PREFACE

Toxicology is of very old concern to humans from the time of stone age to modern era. Excess of any compound will be harmful to life and considered under toxicity studies. In the modern era, use of chemicals and compounds that accumulate or daily are exposed to humans, are harmful in many ways. Over the last 50-60 years many types of man-made chemicals have been manufactured and many of them have become widespread environmental contaminants (Simonich and Hitesl, 1995; Loganathan and Kannan, 1994; Bajerregaard, 1995). There is now growing concern of some of these man-made chemicals (including pesticides, industrial chemicals, plastics, detergents, paints and cosmetics) that are affecting the health of human and wildlife populations (Loganathan and Kannan, 1994; Fry, 1995; Dich et al., 1997; Longnecker et al., 1997). These substances can affect human health by upsetting the balance of the endocrine system, and they are known as hormone-disrupting chemicals or endocrine disrupters. As a result of mankind’s use of vast quantities of such chemicals, the humans and wildlife are continuously exposed to endocrine disrupters (O’Shea et al., 1980). Various Pathological effects of low doses of pesticides in animals and man are as under. The studies directed towards only one or two pesticides, while in nature a large number of pesticides are present and their combined effect has not been measured; which of course will give very dangerous view. The pesticides have pathological effects in animals and man such as immuno-pathologic effects, carcinogenic effects, mutagenicity, teratogenicity, neuropathy, nephropathy, hepatotoxicity and reproductive disorders (Chauhan and Mahipal, 1994).

Environmental contaminant by pesticides has been documented in biotic and abiotic components. These persistent organic pollutants are lipid soluble, non-biodegradable and endocrine disrupters. The effect of various industrial chemicals and other environmental pollutants in altering human endocrine systems has drawn public attention. Man has utilized a wide variety of pesticides to combat the crop pests and vectors of human diseases. Pesticides have been largely responsible for increased yields and improved quantity of cereals, roof crops, frits and vegetables by making them free of insects. Pesticides are such commodities, that the quantities used by farmers are governed by concepts of productivity and increasing expectations promoted by clever advertising. The British report identified four possible outcomes of long-term exposure to pesticides in man-carcinogenicity, mutagenicity, teratogenicity, allergies and effects on the immune and nervous system. Pesticides have been continuously produced with
pressure to do so being compounded by commercialism and encouraged by promises of greater effectiveness and increased productivity. Poisoning cases occur worldwide every year with 2,20,000 deaths, most of which are international (WHO in collaboration with UNEP World Health Organization, 1990).

India is one of the largest users of agricultural insecticides (Allen et al., 1984). Pesticides are by nature toxic to all living things and they not only pollute the environment but also cause harm to humans as well as beneficial organisms (Link et al., 1984). In 1997, WHO estimated that the number of deaths occurred globally due to pesticides was about 20,640 a year. The low doses of certain synthetic chemicals in the environment can mimic hormones and disrupt natural growth and development in animals and humans (Colbron et al., 1996). The most widely used pesticides are found in the form of insecticide organochlorines, organophosphates and carbamates.

The use of insecticides i.e., organophosphate (OP) insecticides in 1960s, carbamates in 1970s and pyrethroids in 1980s and the use of herbicides and fungicides in 1970s-1980s contributed greatly in pest control and agricultural output. The rampant use of these chemicals, under the adage, "if little is good, a lot more will be better" has played havoc with human and other life forms. In India the first report of poisoning due to pesticides was from Kerala in 1958, where over 100 people died after consuming wheat flour contaminated with parathion (Karunakaran, 1958). If the credits of pesticides include enhanced economic potential in terms of increased production of food and fibre, cod amelioration of vector borne diseases, then their debits have resulted in serious health implications to man and his environment. There is now overwhelming evidence that some of these pesticides do pose potential risk to humans and other life forms and unwanted side effect to the environment (Forget, 1993; Iqbedioh, 1991; Jayaratnam, 1985). No segment of the population is completely protected against exposure to pesticides and the potentially serious health effects, through a disproportionate burden is shouldered by the people of developing countries and by high risk groups in each country (WHO, 1990). The Poison Information Centre in NIOH Ahmedabad reported that OP compounds were responsible for the maximum number of poisoning (73%) among all agricultural pesticides (Dewan et al., 1998). Patients of acute pesticides poisoning, muscarinic manifestations such as vomiting (96%) nausea (82%), miosis (64%), excessive salivation (61%) and blurred vision (54%) and CNS manifestation such as giddiness (44%), headache (84%), disturbances in consciousness (44%) were the major presenting symptoms (Agarwal, 1993).
Organophosphate insecticides exert their toxicity by inhibition of Acetylcholinesterase (AChE). Potential exposures of mammals to pesticides and their metabolites are recognized (Frank et al., 1991). Studies have shown altered androgen metabolism (Krause, 1979), the pathological changes in testes and adrenals (Chapin et al., 1979; Usha Rani et al., 1980; Lander and Ronne, 1995; Amena et al., 2007; Pina-Guzman et al., 2006; Narayana et al., 2006; Prashanti et al., 2006). Other mechanisms have been proposed for the toxicity of pesticides in animals and humans, particularly oxidative stress (Akhgari et al., 2003; Ranjbar et al., 2002; Abdollahi et al., 2004; Ranjbar et al., 2005). The risk of acute exposure these compounds are a constant threat and they are responsible for numerous cases of poisoning annually in non target wildlife and for acute mammalian toxicity and neurotoxicity (Lohan et al., 1986; Fautz and Miftenburger, 1994).

Sub-lethal doses of these pesticides lead to alterations in reproductive performance in birds and mammals (Pope, 1999; Samkuli et al., 1987; Ray et al., 1987, 1991; Chapin et al., 1990; Maitra and Sarkar, 1995, 1996). In animals, several physiological and behavioural dysfunctions persist after exposure to high doses of pesticides (Hall and Clark, 1982; Rattner et al., 1987).

Exposure to vertebrate to organophosphate (OP) and carbamates results in the inhibition in the activity of cholinesterase (ChE) enzymes which are fundamental for the normal functioning of the cholinergic system. Sublethal depression of acetylcholinesterase (AChE) activity in the brain has been related to several physiological effects in laboratory rodents, such as changes in nerve conductance (Wison and Cohen, 1953; Greigh-Smith, 1991), respiratory reflexes (Metz, 1958; Nay and Nandi, 1991), and learning capabilities (Banks and Russell, 1967; Reddy et al., 1991). Behavioral consequences of exposure to anti-cholinesterase have also been documented. Many studies on laboratory rodents have indicated that both central and peripheral factors play a role in causing a general behavioral depression in the early phases of intoxication, with specific and/or non-specific alterations of a wide variety of parameters (Bignami et al., 1975). Inhibition of cholinesterase (ChEs) has been used widely as a biomarker to indicate the poisoning of non-target vertebrates with OPs (Greig-Smith, 1991), but there have been few attempts to examine the relationship between the severity of ChE inhibition and alteration in behaviour (Peakall, 1985; Hart, 1993). However, pesticide mediated changes in behaviour may have a significant impact on subsequent survival and indeed it has been suggested that behavioural alterations might provide a tool for predicting the ecological impact of OPs (Grue et al., 1983).
The adverse reproductive effects of pesticides has heightened in recent years as a result of studies which show that several organophosphorous compounds including dimethoate, methyl parathion, malathion, dichlorvos, chloropyrifos, phosphamidon and dimethyl phosphate, monocrotophos etc. impair fertility suppress libido, deteriorate semen quality, vaginal cyclicity, follicles of ovary, testicular degeneration and biochemical contents in rodents following repeated exposure (Krause and Honola, 1974; Krause, 1977; Haas et al., 1983; Dunnick et al., 1984; Bhatnagar and Soni, 1990; Asmathbanu and Kaliwal, 1997; Akbarsha and Sivaswamy, 1997; Sortur and Kaliwal, 1999; Jadaramkunti and Kaliwal, 1999, 2000; Mahadevaswamy and Kaliwal, 2002; Radhika and Kaliwal, 2002; Narayana et al., 2006; Prashanti et al., 2006; Shreelakshmi and Kaliwal, 2007; Amina et al., 2007). And a number of experimental works revealed that organophosphorous pesticides effect on male and female reproductive system (Budreau and Sing, 1973; Sciffer, 1975; Gallo and Lawryk, 1991).

It is very much clear from the above literature that pesticides cause deleterious effects, on nervous, endocrine, excretory, circulatory, digestive and reproductive systems. Biochemical indices are sensitive index to the changes due to pesticide toxicity and can constitute important diagnostic tool in toxicological studies (Dabrowska and Wlasow, 1986). The biochemical responses of non target organisms to pesticides can be used to predict early warning of pesticide toxicity. In non-target animals and these responses are quite effective for rapid detection (Pant et al., 1987; Mandal and Lahiri, 1989). Membrane bound enzymes are markers of tissue damage whereas cholinesterase and ATPases are primary targets of organophosphorus compounds.

Therefore, the present investigation was undertaken to elucidate sub-acute oral toxicity of indoxacarb in male and female albino mice with emphasis on biochemical contents, target enzyme interaction, oxidative stress, vital organs and histopathology. Thesis of the present study was divided into four chapters.

I. Induction of testis toxicity, biochemical and oxidative stress parameters changes in albino mice after exposure to indoxacarb

II. Interruption of vaginal cyclicity, ovarian follicles and biochemical contents of the ovary in mice after exposure to indoxacarb

III. Indoxacarb induces liver toxicity, biochemical changes and oxidative stress parameters in mice
IV. Induction of renal toxicity, biochemical changes and oxidative stress parameters in mice, after exposure to indoxacarb

Each chapter has a separate introduction, materials and methods, observations, discussion, summary and conclusion with pertinent literatures of the earlier works. The relevant literature is cited under references, to avoid disruption in the flow of text. Tables, graphs and figures are placed at the end of each chapter.