei are set in a cytoplasm so flimsy that it is barely discernible and common

appearance is that of nuclei closely knit and lying in an indistinct web- like cytoplasm with cell membrane rarely clearly defined (Chaudhuri, 1973; Wurschmidt *et al*, 1996).

Cancer of the liver refers to the uncontrolled and abnormal growth of cells in the liver. Most cases of the liver carcinomas are not primary but are the result from the metastases of other tumors as that of GI tract and lung cancer. The most frequent, malignant, primary liver cancer is hepatocellular carcinoma (HCC) an aggressive hepatic neoplasm which usually occurs in combination with cirrhosis (Gall, 1960). It has been suggested that HCC arises as a very well differentiated cancer and proliferates with a stepwise process of dedifferentiation of mature cells. Many HCCS seem to arise from dysplastic nodules (DNs) on the basis of evidence of the DNs containing HCC foci, frequent association of DNs in the vicinity of HCC, and clinical progression from DN to HCC (Kojiro and Roskams, 2005).

Microscopically, hepatocellular carcinoma has four cytological and architectural patterns: fibrolamellar, pseudoglandular (adenoid), pleomorphic (giant cells) and clear cells. In well differentiated forms, tumor cells resemble hepatocytes, for trabeculae, cords and nests, and may contain bile pigment in cytoplasm. In poorly differentiated forms, malignant epithelial cells are discohesive, pleomorphic, anaplastic and giant. The tumor has a scant stroma and central necrosis because of the poor vascularization (Hou & McFadzean, 1956; Takayasu *et al*, 2004).

Cholangiocarcinoma constitutes 10-22% of all the primary epithelial cancer of the liver and occurs most often in non-cirrhotic tissues (Menias et al, 2008; Patton & Horn, 1964; Steiner, 1957).It is a malignancy of biliary duct system that may originate in the liver and extrahepatic bile ducts, which terminate at the ampulla of Vater (Lake, 1993). A carcinoma arising from the intrahepatic bile ducts is typically a well differentiated adenocarcinoma that exhibit glandular or acinar structures; intracytoplasmic mucin is almost always observed. Characteristically, cells are cuboidal or low columnar and resemble biliary epithelium. A dense fibrous stroma is characteristic and may dominate the histologic architecture. It tends to invade lymphatics, blood vessels, perineural and periductal spaces, and portal tracts. A dense fibrous stroma is characteristic and may dominate the histologic architecture. It tends to invade lymphatics, blood vessels, perineural and periductal spaces, and portal tracts (Ashley, 1980).

Cypermethrin and other pyrethroids have been used worldwide in the fields, gardens and homes for the last few decades. Although these insecticides have benefits but they also have side effects especially when they are used in increasing amount. Continuous exposure to these insecticides may cause severe disorders especially the mutations in the genome leading to cancer.

The histopathological changes in the lung and liver tissues of cypermethrin exposed mice have shown significant changes. Exposure of the mice to cypermethrin through inhalation induces significant time dependent changes in the histopathology of lung as well as liver tissue. Inhalation is a major route of exposure to air born pollutants such as the pesticides (Emmendoerffer *et al*., 2000; Richards, 2008). Lungs and liver are the organs which are at highest risk to the environmental pollutants especially the air born chemicals (Dixon *et al*., 2008). Cypermethrin has shown the carcinogenic effect in the lung tissues of mice. Exposure to cypermethrin caused a gradual distortion of normal structure of alveoli in the lung. Cypermethrin induces hyperplasia and necrosis among the alveolar cells. There was also inflammation of lung tissue leading to pulmonary edema and alveolitis. It also induced pulmonary fibrosis due to which size of alveolar sac was reduced and alveolar walls became thicker.

Epidemiologic data showed an increase in the number of cancer cases in persons involved in agricultural production using pesticides (Kornuta *et al*., 1996). Toxicological studies suggest

that cypermethrin and other pyrethroids have carcinogenic effects (Shukla *et al*., 2002). There is evidence that pyrethroids induce benign tumors in the lungs of mice (Ishmael and Lithfield, 1988). Inhalation of pyrethroids may cause alveolitis, pulmonary edema, and damage to lung cells (Tian, 1993). Lung cancer develops through a series of progressive pathological changes occurring in the respiratory epithelium (Vineis and Husgafvel-Pursiainen, 2005)

Pyrethroids are known to be genotoxic and may interact with DNA and damage its structure. These induce chromosomal aberrations and single strand breaks in DNA (Kornuta *et al*., 1996; Puig *et al*., 1989). Pyrethroids may lead to the molecular alterations such as loss of heterozygosity; gene mutations and aberrant gene promoter methylation which are potentially promising molecular biomarkers of lung carcinogenesis (Vineis and Husgafvel-Pursiainen, 2005).

It has been suggested that pyrethroids induce the oxidative stress in lungs (Kale *et al*., 1999a). Oxidative stress is caused by an imbalance in the production of reactive oxygen. A particularly destructive aspect of oxidative stress is the production of reactive oxygen species, which includes free radicals and peroxides which cause damage to the cells (Schafer and Buettner, 2001; Rahman and MacNee, 2001; Evans and Cooke, 2004). DNA damage is caused by oxygen-derived species as free radicals resulting from oxidative stress (Abdollahi *et al*., 2004). Oxidative stress may cause pathological changes in the pulmonary epithelium. It may lead to the inflammation of lung tissue. There may be hyperplasia or proliferation of alveolar cells (MacNee, 2001; Erdogan *et al*., 2006). Intense stresses may cause necrosis of the alveolar cells (Lennon *et al*., 1991).

Toxicological studies suggest that pyrethroids may induce inflammation of the lung tissues causing the oxidative stress (Emmendoerffer *et al*., 2000) and collagen deposition leading to the pulmonary fibrosis and edema (Erdogan *et al*., 2006). Idiopathic pulmonary fibrosis (IPF) is found to be associated with lung cancer as the epidemiological studies show greater incidences of lung cancer among the patients having IPF (Park *et al*., 2001). cypermethrin has also been seen to induce the liver injury. Exposure to cypermethrin damages the normal architecture of liver lobules. The number of the hepatocytes was found to be reduced with distorted polygonal shapes and widened sinusoids. Cypermethrin also induces liver fibrosis and necrosis. The magnitude of these findings was time dependent being more prominent in the tissues exposed for greater time (unpublished data).

Pyrethroids are known to have hepatotoxic potential in mammals as they cause histopathological damage of liver through inhalation exposure (Tuzmen *et al*., 2008; Mani *et al*., 2004; Okuno *et al*., 1986; Sakr, 1999). Cypermethrin induces distortion of the normal polygonal shape of the hepatocytes as they become irregular and exhibit cloudy swelling. Histopathological changes induced by the cypermethrin include the liver vacuolar degeneration, enlargement of the sinusoids between hypertrophied hepatocytes, degeneration in hepatic cords and hepatocytes, vacuole formations in hepatocytes, pleomorphism in nucleus, congestion (Yavasoglu *et al*., 2006; Ksheerasagar and Kaliwal, 2006), extensive vacuolated pycnosis and necrosis (Singh and Singh, 2008; Abou-Zaid and El-Balshy, 1995; Sakr and Hanafy, 2002). Evidences have shown that hepatotoxic chemicals as cypermethrin may induce liver fibrosis (Singh and Singh, 2008). As in the case of lungs, liver damage and fibrosis is also induced by oxidative stress (Abdollahi *et al*., 2004). Exposure to cypermethrin introduces significant oxidative stress in the hepatic tissues due to which release of free radicals occurs in the liver. These free radicals cause destruction of the normal hepatic tissues (Giray *et al*., 2001; Kale *et al*., 1999b).

The inhalation exposure of mice to cypermethrin resulted in the development of skin tumor epidermal in origin as reported that cypermethrin and other pyrethroids possess carcinogenic (tumor initiating) and cocarcinogenic (tumor promoting) potential (Shukla *et al*., 2002; Kornuta *et al*., 1996). The carcinogenic property of cypermethrin observed may be attributed to its ability to interact with DNA and damage its structure (Kornuta *et al*., 1996). Such interactions are critical for the initiation of cells to transform into neoplastic cells. Cypermethrin may also induce the frequency of well established markers of genotoxicity such as chromosomal aberrations and micronuclei formation (Suralles *et al*., 1995). Commercial formulations of cypermethrin are reported to cause *in vivo* induction of sister chromatid exchange in mouse bone marrow cells (Chauhan *et al*., 1997). Taken together these reports we can conclude that cypermethrin causes hazardous effects in non target organisms through inhalation exposure. It has potential to induce carcinogenesis and fibrosis of the lungs and liver. Further more severe exposure of cypermethrin may cause the development of skin tumor due to mutations in the genome. However, further studies on carcinogenicity and acute as well as chronic toxicity of cypermethrin and other pyrethroids are required. In the agriculture sector of Pakistan about 70% of the population lives in villages and most of them are involved in agriculture directly or indirectly. The farmers use pyrethroids to save their crops from pest attacks. The tendency of farmers to use pyrethroids is increasing which is alarming. Also there are many malpractices, i.e., the spray men do not follow the necessary precautions. So it is strongly recommended that these workers should be educated about the harmful and toxic effects of the synthetic pesticides. Moreover, they should know the importance of the protective measures during spraying. Rural workers and public health authorities must become aware of the importance of protective equipment, periodic health examinations and reduced environmental pollution in order to lessen occupational risk of field workers and promote improved conditions of life for the population at large scale.

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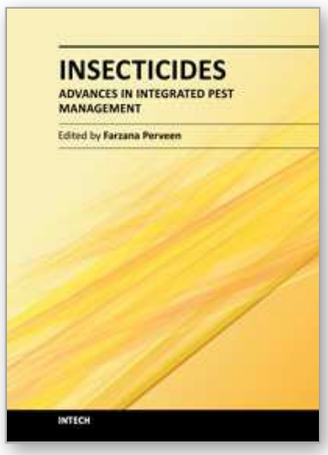

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This book contains 30 Chapters divided into 5 Sections. Section A covers integrated pest management, alternative insect control strategies, ecological impact of insecticides as well as pesticides and drugs of forensic interest. Section B is dedicated to chemical control and health risks, applications for insecticides, metabolism of pesticides by human cytochrome p450, etc. Section C provides biochemical analyses of action of chlorfluazuron, pest control effects on seed yield, chemical ecology, quality control, development of ideal insecticide, insecticide resistance, etc. Section D reviews current analytical methods, electroanalysis of insecticides, insecticide activity and secondary metabolites. Section E provides data contributing to better understanding of biological control through Bacillus sphaericus and B. thuringiensis, entomopathogenic nematodes insecticides, vector-borne disease, etc. The subject matter in this book should attract the reader's concern to support rational decisions regarding the use of pesticides.

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