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The role of Pesticides in Cancer initiation and progression: A comprehensive review

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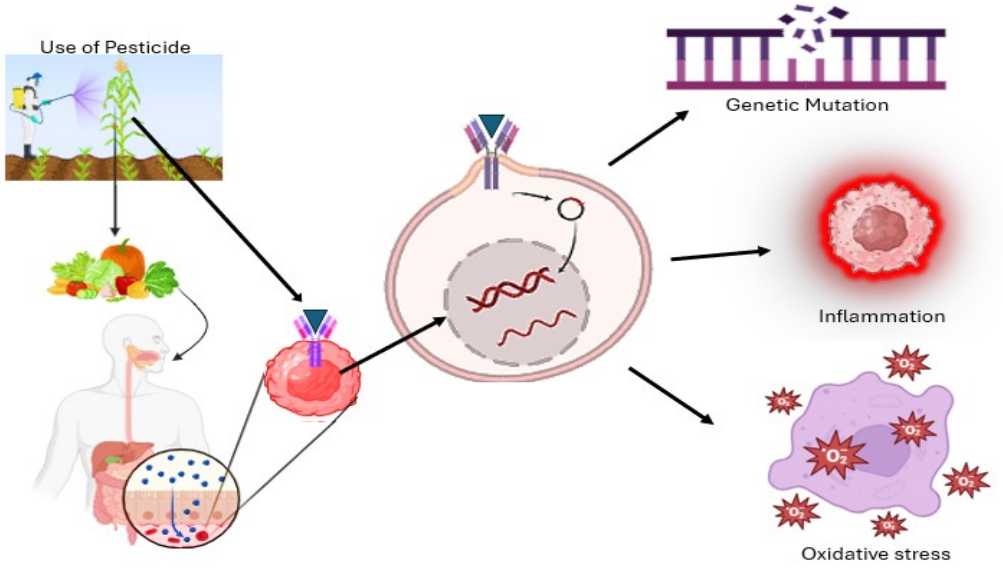
Review



ABSTRACT

Pesticides play a significant role in agriculture globally, yet concerns over their potential carcinogenicity have sparked scrutiny. This review discusses the complex nexus between pesticides and cancer, explaining their classification, properties, and carcinogenic mechanisms. Understanding their diverse chemical structures and modes of action is foundational. Carcinogenicity involves intricate genetic, epigenetic, and cellular pathways, highlighting their capacity to instigate and propagate cancer. Stringent regulatory measures are imperative to safeguard public health and the environment, making risk assessment and mitigation strategies unavoidable. Factors such as exposure levels, duration, and individual susceptibility underscore the multifaceted nature of pesticide-induced carcinogenesis. Pesticides influence crucial cell signaling pathways, implicating them in cellular homeostasis and aberrant proliferation. Interdisciplinary collaborations and innovative technologies are pivotal for advancing our comprehension of pesticide-cancer interactions. Addressing research gaps holds promise for developing targeted interventions and regulatory frameworks to mitigate pesticide-related cancer risks. This review offers a comprehensive synthesis of current knowledge and outlines future avenues for research and intervention strategies in pesticide-induced cancer.

Keywords: Pesticides, Carcinogenicity, Risk assessment, Cell signaling pathways, Regulatory perspective

INTRODUCTION

Pesticides are substances used to control pests, including herbicides for weeds, insecticides for insects, fungicides for fungi, and more. They have been used since ancient times, with the Sumerians using sulfur and the Chinese using arsenic and mercury compounds. The modern era of pesticides began with the discovery of DDT in 1939, which was widely used until concerns about its environmental and health impacts led to bans in many countries. It can be classified as biodegradable, which breaks down the harmless compounds, or persistent, which may take months or years to degrade the use of pesticides is widespread, with herbicides accounting for about 50% of global pesticide use.[1] While they play a crucial role in agriculture by protecting crops from various pests, they also raise concerns about potential carcinogenicity and toxicity to humans and other animals.[2] In 2012, the U.S. spent 21 percent of the world on herbicides including PGRs (plant growth regulators), 14% of global expenditure on insecticides, 10% of the world utilizing fungicides, and 23% of overall residing in fumigants.[3] Pesticides are utilized all over, including our beds and agricultural fields, where they account for an important portion of all pesticide production.[4] In terms of quantity, insecticides are used the most

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often, followed by herbicides.[5] The United States Environmental Protection Agency (USEPA) was established in 1970 because of the discussion that Rachel Carson's book "Silent Spring". The agency was designed to consolidate various federal research, monitoring, standard-setting, and enforcement activities to ensure environmental protection.[6,7]

During the 20th century, illegal pesticides, or those without EPA (Environmental Protection Agency) registration were exported to developing nations.[8] This practice posed heightened risks to the workers involved in handling these chemicals, and the importing countries exposed their larger populations to potential harm. According to estimates, the prevalence of pesticide poisoning in underdeveloped nations was thirteen times greater than in the United State.[9] Pesticide exposure affects people in many ways, and the intensity of these exposures varies, which contributes to the differences in their effects.[10] Pesticides are exposed in different amounts by workers working in the pesticide industry, vendors, farmers, and consumers.[11] Numerous illnesses, including NHL (non-Hodgkin lymphoma), HD (Hodgkin's disease), Parkinson's disease, endocrine disruption, and reproductive and respiratory diseases are linked with pesticide exposure.[12–14] It is also thought that pesticides contribute to human malignancies; for example, Glyphosate has been linked to breast cancer.[15] It has been discovered that insecticides containing amines and alkyl urea are linked to brain cancers. At dosages as low as 0.1 ppm, Aldrin/Dieldrin causes cancer of the mammary gland, lung, liver, uterus, thyroid, and lymphoid tissue in test animals. WHO identified some pesticides as an Endocrine disruptor chemical (EDCs), in 2002.[16] One of the main processes linked to many diseases and aging is oxidative stress.[17–19] Naturally, this problem worsens with age and has an impact on several critical organ functions.[20] A number of pesticides, including paraquat, rotenone, and maneb, lead to stress-related neurodegenerative disorders that are mediated by reactive oxygen species (ROS).[21,22]

Pesticides are chemical substances widely used in agriculture, public health, and households to control pests and enhance crop yields.[23] However, there is growing concern about the potential health risks associated with their use, particularly their link to cancer development in humans.[24–26]

People who were treated with Agent Orange, which was a combination of dioxin [cacodylic acid, picloram, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,4-dichlorophenoxyacetic acid (2,4-D)] was extensively employed by the United States in the Vietnam War, had a higher risk of prostate cancer. In test animals, dieldrin at concentrations as low as 0.1 parts per million develops tumors of the mammary gland, thyroid, uterus, lymphoid tissue, liver, and lung.[27] The World Health Organization (WHO) first identified several pesticides as endocrine disruptor chemicals (EDCs) in 2002. These are exogenous chemicals, either natural or artificial, that disrupt endocrine systems and may harm an organism's development, growth, and reproduction, as well as the development of its offspring. One of the main targets of EDCs is the transcriptional activity of nuclear receptors. It has been discovered that several pesticides, such as pyrethroids, diphenyl ethers, organochlorines, acid amides, carbamates, and organophosphorus insecticides function as agonists of these nuclear receptors [28]. More research has shown a strong correlation between pesticide use and the emergence of cancer in both children and adults. Pesticide exposure has been proven to increase the chance of developing several cancers, including (leukemia, neuroblastoma, Burkitt lymphoma, Wilm's tumor non-Hodgkin lymphoma, soft tissue sarcoma, ovarian cancer, and cancers of the stomach, colon, bladder, and rectum).[29]

The review aimed to offer a clear knowledge of the possible carcinogenic effects of pesticides and identify chemicals or pesticide classes that may provide a greater risk by a thorough study of the existing information. It will also emphasize the difficulties in examining the connections between pesticides and cancer, address any gaps or limitations in the present evidence, and suggest future research possibilities.

2. Classification and Properties of Pesticides

Several variables, including action modes, chemical classes, toxicity, and functional groups, are used to categorize pesticides [27]. Most pesticides either include inorganic like sulfur, copper, ferrous sulfate, copper sulfate, lime, etc., and organic contain carbon and other active components.[28] In contrast to inorganic pesticides, organic pesticide compounds are often more complex and less water-soluble. Additionally, there are two categories of organic pesticides: natural (made from naturally occurring sources) and synthetic (intentionally made by chemical synthesis).[29]

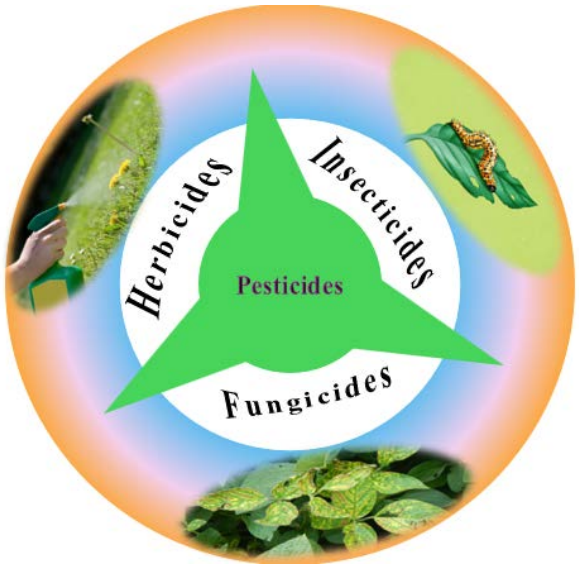


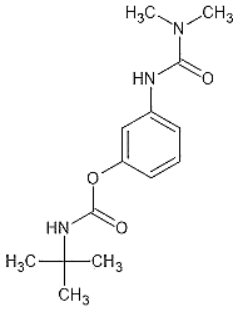
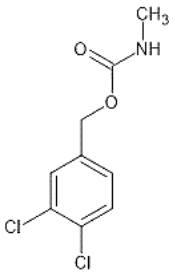
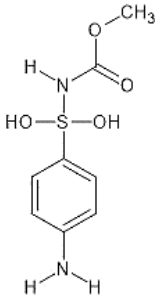
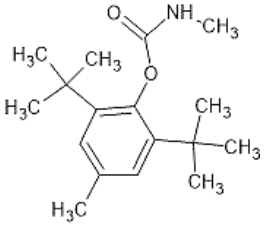
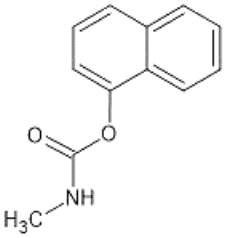
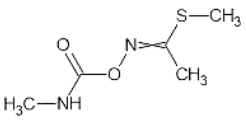
Figure 1. Classification of pesticides based on their target pests and mode of action. Insecticides are pesticides designed to target and control insects, Herbicides are used to control unwanted plants, commonly referred to as weeds, Fungicides are chemicals used to control fungal diseases in plants

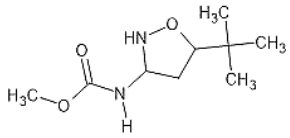
The target pest might be controlled in various ways by different pesticides. Furthermore, certain herbicides can imitate the actions of plant growth regulators, while others can effectively limit a plant's ability to turn light into food. Similar to

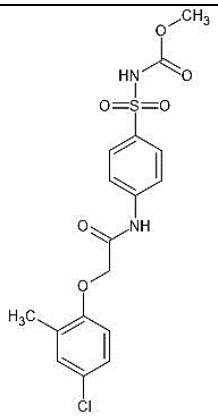
the way one fungicide may impact cell division, others may work well to inhibit the fungus' production of certain chemicals.[30] The specific type of target bug that a pesticide is used on may occasionally serve as a classification for that substance. Miticides, insecticides, and herbicides are used to restrict the development of mites, insects, and weeds in the same way as fungicides are used to inhibit the growth of fungi. Insecticides may kill insects by entering their bodies directly via their skin, mouth, or respiratory system.[31] Herbicides are used to destroy weeds when they are ingested by the stems, leaves, or roots of plants, either directly or indirectly. Some pesticides, after being ingested by plants or animals, may enter untreated tissues. Such insecticides or fungicides may kill certain insects or fungi by penetrating all areas of the treated plants, or pest management, several insecticides have been created that affect pest's neurological systems or affect their endocrine or hormonal systems.[32]

Pesticides are categorized as Herbicides, Insecticides, and Fungicides (Figure 1) based on their chemical compositions, which are determined by their chemical structure and function as shown in Table 1.

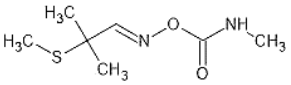
Table 1. Classification of some pesticides and their chemical structures.[33]

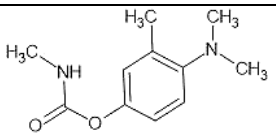
Type of pesticide and Chemical structure	
Herbicides	
 Karbutilate	 Dichlormate
 Asulam	 Terbucarb
 Carbaryl	 Methomyl

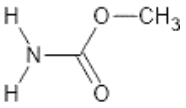

Carboxazole

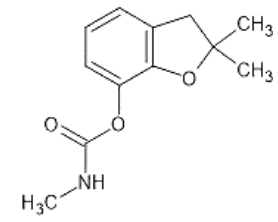

Funasulam

Insecticides

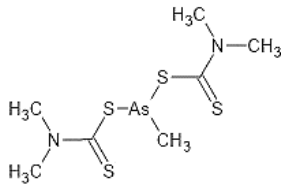

Aldicarb

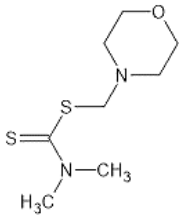

Aminocarb

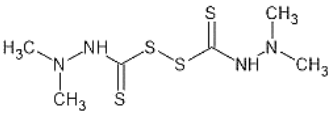

Methylcarbamate

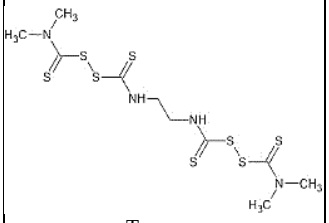

Carbofuran

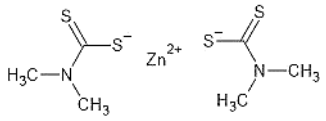
Fungicides

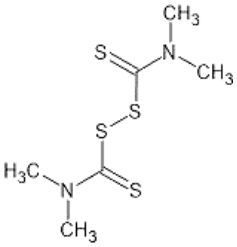

Urbacide


Carbamorph


Azithiram


Tecoram


Ziram


Thiram

Inorganic Pesticides are simple substances that resemble crystalline salts, are stable in the environment, and are typically soluble in water. These were the first chemical pesticides, consisting as a mixture of elements including sulfur, lime, arsenic, copper, mercury, and aluminum phosphide. They might linger in the environment for a very long time and are often harmful.[34]

Organic Pesticides are more complicated chemicals than inorganic pesticides since carbon forms the foundation of their molecular structure. They are easily soluble in fatty acids but often insoluble in water. The two other categories of organic pesticides are natural and synthetic. Natural organic pesticides come from naturally occurring sources like plants, such as pyrethrum, whereas synthetic organic pesticides are made artificially through chemical syntheses. Most contemporary pesticides are (organic compounds, often including sulfur, phosphorus, or oxygen in their molecules). This family of pesticides is further divided into fumigants, carbamates, organochlorines, and organophosphates.[35]

2.1 Organic pesticides classification

Fumigants: Fumigants, which are typically tiny molecules that can permeate many materials easily, are used to control pests from agriculture, buildings, and stored products. They work by filling an area with toxic gases to suffocate or poison the pests within. Common fumigants include methyl bromide, ethylene oxide, sulfuryl fluoride, carbon tetrachloride, and ethylene bromide. They are effective in reaching pests in hard-to-reach areas and are often used for soil treatment, structural fumigation, and commodity protection.[36]

In addition to its widespread usage as a feedstock material in the synthesis of many compounds, carbon tetrachloride finds use as an industrial cleaning solvent. Owing to its capacity to destroy ozone, it has been designated as a regulated substance further down the Montreal Protocol. As such, its use is limited to feedstock applications that yield extremely low emissions, while other substances, like the broad-spectrum pesticide methyl bromide, are subject to a phase-out total ban under the same protocol.[37] As a byproduct of various bromide production techniques, methyl bromide is created from naturally occurring bromide salts. It is eventually released into the atmosphere after being employed as a soil fumigant, which sterilizes the soil by eliminating the great mass of soil organisms. Methyl bromide is a hazardous substance that poses the greatest risk at the actual fumigation site due to its quick dispersion into the sky. Methyl bromide exposure at high concentrations may have particular and severe negative effects on the skin, eyes, and lungs in addition to failure of the respiratory and central nervous systems in humans.[37]

The use of fumigants, among other pesticides, has been pinpointed as a significant contributor to cancer development. Those who come into contact with these chemicals, whether through inhalation, ingestion, or skin contact, face potential risks. Commonly associated cancers with pesticide exposure encompass multiple myeloma, bladder cancer, non-Hodgkin's lymphoma, prostate cancer, leukemia, and breast cancer.[38]

Organochlorines: Pesticides that include organochlorines are often hazardous, long-lasting, and mostly made of carbon, hydrogen, and chlorine. These pesticides are active and persistent for a long time after application because the chlorine atoms stop organic chemicals from degrading quickly in the environment. Therefore, their applications and usage are either prohibited or limited in certain countries. Most applications for organochlorines are as insecticides; they include sprays for seed coating and grain storage as well as pellet applications in field crops. Among the organochlorines, DDT is the least expensive, most durable, and most widely utilized.[33] Organochlorines have been identified as potential endocrine disruptors, with some studies indicating a potential link to increased cancer risk.[39] Specifically, research suggests that exposure to organochlorine pesticides might be associated with a higher risk of breast cancer, as demonstrated by a case-control study conducted among Ethiopian women.[40]

Carbamates: Carbamates and organophosphates are approximately similar in structure. However, whereas organophosphates are derived from phosphoric acid, carbamates are derived from carbamic acid. The class of pesticides is used to control vectors. Products include propoxur, which is used to control insect pests, carbaryl, which is used to dust live animals to prevent fleas, and other chemicals that are used to control bees and wasps. There are differences in the range of activities, toxicity to mammals, and persistence of carbamates. They are often employed as baits or surface sprays in the management of domestic pests and provide a comparatively high risk of harming humans. These chemicals are highly unstable and decompose in the environment in a matter of weeks or months.[33] The effects of carbamate pesticides on the immune system, which may have implications for cancer. These pesticides have been implicated in the increasing prevalence of diseases associated with immune response alterations, such as hypersensitivity reactions, autoimmune diseases, and cancers.[41]

Organophosphates: Esters of phosphoric acid and its derivatives, known as 'organophosphates', are thought to be more dangerous to human health than other pesticide groups. A typical chemical structure of organophosphate consists of a core P (phosphorus group), a leaving group that may be substituted with serine's oxygen at the acetylcholine esterase (AcHE) active site, and the thiophosphoric (P=S) or distinctive phosphoric (P=O) bond. High-hazard pesticides may have harmful consequences that are either short-term or long-term. Their extensive usage has resulted in health issues and deaths worldwide, frequently because of deliberate or unintentional poisonings and occupational exposure.[33] The International Agency for Research on Cancer classifies some OPs as probably carcinogenic to humans (Group 2A) and others as possibly carcinogenic to humans (Group 2B), indicating a need for caution and further evaluation.[42] The Agricultural Health Study demonstrated that exposure to certain OPs, such as malathion and terbufos, was significantly associated with an increased risk for aggressive prostate cancer.[43,44] OPs like malathion have been linked to an increased risk of thyroid cancer and a decreased risk of non-Hodgkin lymphoma.[45]

Table 2. Pesticides Commonly Used by the farmers

Class according to hazards	Chemical Family
Extremely hazardous	
Phorate	Organophosphate
Highly hazardous	
Carbofuran	Carbamate
Monocrotophos	Organophosphate
Profenofos and cypermethrin	Organophosphate
Moderately hazardous	
Cyhalothrin	Organophosphate
Fenthion	Organochlorine
Endosulfan	Organophosphate
Dimethoate	Organochlorine
DDT	Organophosphate
Cyhalothrin	Organochlorine
Slightly hazardous	
Malathion	Organophosphate
Unlikely to present acute hazards in normal use	
Artizine and Triazin	Carbamate
Carbendazim	Carbamate

2.2 Physical and chemical properties of pesticides

Physical and chemical characteristics of pesticides have a significant impact on the biological activity it has toward the target pest species. A pesticide's physical characteristics dictate its mode of action, dose, delivery method, and the ensuing chemo dynamics in the environment. Pesticides chemical makeup and formulation have a significant impact on their physical characteristics.[46]

Molecular form and weight: The physical form (odor and look) and molecular weight (MW) of the active ingredient are often included in certain references, such as the pesticide handbook. A substance's molecular weight is the total of the atomic weights of each atom that makes up the molecule. A pesticide's molecular weight is an intrinsic characteristic that sets it apart from the others, except for stereoisomeric pesticides, which have comparable molecular weight and only vary in the group spatial orientations at certain chiral centers. For instance, the molecular weight of most gas-phase insecticides is 103 or less. However, for complicated compounds with molecular weights of more than 500, it becomes very challenging to anticipate their state and structure. The shape and structure of pesticides are critical factors in determining their binding affinity to proteins [46]. The molecular structure of a pesticide determines how it interacts with biological molecules, such as proteins, within an organism. If a pesticide binds to a protein involved in gene regulation or DNA repair, it can potentially cause mutations. These mutations may lead to genetic amplification, when such genetic changes occur in genes that control cell growth and division, they can lead to cancer.[47]

Vapor pressure (VP): The ease with which a material may volatilize and transition into a vapor (gas state) is measured by its vapor pressure. For pesticides, the ease of volatilization may be advantageous in terms of certain mechanisms on the one hand, but it may also have unfavorable effects on the other hand. For instance, a fumigant pesticide may have a beneficial penetrating power, therefore having a greater vapor pressure is beneficial. On the other hand, vapor drift and environmental contamination may result from high vapor pressure. High vapor-pressure pesticides must be handled carefully to prevent vapors from escaping into the sky. If a pesticide has a low vapor pressure and is water soluble, it may build up in water since it does not migrate into the atmosphere. Pesticides that are not soluble in water have the potential to gather or accumulate in biota or soil.

Solubility: The ability of a material to dissolve in a particular solvent is measured by its solubility. Unless otherwise indicated, water solubility is expressed in ppm (parts per million), which is equivalent to mg/L, or mgs (milligrams) per liter. Technique, molecule size, hydrogen bonding, polarity of the material, pH, and temperature all affect solubility measurements [48]. Pesticides that are highly soluble in water can easily contaminate water sources and may be more readily absorbed by living organisms, increasing exposure risks. Conversely, pesticides with low water solubility tend to accumulate in soils and sediments, potentially leading to long-term environmental persistence and bioaccumulation in the food chain [49]. Like, organochlorine pesticides (OCPs), which are known for their high stability and low water solubility, have been identified as endocrine-disrupting chemicals (EDCs) that can cause cancer by increasing the activity of tumor cells and suppress the immune system [50].

2.3 Overview of Pesticide Exposure and Regulatory Frameworks

Pesticide exposure may occur either occupationally (for example, working in a facility that formulates pesticides or via commercial pesticide application) or ecologically (for example, from foods like fruits and vegetables that have been treated for pests).[51] To mitigate the risks associated with pesticide exposure, countries have established regulatory frameworks that include Legislation, standards, Monitoring and Enforcement, Public health protections, and Global Cooperation. These frameworks are designed to minimize the risk to humans, animals, and the environment, promoting health and safety while allowing for the benefits of pesticide use in agriculture and public health.[52] The Environmental Protection Agency (EPA) has reported on the most widely used pesticides. The Federal Insecticide, Fungicide, and Rodenticide Act, generally known as FIFRA, regulates pesticide registration and regulatory requirements.[53]

MECHANISMS OF PESTICIDES CARCINOGENICITY

In a rat model of liver carcinogenesis, organochlorine pesticides like heptachlor and hexachlorobenzene increased cytochrome P450 expression.[54] Any exposure to a stressor or irritant results in excessive cytochrome P450 elaboration and high levels of estrogen production.[54,55] Estrogens are mitogenic and proliferative when expressed in the incorrect tissues or the incorrect amount.[56] Some pesticides imitate estrogen or work as its inducer, while others act as its inhibitor. Some fungicides are azole chemicals that operate as anti-estrogens by inhibiting aromatases.[57] Letrozole and anastrozole are two common types of aromatase inhibitors used in breast cancer treatment. In the body, estrogen serves as the primary signaling chemical, making its disruption potentially fatal. Although it may seem contradictory, azole insecticides may both induce inflammation and breast cancer.[58]

Any irritant may induce mammary gland inflammation and carcinogenesis when used often and in large doses.[59] So, depending on the biochemical environment of the host, pesticides may either activate or repress the enzymes that are responsible for carcinogenesis. Inhibition of the aromatase in females may result in the development of masculine qualities, while stimulation of the enzyme in males is likely to result in the development of feminine traits.[60] In addition to a long list of other hormonal issues, aromatase disturbance causes breast cancer, polycystic ovary syndrome, ovarian cancer, endometriosis, gastric cancer, hepatic cancer, lung cancer, pituitary cancer, obesity, prepubertal gynecomastia, male hypogonadism, and short height.[61–63] Both hypothyroidism and hyperthyroidism are caused by pesticides. Manganese ions may be chelated by the widely used herbicide glyphosate, which results in a lack of manganese-dependent enzymes. Lack of the manganese-dependent protein phosphatase 1 (PP1) enzyme in the maternal pituitary gland may lower maternal blood levels of thyroid-stimulating hormone (TSH), which can lead to anatomical changes in the fetus's cortical neuron.[64] A thyroid disorder may lead to several unfavorable outcomes. The thyroid gland is indirectly and directly regulated by estrogen.[65]

Brain oxidative stress indicators and the activity of enzymes important for glutamatergic and cholinergic system function are impacted by repeated exposure to glyphosate.[66] Exposure to the herbicides paraquat and maneb modifies the gene expression that controls the cell cycle, including cyclin D1, cyclin D2, Rb1, and p19. These chemicals also boost ROS production and hinder the development of brain stem cells.[67,68] Phosphotriesterases are enzymes that specifically target the breakdown of organophosphate pesticides. They catalyze the hydrolysis of the phosphate ester bond found in these compounds, which is a critical step in their degradation. Organophosphate toxicity may be detoxified with paraoxonase.[69] However, several substances also act as enzyme inhibitors. Therefore, these defensive enzymes are unable to break down pesticides.

More than 70 pesticides have been classified as either "certain" or "perhaps" carcinogenic, according to a database of substances assessed for carcinogenic potential by the EPA's pesticide program released in 2010.[70] Human epidemiological data, investigations of metabolism, and structural interactions with other carcinogens were used to create this categorization.[71] The carcinogenicity of a pesticide may be affected by a wide variety of variables, including but not limited to age, gender, individual sensitivity, quantity, and length of exposure, and associated with exposures to other cancer-causing chemicals.[72] However, pesticide's carcinogenic mechanisms can be investigated in terms of their ability to affect genetic material, either directly through induction of structural or functional damage to chromosomes, DNA, and Histone proteins, or indirectly through impairment of cellular organelles like factors involved in cell homeostasis, endocrine network, nuclear receptors, endoplasmic reticulum, and mitochondria.[73,74]

Table 3 shows results from epidemiological research linking several types of cancer with pesticide use.

Table 3. Pesticides linked to higher cancer incidence in epidemiological studies.

Type of cancer	Pesticide
Lung cancer	Pendimethalin
	Dieldrin
	Chlorpyrifos
	Metolachlor
	Diazinon
Colon cancer	Imazethapyr
	Dicamba
	Trifluralin
	Aldicarb
Multiple myeloma	Permethrin
Leukemia	Fonofos
	Chlorpyrifos
	EPTC
	Diazinon
Prostate cancer	DDT, lindane, simazine
	Butylate
	Methyl bromide
	Chlordecone
Pancreatic cancer	DDT
	EPTC, pendimethalin
Leukemia	Diazinon
	Chlordane/heptachlor
	Fonofos
Bladder Cancer	Imazethapyr
Rectum cancer	Chlorpyrifos
Brain Cancer	Chlorpyrifos

3.1 Arsenic carcinogenicity

Arsenic is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC). Inorganic arsenic compounds are highly toxic, while organic arsenic compounds are less toxic and non-carcinogenic. The carcinogenicity of arsenic is attributed to various mechanisms, including genotoxic damage, chromosomal abnormalities, and epigenetic modifications such as DNA methylation, histone tail modifications, and microRNA activity.[75] Chronic exposure to arsenic, particularly through contaminated drinking water, has been linked to an increased risk of lung, bladder, liver, and kidney cancers.[76–78] The carcinogenic process involves several mechanisms, which can be broadly categorized into genotoxic and epigenetic:

Genotoxic Damage: Arsenic can cause direct DNA damage, leading to mutations. This includes chromosomal abnormalities such as deletions, amplifications, and translocations, which can disrupt normal cell function and lead to cancer.[79,80]

Epigenetic Mechanisms: Arsenic can also cause cancer without directly damaging DNA. It does this through epigenetic changes, which are alterations in gene expression that don’t involve changes to the underlying DNA sequence. These include DNA methylation by which arsenic can alter the methylation patterns of DNA, which can silence tumor suppressor genes or activate oncogenes.[80] By histone modification arsenic can affect the way DNA is packaged by modifying histones, the proteins around which DNA is wound. This can change the accessibility of genes to the transcriptional machinery, affecting their expression.[75] Arsenic can also influence microRNAs, small non-

coding RNAs that can regulate gene expression post-transcriptionally.[79]

The combination of these genotoxic and epigenetic effects can disrupt normal cell processes and promote the development of cancer.[81] Chronic exposure to arsenic, especially through drinking water, is a significant concern, as it has been linked to an increased risk of various cancers, including those of the lung, bladder, liver, kidney, gallbladder, and skin.

3.2. Organophosphorus carcinogenicity

Studies conducted both *in vitro* and *in vivo* have identified the organophosphorus targets; five of these studies were very sensitive: In homogenates of Xenopus embryos, malathion, and naloxone (IC50 = 1-9 nM) inhibits lysyl oxidase, indicating that they modify the posttranslational modification of collagen, leading to external defects in connective tissue; in cultured rat neurons, 'chlorpyrifos and chlorpyrifos oxon (at less than 1 nM)' are reported to Ca2+/cAMP activation response element binding protein, suggesting a potential mechanism for neurotoxicity; Ethyl arachidonic fluorophosphate (at < 1 µM) and diisopropylfluorophosphate (at 100 µM) inhibit platelet-activating factor acetylhydrolase; fenitrothion (at 22 nM) acts as an androgen receptor antagonist *in vitro* and inhibits the development of androgen-dependent tissues *in vivo*. Paraoxon (1–10 nM) causes apoptotic cell death in a leukemia cell line by disrupting mitochondria, which activates caspase-9.[82–84]

Regulatory Perspectives

The likelihood of a person being exposed to pesticides is influenced by several factors, including their age (adult or child), proximity to areas of pesticide application, pesticide treatment in their home, occupation, volatility of the substance, persistence of the pesticides in the environment, and various chemical and physical characteristics of the pesticides.[55,85] All these factors collectively contribute to the level of exposure an individual may encounter. Inhalation and skin contact with pesticides used in the house by someone else is possible. People are also often contaminated by their exposure to food and water. The EPA has prohibited the indoor use of long-lasting pesticides like organophosphate (OP) insecticides to reduce the exposure of the general population to chemicals.[86] Public OP exposures are reducing as pyrethroids, and other short-lived insecticides become more widely used.[87] Considering their developing behavior, diets, and bodies, children may be more vulnerable to the effects of pesticide exposure than adults, according to the National Academy of Sciences.[1] A significant portion of a child's pesticide exposure comes from their diet.[88,89] Since people applying more volatile pesticides (like flying bug spray) and other aerosols would be more likely to be exposed via the respiratory route, it is typically recommended that they wear respiratory protection suitable for the chemical being used [7]. To lower non-occupational pesticide exposures, EPA regulations have made it illegal to use persistent and broad-spectrum pesticides. These chemicals have now replaced OCs since they are more ecologically friendly and do not accumulate in the food chain to the same extent as OCs did during their extensive use in the middle of the 20th century.[90,91]

Additionally, since they demonstrate higher insect-specific lethality than mammals, substances like pyrethroids have grown to be quite alluring for pest management. The chemicals are typically processed and removed from the body as water-soluble metabolites in urine after 24 to 48 hours of human exposure to pyrethroids, OPs, and carbamates.[92,93] To evaluate chemical dosimetry after exposures, physiologically based pharmacokinetic models are utilized, but these models are better established in animal research than in human studies. These models estimate the internal dosage of certain pesticides as a function of time.[94] It seems doubtful that any nation would completely outlaw the use of chemical pesticides soon, thus reducing the risk of cancer from pesticides will rely on determining which chemicals are human carcinogens.[95]

Risk Assessment and Mitigation Strategies

Variations in exposure duration, dose, pesticide type (in terms of toxicity), pesticide mixtures used in the field, and environmental factors in agricultural areas make accurate risk assessment of pesticide effect on human health.[96] People who work with, and people who live near sprayed greenhouses, pesticide storage facilities, regions, or open fields are particularly at risk from these variations.[97,98] High exposure to a moderately toxic pesticide is likely to provide a greater danger to human health than low exposure to a highly toxic pesticide since the risk to human health is a function of pesticide toxicity and exposure. It is unclear, however, whether pesticide residues in the food and water supply pose a significant threat to human health [55,99]. The Environmental Protection Agency (EPA) assesses pesticides for their potential to cause cancer in humans, considering the potency of the chemical and the potential for human exposure.[38]

The regulatory procedures that register pesticides for use in agriculture on a case-by-case basis must give way to market-based and educational methods that consider the whole system to close this gap. These procedures may reduce the dangers connected to seasonal pesticide usage plans, especially in underdeveloped nations. Farmers and their advisers must have access to science-based risk assessments in a format that enables risk-based product comparisons for progress to be made.[100,101]

Pesticides play a crucial role in protecting crops and livestock from yield reductions. However, their use can lead to pollution in agricultural soils and pose risks to the environment. several approaches aimed at mitigating these concerns are Promote Integrated Pest Management (IPM): IPM focuses on using a combination of techniques to manage pests effectively while minimizing pesticide use. It includes biological control, crop rotation, and habitat management.[102] Raise Awareness: Educating farmers, policymakers, and the public about the risks associated with pesticide use is essential. Awareness campaigns can encourage responsible pesticide application and highlight alternatives.[103,104] Encourage Personal Protective Equipment (PPE): Proper protective gear, such as gloves, masks, and coveralls, can reduce exposure to pesticides during application. Training on safe handling practices is crucial.[102]

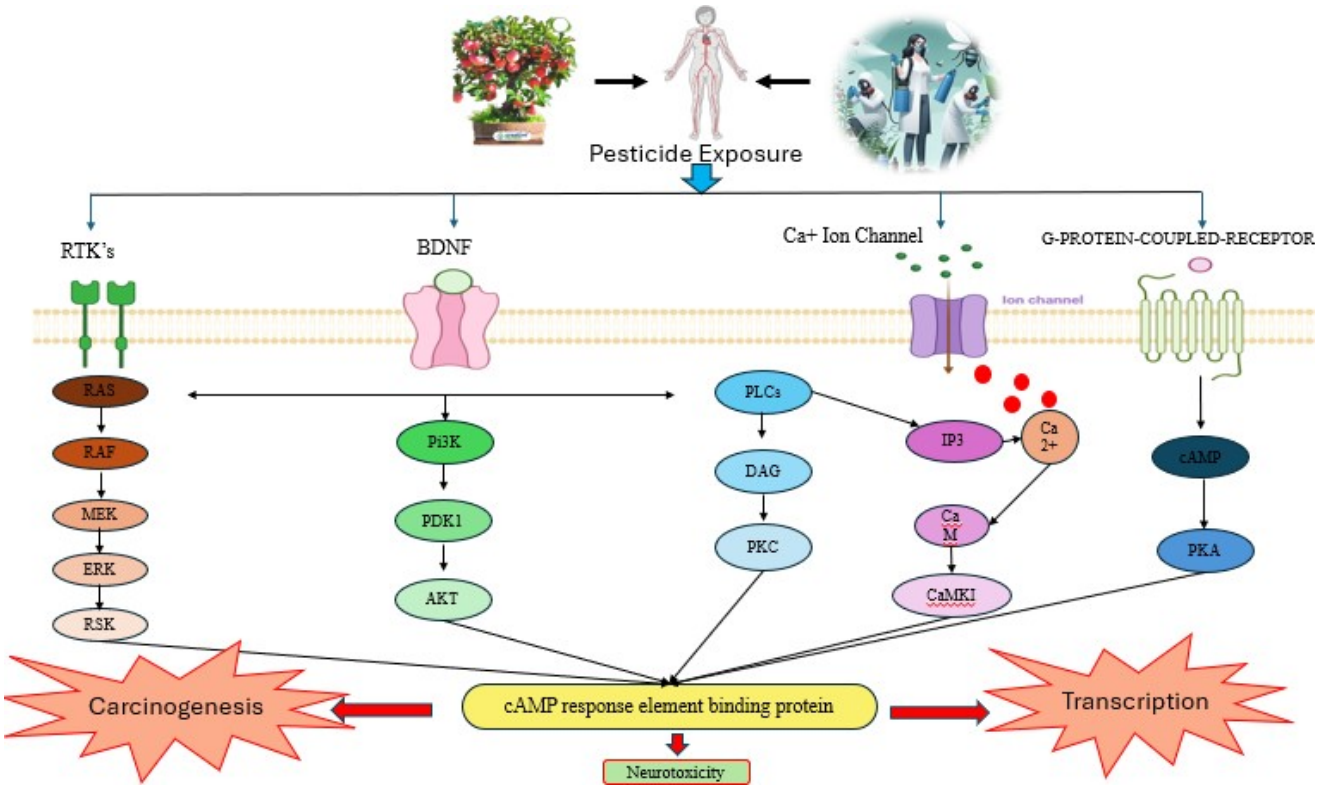


Figure 2. This figure depicts the signaling pathways such as BDNF/TrkB, RAS/RAF/MEK, Pi3K/AKT, PLC/PKC, Calcium–Calmodulin, and cAMP. Pesticides have the ability to modulate gene expression within these pathways. Such alterations may influence CREB phosphorylation, consequently affecting neurotoxicity, carcinogenicity, and cellular transcription.

Advocate for Policy Changes: Stricter regulations and policies can limit pesticide use and promote sustainable alternatives. Advocacy efforts can drive positive changes at local, national, and international levels.[102,104]

A thorough evaluation of pesticide dangers based on data from databases on the characteristics of pesticides and their impacts on the environment and human health. Researchers examined pesticides for which there are sizable databases detailing their characteristics and associated dangers, and which are presently registered in the USA and the EU. Researchers generated risk ratings for each pesticide by using comparable criteria based on previously published risk models, which might be used for comparing its active components.[105]

High-risk pesticides that needed to be mitigated for specific health or environmental risks; pesticides of lower risk that were more likely to be compatible with sustainable IPM (integrated pest management); and HHPs (highly hazardous pesticides), which were officially defined by the FAO (Joint Food and Agriculture Organization of the United Nations) and WHO JMPM (Meeting on Pesticide Management).[100] Researchers further differentiated the lower risk category, dividing pesticides that need some specialist PPE (personal protective equipment), like respirators or face masks, from those that mainly require basic clothing, in acknowledgment of the poorer nations' restricted access to resources and information.[106]

Major Factors that Influence Cancer Risk

Cancer risk is influenced by a multitude of factors, and exposure to pesticides is one significant aspect that has garnered attention in recent years.[38] Many studies show the several major factors contribute to the association between pesticides and cancer risk.[107,108] First and foremost, the chemical composition of pesticides plays a crucial role. Some pesticides contain carcinogenic compounds that, when ingested or absorbed through the skin, may lead to DNA damage and mutations in cells, increasing the likelihood of cancer development. Moreover, the duration and intensity of exposure are critical determinants of cancer risk.[109,110] Individuals with prolonged and high levels of exposure to pesticides, such as agricultural workers or those living near sprayed fields, face a higher risk of developing cancer.[111] Additionally, the timing of exposure is crucial, as certain periods of life, such as prenatal or childhood exposure, may be more susceptible to the adverse effects of pesticides on cellular development.[112] Furthermore, the interaction between various pesticides and other environmental factors, such as pollutants or lifestyle habits like smoking, can compound the cancer risk. As research on the long-term effects of pesticides continues to evolve, understanding these major influencing factors becomes vital for implementing appropriate preventive measures and regulations to protect public health.[113,114]

Approaches to Risk Assessment for Pesticide-Related Cancer Risks

The deterministic risk assessment approach is often utilized in public health and environmental settings. For evaluating risk, it just considers a single factor. The recent study suggests causal relationships between pesticide exposure and cancer, the strongest evidence exists for acute myeloid leukemia (AML) and colorectal cancer (CRC).[115] Deterministic risk assessment has benefits as well as drawbacks. The method's simplicity in comprehension and application makes it advantageous for assessing exposure and health risks. Deterministic risk analysis, however, only accounts for average exposure and health risk.[109] The unpredictability of exposure and risk is not considered by this sort of methodology. For instance, the deterministic method only displays danger if the risk index and average exposure value are above or below a predetermined dosage or risk threshold. This is the situation where, even though 20% of the population may be exposed to levels beyond the reference dosage and standard of risk for one class of chemical, the average exposure and health risk are below these levels. Researchers may conclude that there is no danger based on a deterministic risk assessment, in which case no risk-management measures may be taken.[7,116]

Role of Pesticide in Alteration of Cell Signaling Pathway

By emphasizing elements of different signaling pathways, including BDNF/TrkB, RAS/RAF/MEK, Pi3K/AKT, PLC/PKC, Calcium–Calmodulin, and cAMP, pesticides can also alter the expression of genes. alterations may have an impact on CREB phosphorylation, which may have an impact on the neurotoxicity, carcinogenicity, and transcription of the cell (Figure 2).

Oxidative Stress: Pesticides can cause oxidative stress by generating reactive oxygen species (ROS) and reactive nitrogen species (RNS).[117] This stress is associated with various diseases, including cancer, and can lead to inflammation and DNA damage.[118]

Dioxin Receptor Signaling: Some pesticides can activate the dioxin receptor pathway, which may interact with estrogen receptor signaling and potentially generate genotoxic estrogen metabolites. This interaction can lead to DNA damage and affect the p53-dependent cellular stress response.[119]

Crosstalk with Other Pathways: Pesticides can trigger crosstalk events between different signaling pathways, which may have combined effects that are not observed when assessing the toxicity of individual chemicals alone.[119]

The acetylcholinesterase enzyme structure of humans and insects is similar, which means that pesticides can change the cell signaling pathway and cause unintentional neurotoxicity.[120,121] Organophosphates (dichlorvos, diazinon, parathion, chlorpyrifos, and malathion) and carbamates (ethyl carbamate, polyurethane, and methylcarbamate) are the two main families of pesticides that obstruct the release of acetylcholine.[122–124]

CREB signaling:

Overexpression of CREB is associated with aberrant signal transduction caused by the deregulated expression of downstream genes that control the hallmarks of cancer, such as proliferation, apoptosis, angiogenesis, metastasis, immune surveillance, metabolism, and the generation of tumor stem cells, which lead to the initiation and progression of tumors [125]. In the presence of the coactivated CREB-binding protein molecule, CREB is activated by phosphorylation of the Ser133 residue [126]

BDNF:

The BDNF/TrkB signaling system is impacted by reduced CREB phosphorylation, which also mitigates oxidative damage and neurodegeneration [127]. Studies have also demonstrated that mice exposed to organophosphorus pesticides such as diazinon and chlorpyrifos exhibit decreased transcription of Bdnf/Trkb.[128,129]

PI3K/AKT:

the Pi3K/AKT pathway is a critical signaling pathway in cells that plays a significant role in regulating cell survival, growth, and metabolism. When this pathway is blocked, it can lead to a decrease in the levels of phosphorylated AKT, also known as p-AKT. AKT, or Protein Kinase B, is a key protein in this pathway that, when activated by phosphorylation, promotes cell survival and growth while inhibiting apoptosis (programmed cell death).[130,131] The results showed that fenitrothion-oxon and fenitrothion reduced the phosphorylation of AKT and CREB.[132]

cAMP/PKA pathway:

The calcium-calmodulin kinase-dependent PLC pathway is another possible route by which CREB is activated. Tyr816 residue phosphorylation triggers the PLC pathway, which in turn produces DAG (diacylglycerol) and IP3 (inositol triphosphate). Calcium is released from intracellular reserves when the Plc/Ip3 cascade starts the calcium/calmodulin-dependent protein kinase (CaMK).[120,133]

RAS/MEK/ERK and RAS/MAPK pathway:

According to the study, avermectin, a pesticide residue, activates the RAS/RAF/MEK/ERK pathway, which results in neurotoxicity.[134,135] Atrazine significantly reduced the MEK/ERK/CREB pathway's mRNA and protein expression levels in the rat hippocampal tissues.[136,137]

PLC/PKC:

Phospholipase C (PLC) activity causes Ca2+ to be released from cellular reserves, facilitating entrance into the plasma membrane.[138] Protein Kinase C (PKC) activity in the brain is triggered by exposure to pesticides that are known to induce oxidative damage, such as organophosphates (chlorpyrifos) and organochlorines (chlordane and DDT).[120,139,140]

Future Prospects and Research Imperatives

Pesticides are used to prevent, eliminate, or manage pests, but several studies have raised concerns about their environmental and health impacts. Large-scale trials to directly investigate pesticide-related health issues have significant drawbacks. However, statistical links between pesticide exposure and cancer are convincing and cannot be disregarded. Few studies have examined the long-term effects of pesticide use on growth and development. Longitudinal studies of people exposed to long-term pesticides are needed to better understand the increased risk. Pesticides are often mixed with other chemicals. The goal of the investigation should be to comprehend how these substances

could encourage the development of cancer. The best pesticides for environmental and ecological management should be identified. Therefore, agriculture should make use of helpful bacteria, viruses, insects, and nematodes. More money must be put into registration, product testing, product development, research, pesticide usage plans, and public education by government agencies, NGOs, and businesses.

CONCLUSION

It was challenging to quantify cancer risk due to occupational pesticide exposure because of its variability, the short half-life of pesticide metabolites, and the imprecision of biomarkers. Assessing environmental pesticide cancer risk is considerably harder. However, scientific data suggests that pesticides cause cancer in both direct users and indirect users. In poor countries with lax regulations, the situation may be worse. Pesticides cause cancer via several unknown methods. Cancer risk seems to be independent of pesticide functional class (e.g., fungicide, insecticide, or herbicide) or chemical class (triazines, OCs, or OPs). Nongenotoxic pathways may be as significant as direct genotoxicity. The illness process may include genetic vulnerability to pesticide carcinogens. The genetic susceptibilities found to date are widespread, making them unsuitable for risk assessment. Limiting cancer risk requires exposure control.

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