Review of Literature
REVIEW OF LITERATURE

The impact of xenobiotics on immune system has been studied by several workers; most of them have explained the immunosuppressive function of drugs, chemicals, polycyclic aromatic hydrocarbons, halogenated aromatic hydrocarbons etc. Immunotoxicity of pesticide is comparatively less studied in mammalian system. According to Banerjee et al. (1986) the toxic pesticide chemicals have become an integral part of the ecosystem and the human health effects of these agents are yet to be satisfactorily defined. They have also stated that pesticide induced immunomodulation endangers humans and animals.

The xenobiotic induced immunotoxicity in fish has been well explored (Waller, 1940; Chollar et al., 1969; Bligh, 1970; Tregan, 1975; ‘O’ Neill, 1981; Sinderman, 1983; Van et al., 1985; Michael and Meenal, 1990; Pietseh et al., 1990; Sizemore et al., 1991; Saxena et al., 1992; Wester et al., 1994; Sudhan and Michael, 1995 and Arunkumar et al., 2000) and the impact of heavy metals on immune system of rodent models are also well documented (Peterson, 1971; Koller and Kovaic, 1974; Cook et al., 1975; Nakano, 1976; Brown et al., 1978; Amoruso et al., 1981; Blakely and Archer, 1981; Aranyi et al., 1983; Michaelson et al., 1985; Banerjee et al., 1988, 1997, 1999 and 2000; Dean et al., 1991; Dean, 1994 and Seth et al., 2001 and 2002). However the immunotoxicity of pesticides on humans and animals and cellular and molecular damages underlying pesticide induced immune alteration has been less studied (Banerjee et al., 1996). They have stressed the need
or research in basic mechanism of immunotoxicity and identification of susceptible actor, which predispose to these reactions.

Several lines of experimental and clinical evidence have emphasized the need to study the immunotoxicity of pesticide (Banerjee et al., 1982; Banerjee et al., 1983; Balakrishnan et al., 1985; Dean and Adams, 1986; Aller, 1990; Bencko et al., 1990; WHO, 1990; Banerjee et al., 1992, 1995 and 1999 and Seth et al., 2001). There are few studies where attempts have been made to delineate the molecular vents that lead to the immunomodulation by these pesticide chemicals (Friends and Trainer, 1974; Blaylock et al., 1982; Dean et al., 1983; Cassale et al., 1984; Steizer and Michael, 1984 and Dean et al., 1985). Polyhalogenated hydrocarbons interact with DNA following a complex formation with a cytosolic receptor and are believed to result in gene activation and the induction of monoxygenase enzyme in hymus and other tissues (Gillis and Smith, 1979). These chemicals may act directly or indirectly on lymphoid cells to alter lymphocyte maturation, IgM to IgG switching mechanism, lymphoid cell distribution, immunoglobulin metabolism or T cell / B cell / macrophage / co-operation, resulting in altered serum immunoglobulin expression (Coffin and Gardner, 1972; Brummer et al., 1977; Vos, 1977; Bice, 1985; Bick, 1985; Abbas, 1988; Bissonette et al., 1989; Bottomly et al., 1989 and Dean et al., 1990).

Bhatia et al. (1997) studied the alterations of functional cell mediated immunity by exposure of Malathion. Though a number of studies have been carried out to find out toxic potential and toxic limits of pesticides, but one domain immunotoxicology remained a neglected field for a long time (Kimber, 1991 and
3hatia and Kar, 1993). However, recently an increase in awareness of the environment has drawn the attention of the researchers towards this field. A review of literature from 1981 - 1993 and WHO report on pesticide and immune response reveals that the pesticides are immunosuppressive and their exposure paves for the development of decreases or increase the magnitude of already existing diseases. 3hatia et al. (1995 and 1996) studies reveal that chemical pesticides like Aldrin, Malathion and Methyl Parathion. Suppressed the humoral immune response or affected the non-specific immune parameters. Immune system is subject to modulation by changes in endocrine function and nutritional balance (Brain, 1986; Banerjee et al., 1988; Clark et al., 1991; Dean et al., 1991; Tulinska et al., 1995; Barnes and Lindani, 2004 and David, 2005).

Some previous workers have established that animals given organochlorine and organophosphate compounds show alteration in levels of hepatic enzymes, cortico steroids and catecholamines (Vos, 1977 and Banerjee et al., 2005). Although these are not immunologically mediated responses, but their multiple effects offer reasonable evidence to assume that the pesticides are responsible for significant physiological alterations in the animal which in turn may affect their immunological response and resistance to infectious diseases. The organochlorine compounds interact with many biological systems and affect the cellular functions including receptors, cell membrane transport and the enzyme activation. But the mechanism of action of immunotoxicity is still unclear.
The pesticide induced immunosuppression has been consolidated and given below,


2. An increase in tissue acetylcholine concentration and interaction of this neurotransmitter with lymphocytes and/or accessory cells (Cassale, 1983; Tamang et al., 1988 and Patel et al., 1996). It has been suggested that cholinergic stimulation leads to suppression of PFC response during organophosphate (Malathion) exposure and may be mediated by a direct effect of acetylcholine upon specific components of the immune system, which are critical to PFC response. The cholinergic receptors have been identified on lymphocytes and macrophages (Whitaker et al., 1991).

3. Organochlorine and organophosphate compounds have many effects on humoral functions. Glucocorticoids are found to have immunosuppressive action by various mechanisms (Bozelka et al., 1986; Dean and Adams, 1986 and Kohn, 1986). The observed immunosuppression by pesticides might be mediated by glucocorticoids released in response to the toxic chemical stress. Elevation in plasma corticosterone concentration has been observed in rats given sublethal doses of Parathion. The hormonal changes due to pesticide stress may modulate immune responses (Bayter, 1994).

4. An inhibition of \( ^3 \)H thymidine and \( ^3 \)H-5\(^1\)-cytidine incorporation in phytohaemagglutinin (PHA) has been reported to stimulate human lymphocytes. It was suggested that the pesticide lindane could prevent PHA activation of lymphocytes by interfering with the stimulation of phosphatidylinositol turnover (Banerjee, 1996).

Similarly the concentration of \( 10^{-4} \) M lindane exerted an inhibition on the acromolecular biosynthesis (Ramachandran et al., 1984). Lindane decreases the protein and RNA synthesis. Similar to the effect on DNA synthesis, lindane results
n shrinking of the cellular soluble part of nucleic acid labeled precursor and blocks the aggregation of stimulated lymphocytes by acting on the surface membrane of the cells at $10^{-4}$ M concentration (Banerjee, 1996). Inhibitory effect was observed in $^3$H thymidine incorporation in DNA synthesis at 1 mM concentration of DDT. Further significant reduction in DNA synthesis was shown at 0.1 (50%); 0.01 (45.9%) and 0.001 mM (38.2%) concentration of DDT respectively. In another experiment pp DDT was found to inhibit the human lymphocyte mitogenic response to PHA by 50% at $10^{-4}$ M concentration (Lee and Park, 1979). Similarly, pp 1 DDT inhibited the lymphocyte mitogenic response to PHA and decreased lymphocytes intracellular ATP concentration (Lee and Park, 1979). Extrapolation of these *in vitro* results to *in vivo* can be considered as one of the possible explanation for the immunosuppressive activity of these pesticides in animal nodals. It is important to note that the concentration of pesticides used in *in vivo* studies are usually higher than concentration required to induce any effect on human lymphocytes as reported in *in vitro* studies (Banerjee *et al.*, 1996).

Some *in vitro* studies suggest for a possible biochemical basis of organochlorine toxicity on lymphocytes. These aforesaid observations also explain that DDT and HCH may have direct effects on the lymphocyte population Banerjee, 1996). The defective lymphocyte transformation by organochlorine pesticides, one of conservable immunological significance and can be value for extrapolation from *in vitro* to *in vivo* conditions.

Due to obvious limitations in human studies, an understanding of these risks depends to a great extent upon the clarification of cellular and molecular events.
underlying pesticide induced immune dysfunction in experimental animals. This study in experimental animals and our current knowledge about the pathogenesis is of disease. Support the possibility that pesticide induced damage to the immune system may be associated with a wide spectrum of diverse pathologic conditions. Some of which may only become detectable after a long latency. However, whether exposure to pesticide present in the environment influences immuno competence of the general population under normal circumstances is still not known. Studies concerning the effect of pesticides on immunological memory in terms of secondary immune response might be of particular importance. It is now important to elucidate the phenomenon in order to understand their mechanism of immunosuppression and possible health hazard due to continued use of these pesticides. The present study would contribute to the understanding of the mechanism of action of these pesticides at cellular level and could be utilized for a meaningful extrapolation of poisoning in humans.

From the reviews it's clear that the immunotoxicological studies are of paramount importance as one of the premier research areas in this decade. But here is no work on the immunotoxicity of selected pesticide Acephate, Quinalphos, Endosulfan and Nimbecidine. Some of the previous report on the immunotoxicity of Endosulfan is based on limited number of assays. Further there is no work to compare the immunotoxicity of chemical pesticides with bio-pesticides. Any workers had not attempted Immunotoxicological comparison of bio-pesticide, Nimbecidine with other pesticides. Hence, it becomes imperative to compare the immunotoxicity of various pesticides and to find how far bio-pesticides are safe with this motive the present investigation was designed. As many workers (Cook
and Karns, 1978; Banerjee et al., 1996; Sreekumaran, 2002; Barnes and Lindani, 2004 and David, 2005) have stressed the need to assess immunotoxicity using different methods, a battery of immunotoxicological assays had been used in the present study to establish the toxic potential of pesticides. In the present study direct as well as indirect immunotoxicity assessment had been carried out to find out the toxicity of pesticides. The biopesticide, which is suggested as a safe chemical has also been tested for immunotoxicity and its toxic potential has been compared to other pesticides. The result of present study could help the farmers and officials to select the safe and non-immunosuppressive pesticide for the future use.