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Effect of Pesticides on Nervous System or Neural Health

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Abstract

Pesticides will be utilized to manage pests that are important to agriculture and health care, and they will continue to be necessary for the future related to food security and prevention and control. Pesticides are unlikely to be phased out in the foreseeable future, but they should be handled with prudence. The majority of pesticides are hazardous to humans and can cause serious health problems which lead to death. During chemical spraying, skin contact accounts for about all of the body exposure. Contamination, such as for local farmers in open vegetable farming or pesticide industry employees, may result in direct exposure. Indirect exposure can occur through dietary goods such as food and drinking water, as well as the usage of repellents in homes. Some neurotoxic effects are immediately apparent, while others might take months or even years to appear. A variety of variables, including the toxin's characteristics and the dosage a person, is exposed to, determine the consequences of neurotoxicity. Amyotrophic Lateral Sclerosis, Intermediate syndrome, Parkinson's disease, and Alzheimer's disease are diseases that highly damage the mental health and the neural health of a person. This review is mainly focused on types of pesticides, route of pesticide entry in body, their effect on human health, and how these pesticides induce neural diseases.

Keywords: Pesticides, Neurotoxicity, Alzheimer, Parkinson, Amyotrophic Lateral Sclerosis, Intermediate syndrome

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Introduction

Pesticides are a broad and varied chemical family. Fungus, insects, rodents, and weeds are all killed and eradicated using these pesticides. Fungicides, herbicides, insecticides, molluscicides, nematicides, rodenticides, and plant growth regulators are some of the examples of pesticides [Figure 1].[1]

Maximum pesticides have the main site of action in the neurological and endocrine systems, making them potentially hazardous to humans with substantial direct and indirect health consequences. Pesticides are directly or indirectly ingested by humans. Ingestion of tainted food and water, as well as absorption of pesticide droplets from the drift, are all examples of direct exposure in agriculture, public health, and livestock, as well as fumigation. Due to their physical constitution, temperament, and physiology, children are more sensitive to pesticides than adults, and even modest amounts of exposure during the early stages of development can create health problems. These pesticides can also cause neurotoxicity which damages the several function of the nervous system and cause neural disease.

According to existentialist philosophy, the nervous system is a complex component of an organism that governs its activities and sensory information by conveying impulses throughout the body. The central nervous system (CNS) is a marvel of intricate biomolecular connections that keep life moving and maintain homeostasis. The CNS, on the other hand, is not immune to alterations that generate neurological disease, which may be brought on by latent viral infections, chronic, or acute. Numerous viruses may infect resident cells in the CNS, including neurons. The nervous system detects changes in the environment that produces acute and then responds with the help of the endocrine system. The nervous system gets its name from nerves, which are cylindrical bundles of fiber (neuronal axons) that originates from the brain and spinal cord and branch out to innervate every part of the body. Nerves, which are cylindrical bundles of fiber (axons of neurons) arise from the brain and spinal cord and branch repeatedly to innervate every area of the body, are the foundation of the nervous system.[2,3]

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The direct or indirect influence of chemicals on the neurological systems of people and animals is referred to as neurotoxicity. In humans, a variety of substances may cause neurotoxic illnesses. Although there may be a long delay between exposure and the emergence of neurotoxic consequences, neurotoxicity is typically self-limiting when exposure ends and seldom progressive in the absence of ongoing exposure.[4]

Types of Pesticides and their Drawbacks

Herbicides

Herbicides may induce deformities by interfering with cell division, photosynthesis, and amino acid production. The harmful therapeutic action of herbicides, as well as the method of administration, have a significant impact on their prospective consequences.[5]

Insecticides

Insecticides have a variety of consequences. Some pesticides disturb the neurological system, while others destroy the exoskeletons of pests, repel insects, or manipulate humans in other manners. Due to these variables, each pesticide may offer a varying amount of danger to non-target insects, humans, pets, and the environment.[6]

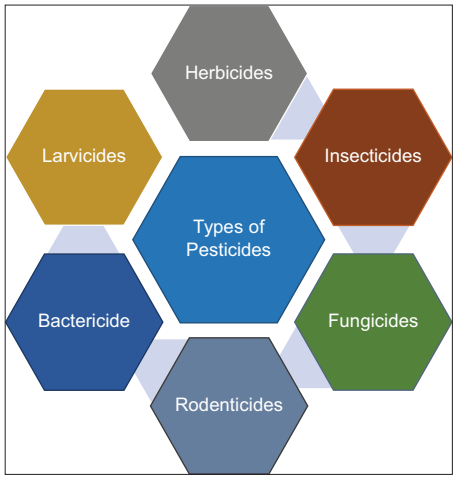

Figure 1: Types of pesticides

Fungicides

Fungicides are insecticides that effectively eliminate the spread of fungus and its spores. Plant-damaging fungi such as rust, mildews, and blights may be controlled using them. Fungicides work by destroying fungal cell membranes or preventing infected cells from producing energy.[6]

Rodenticides

Rodenticides are pesticides that are used to eliminate rodents. Squirrels, woodchucks, chipmunks, and porcupines are species of rodents.[7]

Bactericide

Bactericide is a substance that inhibits the growth of bacteria. In coatings, bactericides are often used as corrosion inhibitors and additives.[8]

Larvicides

Mosquito larvae in the nesting area are targeted with larvicides before they mature into adult mosquitos and disseminate. Larvicide is also available in tablet, pellet, granular, and briquette form for mosquito control.[9]

Pesticide and Human Health

Pesticides are cost-effective, suitable, and easy to use for pest management. In addition to eliminating the target species, they attack or damage non-target organisms, including people. Pesticides are more likely to destroy young and intriguing animals. Pesticide poisoning is a serious public health issue that destroys over 300,000 people each year. Pesticides may be absorbed in several ways, making exposure inevitable. Pesticides enter the human body through four main routes: The oral, cutaneous, ocular, and respiratory tracts. These disorders may be fatal and have a significant impact on a person's mental health if they are not addressed. Pesticide exposure develops when a pesticide came in contact with an organism. During chemical spraying, skin contact accounts for about all of the body exposure. Chemical risks' cytotoxicity is determined by the amount of chemical employed and the duration of its persistence, or how long it stays in the blood.[10-13]

Soft-tissue sarcoma, Burkitt lymphoma, neuroblastoma, non-Hodgkin lymphoma, rectum cancer, leukemia, lung cancer, Wilm's tumor, and ovarian cancer have all been associated with pesticide exposure. A connection between pesticide toxicity and indications of contributing to high asthma has been shown in several epidemiological and clinical studies. By causing inflammation, irritation, or immunosuppression, pesticide exposure can aggravate asthma. Exposure to natural toxicants has been connected to diabetes, according to emerging scientific evidence. Pesticides, particularly organophosphorus chemicals, impact male reproductive processes by altering sperm activity and sperm DNA. They affect immune function and may raise cancer risk in a variety of ways. Exposure to pesticides has been linked to an increased risk of type 2 diabetes and its symptoms. They influence immunological function and can increase the risk of cancer in a range of methods.[14,15]

Pre-mutagenic damages such as DNA strand breaks and DNA adducts, as well as gene mutations including injection, exclusions, rearrangements, and translocations, may trigger pesticide-induced genetic harm. Polyploidy, clastogenicity, and translocations are all possible chromosomal irregularities. Pesticide damage may result in genetic alterations that result in polymorphisms that influence their affinity on their ligand or the expression of gene transcription. The presence of pesticides in the environment increases the risk of occupational exposure. The amount of exposure varies depending on the pesticide composition. Chemical spills, leaks, and malfunctioning spraying equipment may all lead to exposure. If employees do not follow pesticide application requirements correctly, pesticide exposure is increased.[16]

Route of Pesticide Exposure

Pesticides enter the human body through three main routes: Touch, ingestion, and inhalation [Figure 2].

- **Touch or Contact**: The most likely pathway of exposure to pesticides in visitors is through skin absorption. When handling pesticides (mixing, loading, or disposing of them), splashes and spills may cause dermal absorption. The degree of harm posed by dermal absorption is determined by the pesticide's toxicity to the skin, the period of exposure, the pesticide formulation, and the contaminated body part. Pesticides that include solvents and pesticides that are oil-based are generally absorbed more rapidly.
- **Ingestion:** Pesticides that enter the body through the mouth (oral exposure) may cause significant disease, damage, and death. When hands are not adequately cleaned before eating or smoking, exposure might occur. Pesticide poisoning deaths have a substantial role in suicide trends, especially in rural parts of developing countries.
- **Inhalation:** Inhaling pesticides may significantly damage the tissues of the nose, throat, and lungs. Vapors and very small particles provide the highest risk of toxicity through respiratory exposure. When measuring or combining powerful and dangerous pesticides, eye protection is required at all times.[17]

Human Health Risk factor

Pesticides are nine of the 12 most harmful and persistent chemicals, as per the Stockholm Convention on POPs. Pesticide damage can lead to chronic and acute risk factors. Nearly, pesticides are

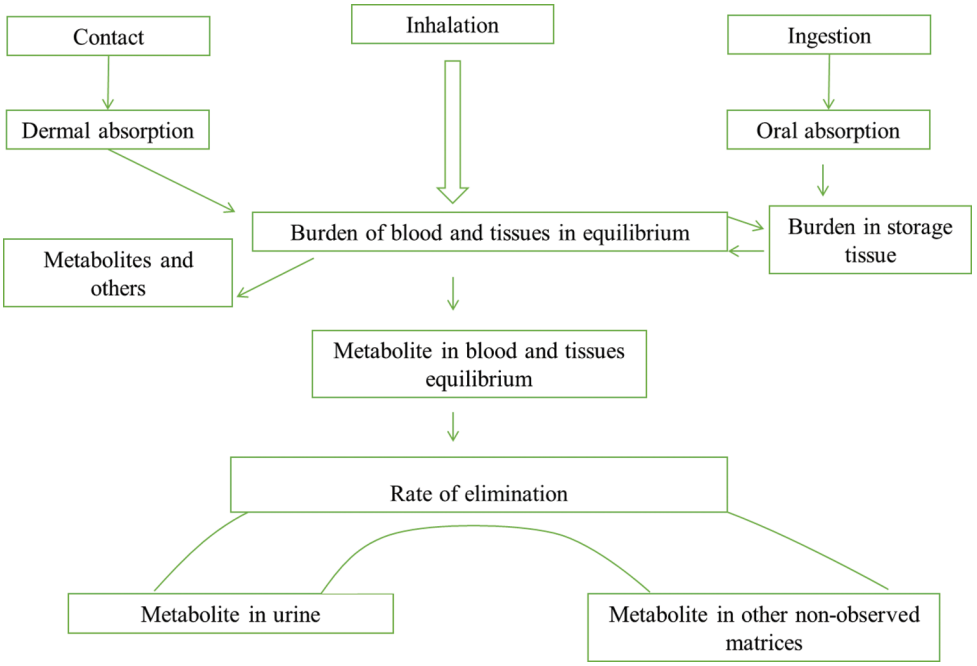

Figure 2: Different route of pesticide exposure

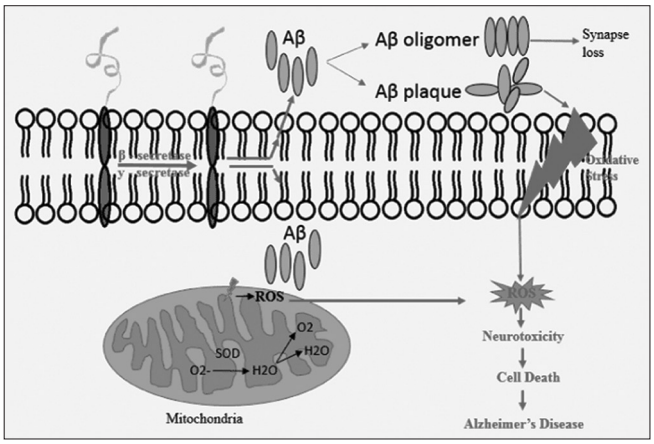

Figure 3: Oxidative stress and A plaques APPs are cleaved by β- and y-secretases, which generate Aβ units. These proteins can cause synapse loss and oxidative stress outside of cells. Aβ units may cause neurotoxicity and increased generation of reactive oxygen species (ROS) within cells causes cell death.[39]

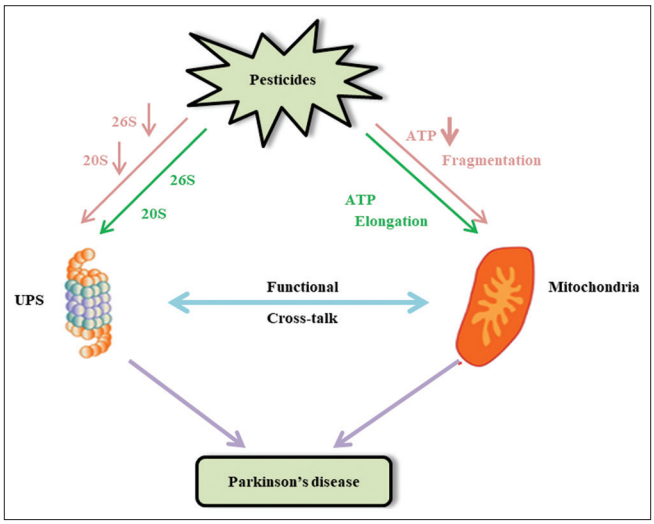

Figure 4: Pesticides' effects on mitochondria and the Ubiquitin-Proteasome System in Parkinson's disease.[47]

extremely deadly to humans, and even limited droplets in the oral or on the skin may have disastrous consequences. Other pesticides are less hazardous, but they can nonetheless cause harm if used inappropriately.

A helpful equation to remember is:

Hazard= Exposure X Toxicity.

It depends on the toxicity of the pesticide and the length of exposure.[18]

Pesticides May Have Three Types of Negative Consequences

- Allergic Effect: After the initial interaction with pesticide, the body develops a repellent reaction, but further exposures result in an allergic reaction. A few examples include potentially life-threatening shock, skin irritation such as eye and nose inflammation, rashes, open sores, and asthma [Table 1]. It is difficult to figure out who is hypersensitive to specific pesticides.[19]
- Chronic Effect: "Chronic impacts" refers to any negative consequences over time as a result of little doses. Chronic toxicity of a pesticide is more difficult to quantify in a laboratory than acute toxicity. Repeated exposure to sub-lethal pesticide doses over time causes chronic illness in people. Farmers who work in agriculture are particularly vulnerable. However, polluted food and water, as well as toxins floating from the fields, may affect the general population.[20,21]
- Acute Effect: Neurological, epidermal, and ocular irritation and

Table 1: Acute effects of pesticide poisoning[23]

Receptor	*Organ*	*Clinical effect*
Neuromuscular junction Nicotinic	Undernourished muscle	Comparable, paralysis, and weakness
Autonomic nervous system	Lungs	Bronchorrhea, bronchospasm
	Heart	
Postganglionic muscarinic (parasympathetic)	Eyes	Bradyarrhythmia
	GI tract	Miosis, lacrimation
	GU tract	Miosis, lacrimation
	Mouth	Urinary incontinence Salivation
CNS Muscarinic/nicotinic	Cerebrum	Coma, seizures, depression, CNS, agitation

damage include stomach pain, headaches, nausea, vomiting, dizziness, tiredness, and systemic poisoning. These symptoms may appear immediately after pesticide exposure or within 24 h. These consequences have usually evident and typically recoverable if proper medical treatment is performed. Asthma and neurotoxic effects are examples of acute effects.[22]

Pesticides and Neurotoxicity

Neurons are message-processing cells found in the brain and nervous system. Neurotoxicity occurs when natural or man-made hazardous chemicals (neurotoxicants) disturb the nervous system's normal development. This may damage or even kill neurons, which transmit and receive information. Chemotherapy, radiation therapy, pharmacological treatments, and organ transplants can all cause neurotoxicity, as can heavy metals such as mercury and lead, industrial and/or cleaning solvents, some food additives, cosmetics, pesticides, and several naturally occurring compounds.[24]

Neurotoxic illnesses usually occur during and soon after exposure, when the pathogenic processes that have already begun to unfold may take time to resolve before stabilization or recovery may begin. The existence or absence of tissue injury, the magnitude of the damage, and whether neuropathological alterations have occurred in the central nervous system (CNS) all influence functional recovery (poor prognosis). There are a few signs and symptoms of neurotoxicity which include – immobilized or feeble limbs, headache, memory, intense tingling and numbness in the limbs, loss of vision, and concentration ability, loss compulsive, and Obsessive conduct that are out of control, problems with personality, sexual adversity, depression, cardiovascular problems, imbalances, and influenza.[25]

- Consequences: Some neurotoxic consequences are apparent right once, on the other hand, which require months or years to develop. The effects of neurotoxicity are influenced by a range of factors, including the neurotoxin's properties, the dose an individual is exposed to, structures to recover, the ability of affected mechanisms, the toxin's ability to metabolize, and excrete it, and the vulnerability of a target for cells. Certain compounds (acrylamide) can cause neurological damage after a single big exposure. Smaller doses over time can also cause neurological damage, although the pattern of neurological deficiency in the two dosing situations may be different.[25,26]
- Diagnosis: The nerve conduction test is the best technique to see whether the peripheral nervous system has been compromised. Computerized balancing heart rate variability, Pupillography, neuropsychological testing, and brain imaging using the triple-camera SPECT system are some of the tests used to diagnose brain injury.[28]
- Treatment: The treatment options for neurotoxicity include the removal or reduction of the toxic substance, as well as therapy to alleviate symptoms or provide support. The treatment may also comprise immunological modulation, exercise, avoiding contaminants in the air, food, and water and massage are some of the methods used to treat neurotoxicity.[27]

Diseases Associated with Nervous System or Neural Health

Alzheimer

Alzheimer's disease (AD) is now the most progressive sensory illness among those aged over 65. Late-onset Alzheimer's disease is primarily sporadic, with those having gene mutations known to cause the familial form of the condition accounting for fewer than 5% of all cases. Two pathogenic traits are similar in the brains of Alzheimer's patients and animal models. Extracellular amyloid is insoluble clusters of amyloid (A) peptides that form when the amyloid precursor protein is proteolytically processed. The hyperphosphorylated version of the microtubule-binding protein tau is abundant in intraneuronal neurofibrillary tangles (IFTs). Acute cytotoxicity and neurotoxicity would develop from pesticides used in high quantities. Low-dose environmental/occupational exposure, chronic, on the other hand, is likely to be of clinical significance in late-onset sporadic AD. By influencing the two key etiopathological variables, A and tau, pesticides might hypothetically enhance the onset or accelerate the progression of Alzheimer's disease. Rotenone, a pesticide, promotes hyperphosphorylation of tau and A aggregation in cultured rat neurons. Deltamethrin, a pyrethroid insecticide, and Carbofuran, a carbamate pesticide, caused hyperphosphorylation of tau in rats by activating GSK-3 and inhibiting protein phosphatase-2A. (PP2A) [Figure 3]. Male rats experienced better cognitive and behavioral deficits than female rats, which were consistent with Chlorpyrifos' acceleration of neurodegeneration in males, as per the researchers. The pathophysiology of amyloid and tau did not change much, as per the researchers. A surge in microglia numbers and activation, on the other hand, has been seen as a long-term pathogenic change. In the neurotoxic and neuropathological mechanisms underlying pesticide exposure, the more general deleterious processes of osmotic damage and neurotoxicity may be involved. On the other hand, certain A and tau-related systems and events might be initiated or implicated. These pathways are closely connected to A production and tau phosphorylation in the aged brain.[29-38]

Parkinson

Parkinson's disease (PD) is the second most common neurological illness after Alzheimer's disease, and the neurological ailment with the largest increase in age-standardized incidence between 1990 and 2015. The pathogenesis of Parkinson's disease is multifaceted, involving both hereditary and environmental influences. Professional pesticide exposure was associated with a higher risk of Parkinson's disease, but due to the wide range of pesticides available and how chemicals vary over time, it is unclear if certain products are more directly related. Herbicides (such as rotenone and paraquat), insecticides (such as organochlorines), and fungicides have all

Table 2: Indications of developmental neurotoxicity generated by pesticides among groups with identical neurotoxicity pathways.

Group of Pesticide	*Developmental neurotoxicity reported in an organism*	*References*
Chlorophenoxy herbicides	• A child with significant mental disability and cephalic deformities whose parents were severely exposed to 2,4-D.	[62,63]
Organophosphate	• Infants with a smaller head circumference and abnormal primitive reflexes (Chlorpyrifos). • Infants have faulty reflexes and delay intellectual development. • Short-term memory and attention were impaired (Methyl parathion).	[64,65]
Bipyridyl herbicides	• The role of developmental paraquat exposure in the later development of PD-like characteristics in mice.	[66,67]
Dithiocarbamates (EBDCs)	• In mice, maneb (in conjunction with pesticide) causes neuronal cell loss in the nigrostriatal pathway compacta.	[68-72]
Pyrethroids	• Modifications in rat motor function. • Modifications in auto-completion density, enhanced muscle activity, and lack of habituation in mice. • Improvements in the permeability of the blood-brain barrier in rats.	[73-77]

been mentioned in certain research (e.g., maneb).[40-44] Pesticide expenditures were only employed in a few studies to determine pesticide exposure. This strategy eliminates recall prejudice and enables researchers to look into dose relationships. This strategy eliminates recall prejudice and enables researchers to look into dose relationships. It was used to investigate congenital defects, issues with the human sexual organs, and cancers. Only three research, to the best of our knowledge, have utilized this method to investigate, whether pesticide usage and PD prevalence are linked, but why endorphin cells die is still a mystery to scientists.[45,46]

Amyotrophic Lateral Sclerosis

Motor neurons that regulate voluntary movements degenerate and die in ALS. The deterioration of motor function is caused by a rise in muscular atrophy, wasting, stiffness, and fasciculations. Patients lose strength and have speech, respiratory, and swallowing problems. The sporadic or non-familial type of ALS is the most frequent, accounting for 90–95% of all cases, whereas familial versions are inherited, usually in an autosomal dominant pattern. The SOD1 gene, which encodes the superoxide dismutase 1 enzyme that protects cells from oxidative stress, is the most frequent mutation for the familiar variants.

Various environmental variables, such as metals and agrochemicals, are considered to have a part in the disease's etiology. Kamel *et al*. looked at data from a variety of epidemiological research, including seven case–control studies and a major cancer cohort study. The results of the meta-analysis revealed that pesticide exposure may raise the incidence of ALS [Figure 4].[48-55]

Intermediate Syndrome

The intermediate syndrome is muscle weakness and paralysis that develops 1–4 days after the initial cholinergic toxidrome caused by organophosphate exposure resolves. In comparison to organophosphate-induced delayed polyneuropathy (OPIDP), the pattern of insufficiency in delayed neurotoxicity affects the distal musculature while sparing the cranial nerves and respiratory muscles. It differs from the acute cholinergic crisis seen in early organophosphate overdose, because it lacks additional muscarinic symptoms and does not respond to atropine. In individuals with pesticides toxicity, the frequency of the intermediate syndrome has been estimated to be between 5 and 65%. The incidence of the intermediate syndrome has been estimated to be between 5 and 65% in people who have been exposed to pesticides.[56-61]

Table 2 mentions the different research in field of pesticides causing neurotoxicity.

Conclusion

Pesticides are used to boost agricultural productivity, prevent vector illnesses, and kill or suppress dangerous pests, among other things, but on the other hand, have unmistakable negative consequences, which harms animals, birds, plants, and even humans. Chronic low-dose exposure to some pesticides may have a role in the genesis of various neurological disorders and other less well-defined behavioral changes, which is a source of public concern. Furthermore, the hypothesis that developmental pesticide exposure contributes to developmental abnormalities in children, such as autism, attention deficit hyperactivity disorder, or learning difficulties, must be researched further.

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