

Toxic Effects of Chlorpyrifos on Biochemical and Haematological Parameters in Albino Mice (*Mus musculus*) and the Reversal Potential of Onion (*Allium cepa*)

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Abstract—People have been using pesticides for days back thousands of years, with early humans using natural chemicals like Sulphur, mercury, and arsenic to tackle pests and guard crops (Pimentel, 2005). In ancient Greece and Rome, extracts of plants like hellebore and tobacco were applied to resist insects. The modern era of pesticides, however, started in the mid, 20th century with the epiphany and large, scale application of synthetic formulas namely dichlorodiphenyltrichloroethane (DDT). DDT earned spotlight amidst World War II when it was successfully used to clash malaria and typhus, but soon issues about its environmental tenacity and bioaccumulation were lifted (Carson, 1962). Rachel Carson's landmark book *Silent Spring* agitated worldwide talks and policy changes, leading to stricter regulations and ultimate bans on DDT in numerous countries. Today, pesticides have become a necessary factor in modern agriculture, and through their application, they play a major role in both increasing crop productivity, and precluding post, harvest loss. Subsequently, they also contribute to food security (Cooper & Dobson, 2007). Nevertheless, this substantial reliance has also given birth to a double- edged sword—raising agricultural productivity at the expense of the environment and human health in the long run.

Index Terms—Pesticide, Chemical, Synthetic, Policy, Malaria

Classification of Pesticides

Pesticides are broadly classified according to the organisms they are meant to control:

- Insecticides (target insects).
- Herbicides (target weeds).
- Fungicides (target fungi).
- Rodenticides (target rodents).

From among them, insecticides hold a special place in agriculture since they help the farmers to protect the crops from the insect pests. From the chemical point of view, pesticides can be divided into several major groups:

1. Organochlorine – e.g., DDT and lindane. Well, known for their feature of lingering in the environment and accumulating in the food chain.
2. Organophosphates – e.g., chlorpyrifos, parathion, malathion. They exert their action through the inhibition of acetylcholinesterase, which is a key enzyme in nervous system functioning (Eddleston et al., 2008).
3. Carbamates – e.g., carbaryl and aldicarb. They have a mechanism of action similar to that of organophosphates; however, they usually have a much shorter life.
4. Pyrethroids – synthetic analogs of natural pyrethrins derived from chrysanthemum flowers, considered relatively safer due to lower mammalian toxicity (Casida & Durkin, 2013).
5. Neonicotinoids – a newer class, effective against sucking pests but increasingly controversial for their links to pollinator decline (Goulson, 2013).

This classification demonstrates both the variety and the complexity of chemical means, where each group has its own set of benefits and drawbacks.

Global Scenario of Pesticide Usage

Worldwide, pesticide usage has been highly increased during the last five decades mainly as the result of the Green Revolution, and the desire to extract the maximum yield from the crops. According to the Food

and Agriculture Organization (FAO, 2020), the global pesticide application is over 4.1 million metric tons annually, with Asia as the largest consumer. Along with many developing countries, India too has experienced a rapid increase in pesticide consumption as a result of intensified agriculture. However, good practices for safe use and the establishment of regulations usually come at a slower pace. The United States, China, Brazil, and India are among the largest consumers of pesticides both by volume and spending (Schreinemachers & Tipraqsa, 2012). Pesticides have played an important role in reducing crop losses, but on the other hand, the World Health Organization (WHO, 2019) has estimated that pesticide poisoning cases number approximately three million per year worldwide, with deaths exceeding 200,000 — mostly in developing countries. This sharp difference shows how knowledge, training, and infrastructure for the safe use of pesticides are not equally distributed worldwide.

Public Health Concerns and Ecological Implications

The heavy application of pesticides has resulted into major health issues being discussed in the public sphere. Farmers becoming victims of the pesticides they work with, children who may accidentally ingest poisoned food, and pesticide residue in food are the major avenues through which humans get exposed (Jeyaratnam, 1990). Long-term exposure to these harmful chemicals has been shown to result in damage to the nervous system, hormone imbalance, and toxicity to the reproductive system, and even development of cancer (Mostafalou & Abdollahi, 2013). To illustrate, organophosphates cause nerve cell overstimulation by inhibiting the enzyme acetylcholinesterase that breaks down acetylcholine; this may result in convulsions, paralysis, or death (Eddleston et al., 2008). The use of pesticides is causing disruption of biodiversity through destruction of not only target but also non-target organisms. For example, the disappearance of honeybee colonies has been partially blamed on the use of neonicotinoids (Goulson, 2013). The contamination of rivers, lakes and groundwater by pesticide residues transferred by surface water is also detrimental to fishes and amphibians (Stehle & Schulz, 2015). The presence of pesticides on land has resulted in soil organisms, which play a vital role in nutrient cycling, being damaged.

From General Use to Focus on Organophosphates

Organophosphates (OPs) are a class of pesticides that have received particular attention among all pesticides classes because of their extensive utilization and high level of acute toxicity. At first, they were made as nerve agents for the military purposes in WW2. After that, they were converted into herbicides and insecticides. Chlorpyrifos, diazinon, and malathion are a few examples of such pesticides which are very commonly used in crop protection to this day. (Eddleston et al., 2008) One of the reasons why organophosphates have replaced the older type of pesticides such as organochlorines is that organophosphates degrade much faster in nature and therefore do not stay in the environment for a long time. Nevertheless, their very harmful effects on both the organisms that are targeted and the non-targeted ones are still very severe. Moreover, the risk of accidental poisoning due to the use of organophosphates is much higher than that of pyrethroids or biopesticides not only because the effectiveness of the protective gear and the knowledge of handling these substances might be insufficient, but also because, in the first place, the people who are exposed to these pesticides might not be aware of it (Jaga & Dharmani, 2003). Organophosphates have been in the spotlight mainly because of their toxic effects and the damage they cause to both agricultural produce and human health. This fact highlights the significance of conducting experiments on albino mice to examine the effects of organophosphates on the biochemical and hematological parameters, as well as the importance of testing agents with possible protective effects, such as onion (*Allium cepa*) which could be used as a remedy for toxicity caused by organophosphates.

I. ORGANOPHOSPHATES AND CHLORPYRIFOS

Chemistry, Mode of Action, and Widespread Application of Organophosphates

Among the numerous groups of synthetic pesticides, organophosphates stand out as one of the most significant. The chemistry of these compounds is based on phosphorus elements, and most of them were first made in the early 1900s. The study of these compounds was greatly intensified during the Second World War because of their possible use as nerve agents, which is a sad reminder of their strength and

toxicity. After the war, these compounds were changed into agricultural chemicals, thus providing a cheap method to control insect pests on a large scale. Organophosphates are primarily known for their disturbing effect on the nervous system of living organisms. They act by blocking the enzyme acetylcholinesterase which is responsible for the degradation of acetylcholine. Acetylcholine is a neurotransmitter which helps in the transmission of the nerve impulses from one neuron to another. Hence by unblocking this enzyme, organophosphates facilitate accumulation of acetylcholine resulting in overstimulation of nerve cells and ultimately to neurological disorders (Eddleston et al., 2008). Being highly potent, these compounds were rapidly availed at every corner of the world to fight pests ranging from insect pests that are harmful to crops to those pests that are a nuisance at home. The use of organophosphates like malathion, diazinon and parathion were encouraged in farming whereas some were used in public health sector to fight vector, borne diseases like malaria. This and the fact that they were cheaper than the older pesticides like organochlorines, made them the mainstay of modern agriculture (Costa, 2018).

Chlorpyrifos: Structure, Discovery, and Agricultural Use

Chlorpyrifos, which is one of the best, known organophosphates from the Dow Chemical Company's discovery in 1965, belongs chemically to the phosphorothioate group, which is distinguished by having a sulfur atom in its structure. Its chemical name is *O, O-diethyl O-3, 5, 6-trichloro-2-pyridyl phosphorothioate*. This particular molecular structure makes it highly effective as an insecticide against a wide range of pests. Chlorpyrifos was first marketed as a broad, spectrum insecticide and very soon it became the most widely used pesticide in agriculture. It helped farmers to keep the yield of crops such as maize, cotton, rice, and fruit orchards free from pests. Besides agro, chemical uses, the chemical was also sold for pest control in households (e.g. termite and mosquito extermination). During the first several decades of its commercial life, chlorpyrifos was considered a must, have pesticide, especially in the areas where the problem of pests was threatening the supply of food and people's economic well, being (Marrs, 2012). Nonetheless, the greater the extent of its use, the more widespread was the evidence of its

negative effects. There were accounts of the poisoning of farm workers, food products contaminated with pesticide residues, and the environment being harmed, which "we" subsequently constantly hear "about". Chlorpyrifos, which was once considered a less dangerous alternative to the very stable organochlorines, shortly became infamous for its acute toxicity and the possible detrimental effects on human health in the long run.

Mechanism of Toxicity: Inhibition of Acetylcholinesterase

The main way chlorpyrifos kills or makes sick is by blocking an enzyme acetylcholinesterase (AChE). This enzyme normally works very quickly to break down the neurotransmitter acetylcholine (ACh) at nerve endings so that one nerve impulse is separated from the next. Once inside the body, chlorpyrifos is first converted to chlorpyrifos, oxon, the metabolite responsible for its toxicity. This metabolite attaches to the enzyme AChE's active site and thus inactivates the enzyme.

Therefore, there will be a large quantity of acetylcholine in the nerve stem, and this will cause the muscles, glands, and CNS pathways to be continually stimulated. A person's symptoms range from the initial headache and dizziness to the late stage chest breathing, convulsions, and possibly death. The intensity of the symptoms is dependent upon the amount of the poison and the length of time the individual has been exposed to it. High doses causing acute intoxication are generally associated with a one, time event, whereas low doses over a long period may cause the poison syndrome to progress gradually (Eddleston et al., 2008).

There is a huge number of experiments on animals that have confirmed that animals exposed to chlorpyrifos not only show functional changes in their nervous system but also their biochemical and hematological parameters are affected. These systemic adverse effects reflect the broad toxicity of the chemical and thus make it reasonable to assess the toxicity of the chemical like albino mice.

Acute vs. Chronic Exposure Effects

The health effects caused by chlorpyrifos vary mainly depending on whether the exposure is acute or chronic.

- Acute Exposure: The most vulnerable to such exposures are certainly farmers and pesticide

applicators. An exposure through inhalation, dermal absorption, or ingestion of very high amounts can produce immediate symptoms such as salivation, muscle twitching, abdominal cramps, vomiting, and in extreme cases paralysis and respiratory failure due to the toxic effect of the substance. Cases of poisoning due to mishandling have been disseminated particularly where people lack safety equipment and training (Jaga & Dharmani, 2003).

- **Chronic Exposure:** The low, level exposure over an extended period is a greater hidden hazard. It is suggested by studies that exposure to low levels of chlorpyrifos for an extended period may lead to neurodevelopmental toxicity in children resulting in problems with memory, lowered cognitive function, and even behavioral abnormalities. Prenatal and early childhood exposure, in particular, has been linked to neurodevelopmental disorders. This is why chlorpyrifos has been under the spotlight in the ongoing debate over pesticide safety in food production (Rauh et al., 2011).

The combined risk of immediate and long, term toxicity is a significant factor in the hazardous nature of chlorpyrifos. Not only does it pose a risk to the health of those who handle the chemical, but it also causes concerns around the safety of food and the preservation of the environment.

Regulatory Bans and Restrictions Worldwide

As a result of the growing evidence of harm, a number of countries started to evaluate the safety of chlorpyrifos once again. In the U.S., the Environmental Protection Agency (EPA) limited the use of chlorpyrifos in homes in 2001 as a result of child neurotoxicity concerns. The agency further took a step to ban the pesticide in 2021 when it cancelled all food tolerances for chlorpyrifos, thus banning its use in food crop production. The European Union has had a chlorpyrifos ban since 2020 over concerns of human health risks. Nevertheless, chlorpyrifos is still being used in India although more and more people are questioning this decision. Despite the resistance from health advocates and environmentalists, the pesticide is still used on such crops as paddy, cotton, and fruits. This gap in the regulation reflects the worldwide pesticide policy division, whereby fledgling countries often keep compounds banned in other places since

they have to face economic and agricultural pressures (FAO, 2020).

The worldwide political context of chlorpyrifos shows a slow but sure move to harsher restrictions. At the same time, there are still big problems with enforcement and supervision in many places resulting in the continued exposure of humans and the environment to pollutants.

Persistence, Bioaccumulation, and Entry into the Food Chain

One of the problems with chlorpyrifos is that it can stay in the environment for a long time. In general, organophosphates break down more rapidly than organochlorines, but chlorpyrifos residues have been found in soil, water, and food products even after a long time since application. Researches have revealed that under different environmental conditions, the half, life of chlorpyrifos in the soil may be anywhere from a few days to several weeks. This lasting nature of the chemical is a cause for concern as it can go up the food chain.

Chlorpyrifos residues in fruits, vegetables and grains have been reported and often in countries where the monitoring system is weak, the residues are above the permissible limit. When the residues are eaten, they get deposited in the tissues of animals such as milk and meat, thus increasing human exposure through dietary intake. Aquatic ecosystems are another victim of chlorpyrifos as the runoff from the agricultural fields pollutes the rivers and lakes and hence the fish and amphibians are at risk too (Stehle & Schulz, 2015).

This biologically accumulated toxic chemical is not only a threat to human health but also to biodiversity. Besides other non, target organisms, pollinators and soil microbes get their normal functioning disrupted, thus causing an imbalance in the ecological systems. The persistence, bioaccumulation, and food chain entry cycle expose the deep and broad consequences of the use of chlorpyrifos that go far beyond the initial target of pest control.

II. ALBINO MICE (MUS MUSCULUS) AS EXPERIMENTAL MODEL

Importance of Animal Models in Toxicology Studies
Toxicology heavily depends on experimental models to unravel the ways chemicals interact with living organisms. Since human trials are both unethical and

risky, scientists employ laboratory animals to simulate human reactions. Of all the animals, mice are of particular significance. Animal models enable scientists to test the safety and hazards of pesticides, pharmaceuticals, and industrial chemicals before these agents are introduced to the human population. For organophosphates such as chlorpyrifos, animal studies offer critical knowledge on the mechanisms of toxicity, dose, response, and the potential use of protective agents.

Animal experiments also allow researchers to track changes at different biological levels. Changes in genes, enzymes, organs, and even the behavior of the animals can be studied under the same roof. Such a regulated set, up guarantees that the findings are not only reproducible but also scientifically valid. Furthermore, the results of animal studies frequently become the groundwork for legal measures concerning pesticide safety, setting maximum residue levels in foods, and defining safe working environments.

Why *Mus musculus* is Widely Used

The house mouse (*Mus musculus*) is the mammalian model used in biomedical and toxicological research more than any other animal. Its supremacy in the field can be attributed to various reasons. The foremost is the incredibly high genetic similarity between mice and humans almost—95-98% of the human genes can be found in the mouse genome. Hence, the biological pathways that get altered due to toxicants in mice are likely to be the same as in humans (Rosenthal & Brown, 2007).

Another reason is the quick reproductive cycle and the short life of mice that make them perfect for the multi, generational and long, term toxicity studies. A female mouse can give birth to a large number of pups several times a year, which helps researchers in studying genetic, developmental, and transgenerational effects over a short span. Also, their small size and the fact that they are easy to handle make them very popular as they occupy less space and require fewer resources than larger animals.

Physiologically, mice have organ systems that are very much like those in humans, thus their liver enzyme functions, immune responses, and hematopoietic processes are equivalent. Such resemblance makes it possible for researchers to accurately infer from mice studies results that concern biochemical and hematological parameters. On top of it all, scientists

also have at their disposal inbred and genetically modified strains which provide them with very sophisticated instruments to investigate particular pathways, genes, or mechanisms that mediate toxic responses.

Ethical Considerations and CPCSEA Guidelines

Animal models are vital in toxicological studies but their use poses significant ethical issues. To resolve these issues, laws and moral boards have been set up globally to supervise the welfare of animals. In India, the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) is the highest authority that regulates animal experiments. It sets the guidelines for lessening the pain, distress, and suffering during research and thus upholds the 3Rs principle: Replacement, Reduction, and Refinement.

Replacement highlights the preference for substitutes such as in vitro techniques, computer simulations, or non, mammalian species to be used as a first choice. Reduction aims at using the minimal number of animals necessary for obtaining scientifically valid results. Refinement is about making changes of the experimental conditions for the least suffering of animals and the highest possible quality of animal care. A researcher using albino mice has to get the approval of the Institutional Animal Ethics Committee (IAEC) before starting the project, continue to meet the set standard of housing, and give proper veterinary care throughout the period of study (Gupta, 2015).

Besides legality, ethical considerations are the basic requisites of science. Stress, bad living conditions, or neglect of animals might lead to changes in the experimental results due to altered biochemical markers or immune reactions. Therefore, the upkeep of animal welfare is a matter of both the facts and the reliability of toxicological tests.

Relevance of Hematological and Biochemical Markers

Among the numerous benefits of albino mice, a very important one entails their great fit for experiments that are based on hematological and biochemical changes due to toxic stress. As a physiological change, blood is very sensitive and, hemoglobin level, red blood cell count, white blood cell count, and platelet count when measured give an idea about toxicants effects on the circulatory and immune systems.

Chlorpyrifos, an organophosphate, is one among such chemicals which is disturbed these parameters. Therefore, haematology remains a major aspect in toxicology research.

Besides, biochemical markers depict different aspects of the damage to the body and the general impairment of the system. For instance, liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serve as markers of liver damage, whereas creatinine and urea levels are indicative of kidney functions. Besides, determining oxidative stress markers such as malondialdehyde (MDA), glutathione (GSH), and antioxidant enzymes like superoxide dismutase (SOD) is useful for measuring the extent of pesticide, induced cellular damage (Costa, 2018).

Together the study of hematological and biochemical markers offers an all, round visualization of toxicity. The use of albino mice allows the scientists to draw up clean dose, response curves, detect the very first universal alarm signals of toxicity and test the capacity of protective agents such as onion (*Allium cepa*). These results are a great source of knowledge both for the extension of pesticide toxicity understanding and for public health policy/planning and preventive measures.

Albino mice (*Mus musculus*) have been a staple of toxicological investigations given their genetic closeness to humans, physiological similarity, and overall convenience in experimental setups. Their deployment in pesticide trials, especially with organophosphates like chlorpyrifos, is instrumental in revealing the comprehensive systemic repercussions both at compound and blood cell levels. Though the ethical dimension should always be paramount in animal testing, experiments with mice that are well, thought, out play a significant role in localizing the scenario of human health risk from shaping a neat line of laboratory evidence to real, life exposure.

III. BIOCHEMICAL PARAMETERS UNDER PESTICIDE STRESS

Biochemical parameters studies offer very valuable information on the extent to which toxic substances change the internal workings of living organisms. Biochemical markers in toxicology serve as very sensitive indicators of stress, tissue damage, and metabolic disturbances. Prolonged exposure of an

organism to pesticides such as organophosphates leads to significant changes within the internal biochemical equilibrium of the organism. These changes can be traced through the alterations of enzyme activities, protein concentrations, or lipid metabolism. Thus, they help in unravelling the chain of events that start from chemical exposure to the occurrence of physiological disorders.

Due to the multi, organ effects of chlorpyrifos in albino mice, biochemical studies have been at the forefront of toxicity testing. Besides the nervous system, the pesticide has its footprint on the liver, kidneys, and other organs which are mainly involved in detoxification and metabolism. Hence, the monitoring of biochemical parameters sheds light not only on the direct effects of chlorpyrifos exposure but also the indirect ones.

Liver Function and Enzyme Activity

The liver is very vulnerable to pesticide, induced oxidative stress because it serves as the chief organ where xenobiotic metabolism takes place. Once pesticides are inside the body, they are metabolized through enzymatic reactions that are meant to transform toxic compounds to more water, soluble ones for easier elimination. Nevertheless, during the process, a formation of highly reactive intermediates is possible, which causes oxidative stress and thus, hepatocellular damage.

The liver enzymes most frequently assayed in toxicity studies are alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). A rise in these enzyme levels in serum is indicative of their leaking from injured hepatic cells and it is therefore a very early marker of liver malfunction. Chlorpyrifos, an organophosphate chemical, has been reported to cause a drastic rise in these enzyme levels, thus the article implies liver stress and necrosis. The drastic decrease of the total protein levels is in fact because of the impaired protein synthesis as a result of the liver damage, the article continues.

The hepatic detoxifying system utilizes cytochrome P450 enzymes that metabolize pesticides; however, this process commonly leads to the generation of reactive oxygen species (ROS). These oxygen radicals invade cell membranes through lipid peroxidation and damage the phospholipid bilayer, thus depriving cells of protective barrier against the environment. As a

consequence, hepatic tissues become prone to both morphological and functional alterations. The biochemical changes that take place are to some extent reversible upon the removal of exposure or by the administration of antioxidant compounds, which highlights the rationale for evaluating the efficacy of naturally occurring substances such as onion (*Allium cepa*) in the prevention of chemically induced liver damage.

Kidney Function and Renal Markers

The kidney is a major organ responsible for maintaining internal homeostasis through waste excretion and electrolyte regulation. A route for toxicants from the bloodstream to the kidney is renal tissue where they can accumulate leading to a loss of filtration capacity and nephron damage. Two of the most sensitive markers of kidney health are the levels of serum **urea** and **creatinine**. Thus, under pesticide stress, mainly organophosphate poisoning, the levels of these biomolecules tend to increase by virtue of the fact that the kidneys are inefficient in eliminating the products of metabolism.

In vivo, chlorpyrifos administration was found to cause histopathological changes including glomerular congestion, tubular degeneration, and renal cell necrosis. This was accompanied at the biochemical level by elevated urea and creatinine levels. Such changes in these biomarkers enable investigators to gauge the severity of the renal damage as well as the efficacy of the natural antioxidant substances tested for their protective action. One way the kidney gets damaged by oxidants is through the degradation of biomolecules, which may be prevented by flavonoid, type plant extracts that assist antioxidant enzymes in vivo. The restoration of kidney function parameters that results from the intervention with these agents indicates that the organ is able to heal when oxidative stress is controlled.

Lipid Profile and Energy Metabolism

Pesticides inhibit the proper functioning of detoxification organs and also disrupt lipid metabolism. Lipids are the basis of the cell membrane, hormones are derived from them, and they also serve as an energy reserve. When cells are stressed, lipids get oxidized— results in the formation of malondialdehyde (MDA) that is used as a marker of oxidative damage. Thus, an increase in MDA

concentration reflects the cellular damage level and can be used as a measure of oxidative stress.

Changes in lipids such as cholesterol and triglycerides concentrations are typical in animals exposed to pesticides. Such variations may lead to the disruption of energy production and cell signalling. In addition, the decrease of HDL and increase of LDL may be a harbinger of cardiovascular diseases. These changes at the biochemical level show that the effect of pesticides is not limited to the manifestation of their immediate toxicity but they also may be a source of chronic metabolic diseases.

Glucose and Protein Metabolism

Exposure to pesticides such as chlorpyrifos alters glucose metabolism by breaking down insulin signalling and pancreatic function. Hyperglycemia or raised blood glucose levels has been found in several experimental models after organophosphate exposure. This change is a consequence of stress, induced activation of the hypothalamic-pituitary-adrenal axis and the following release of cortisol, which stimulates gluconeogenesis.

Protein metabolisms go on the same way. Reduced values of total protein and albumin indicate either decreased protein synthesis in the liver or increased protein breakdown due to stress. These biochemical parameters are central to the evaluation of systemic toxicity as they reflect the nutritional and metabolic status of the whole organism. Normalization of glucose and protein levels after treatment with natural antioxidants is additional evidence that the biochemical reversibility of pesticide, induced damage is very possible.

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