Chapter 3

Environmental Exposure and Health Effects Associated with Malathion Toxicity

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Additional information is available at the end of the chapter

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Abstract

Malathion (O,O-dimethyl-S-1,2-bis ethoxy carbonyl ethyl phosphorodithionate) is a non-systemic, wide-spectrum pesticide. It is widely used throughout the world for agricultural, residential, and public health purposes, mainly to enhance food production and to provide protection from disease vectors. Malathion preference over other organophosphate pesticides relates to its low persistence in the environment as it is highly susceptible to hydrolysis, photolysis, and biodegradation. However, numerous malathion poisoning incidents including acute and chronic cases have been reported among pesticide workers and small children through accidental exposure. Malathion toxicity is compounded by its reactive metabolites and also depends upon the product purity, route of exposure, nutritional status, and gender of exposed individuals. Its metabolic oxidation in mammals, insects, and plants leads to the formation of malaoxon which appears to be several times more acutely toxic and represents the primary cause of malathion's toxicity. Depending on the level of exposure, several signs and symptoms of toxicity including numbness, tingling sensation, headache, dizziness, difficulty breathing, weakness, irritation of skin, exacerbation of asthma, abdominal cramps, and death have been reported. Similar to other organophosphate pesticides, malathion exerts it toxic action by binding to acetylcholinesterase enzyme and inhibiting its activity, leading to accumulation of acetylcholine in synaptic junctions, which in turn results in overstimulation of cholinergic, muscarinic, and nicotinic receptors, and subsequent induction of adverse biologic effects. This chapter provides an update and analysis of the production and use, environmental occurrence, molecular mechanisms of toxicity, genotoxicity and carcinogenicity, and adverse human health effects associated with malathion exposure.

Keywords: Malathion, production and use, environmental occurrence, mechanisms of toxicity, genotoxicity, carcinogenicity, adverse health effects

1. Introduction

Organophosphate (OP) pesticides are a group of chemicals that have many domestic and industrial uses; historically, they have been most commonly used as insecticides and have been responsible for a number of pesticide poisonings. Accounting for about 70% of pesticide use in the United States, OPs have become the most commonly used pesticides because of the high persistence, accumulation, and toxicity of organochloride insecticides such as DDT and BHC. OPs are phosphorous-containing insecticides that were originally developed in the 1940s as highly toxic biological warfare agents. This group of chemicals includes insecticides such as malathion, diazinon, chlorpyrifos, methyl parathion, and parathion [1]. These compounds were first used in Germany during World War II as toxic nerve agents. Their modern derivatives include highly neurotoxic agents such as sarin, soman, and tabun. The main mechanism of toxic action of OPs is the inhibition of acetylcholinesterase enzyme activity, causing nervous and respiratory damages that may potentially result in death [2, 3]. It was not until World War II that the magnitude of detrimental effect on organisms was discovered from the research conducted to determine the toxicity of nerve gases used for military purpose [1]. Although they were produced during the World War II era, nerve gases were not used until the Iran–Iraq War and during an incident in Tokyo, Japan. During the Iran–Iraq War (1981–1988), it was reported that Iraq used nerve agents such as tabun and sarin. In March 1995, Aum Shinrikyo, a religious cult in Japan used bags of sarin on a subway train in Tokyo. The released gas killed 12 individuals and sent more than 5,000 to the hospital. They are generally lipid-soluble and are capable of penetrating the skin, the blood brain barrier, the placenta, and into the fetus [4].

2. Physical and chemical properties of malathion

As an OP insecticide, malathion was first registered for use in the United States in 1956 by the United States Department of Agriculture (USDA). It is currently regulated by United States Environmental Protection Agency [1]. Malathion is a broad-spectrum insecticide used to control a variety of outdoor insects in both agricultural and residential settings. Estimation by the U.S. EPA indicates that over 30 million pounds of malathion are used annually [5]. About 60 percent is often used in federal and state programs to eradicate insects such as boll weevils, grasshoppers, and fruit flies. It is also used as a potent insecticide for mosquito control in residential areas as well as for insect control on a variety of food crops. Malathion has also been approved by the United States Food and Drug Administration (FDA) for addition in shampoos in order to control head lice [1]. Signal words ranging from “caution’’ to “danger”

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have been developed; depending on the combined toxicity of the active ingredient and other product components. Uses for individual malathion products vary widely; therefore, proper precautions should be taken to minimize their toxicity. The chemical structure of the technical grade of malathion is shown in Figure 1, and its physicochemical properties are presented in Table 1 [1, 3, 6, 7, 8].

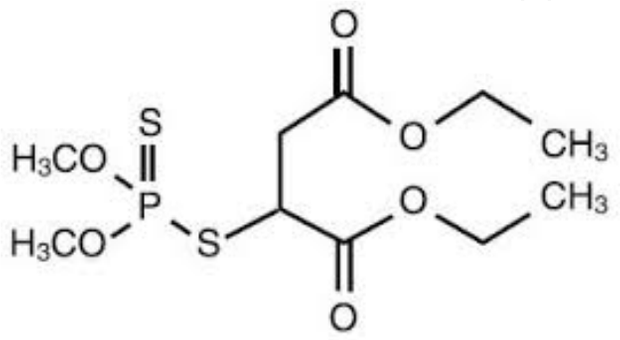

Figure 1. Structure of malathion

Properties	Malathion	Reference(s)
CAS Reg. No.	121-75-5	
Synonyms	Dimethyl dithiophosphate of diethyl mercaptosuccinate	[1]
Molecular Weight	330.4 g/mol	[1]
Color	Colorless to amber	[6]
Physical State	Liquid	[3]
Melting Point	2.85°C	[3]
Boiling point	156°C	[7]
Density/Specific gravity	1.2076	[7]
Odor	Skunk/garlic like	[3]
Solubility Water (mg/L)	145 mg/L	[6]
Vapor pressure (mmHg)	1.78×10^{-4} mmHg at 25^0C	[3, 6]
Henry's Law Constant	$2.0\ (+1.2) \times 10^{-7}$	[8]
Soil Sorption Coefficient (K_{oc})	30, 93–1800 depending on soil type and environmental conditions	[3, 7]

Table 1. Physical and chemical properties of malathion

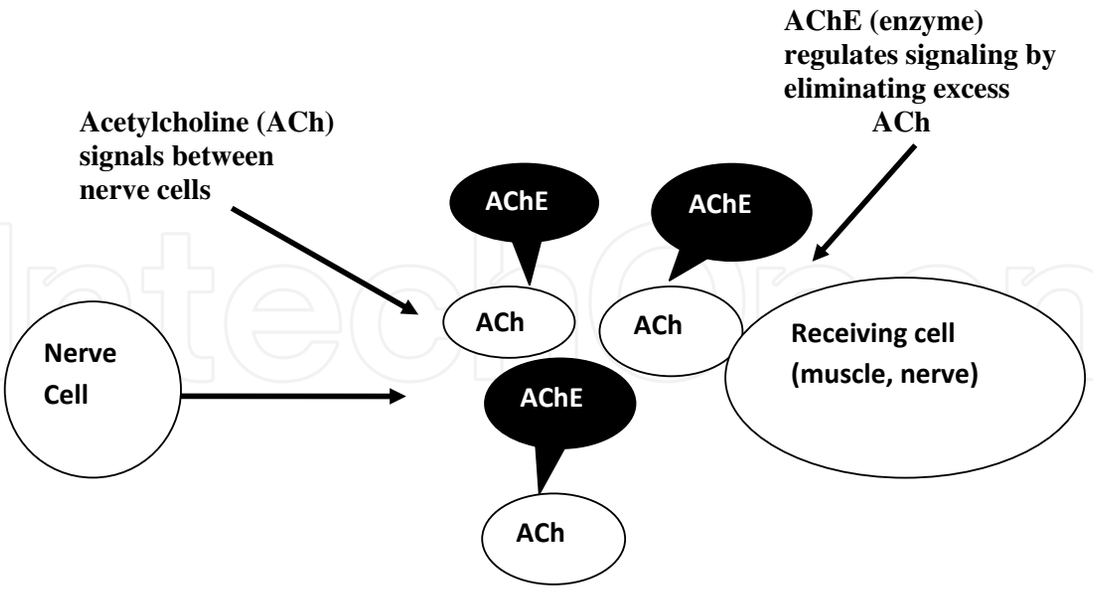

Figure 2. Normal nerve signals

3. Sources/environmental occurrence

OP introduced in the 1930s, are manufactured chemical substances that are produced by the reaction of alcohols and phosphoric acid. Their primary effect as insecticide was discovered during military operations when initially used as nerve gases [9]. Malathion, an OP compound, is also known as carbophos, maldison, and mercaptothion. Being a non-systemic, wide-spectrum insecticide, malathion is one of the most frequently used OP pesticides. It has been used for various eradication programs and for public health purposes throughout the United States and other countries. Some of the common areas of usage include agricultural, industrial, and use by the general public.

Malathion was developed during World War II, in the 1950s, and has been known for its high insect potency, but low mammalian toxicity. Considered to be one of the safest OP compounds, malathion is known as one of the most selective OP insecticides. It has been effective in the control of pests on vegetables, field crops, fruits, agriculture, commercial extermination, fumigation, domestic animals, and veterinary practices. Hence, it has many applications in agricultural, nonagricultural, and public health purposes. It is commonly used on agricultural crops (alfalfa, apple, apricot, asparagus, avocado, barley, bean, beats, blackberry, blueberry, boysenberry, broccoli, cabbage, carrot, cauliflower, celery, chayote, cherry, clover, corn, cotton, cucumber, dewberry, eggplant, potato, fig, garlic, grape, grapefruit, hay grass, horseradish, leek, lemon, lettuce, lime, loganberry, mango, pepper, pineapple, pumpkin, reddish, raspberry, spinach, wheat, squash, strawberry, tangerine, tomato, walnut, watermelon, wild rice, yam, and indoor-stored commodity treatment and empty storage facilities for barley, corn, oats, and wheat), stored products, golf courses, home gardens, trees and shrubs, mosquito control,

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Mediterranean fruit flies (medflies), fleas on pets, treatment of head lice (humans), household insects, Boll Weevil Eradication program, Christmas trees, lawn, etc. [1,3,4]. Homeowners use malathion for the following purposes: on ornamental flowers, shrubs, and trees, outdoor garbage dumps, irrigation and sewage systems, pastures, and range land. It can also be used to control ectoparasites of cattle, flies, and human head and body lice [3]. On the other hand, malathion's targeted pests include: ants, aphids, apple mealybug, armyworm, bagworm, beetle, borer, bug, fireworm, blueberry maggot, caterpillars, cattle lice, cockroaches, cherry fruitworm, rootworms, cotton fleahopper, cotton leafworm, cranberry fruitworm, European fruit lecanium, fleahoppers, fleas, flies, grasshoppers, green cloverworm, imported cabbageworm, leafhoppers, mosquitoes (adult, larvae), moths, mushroom flies, orangeworms, pepper maggot, pickleworm, plant bugs, poultry lice, sawflies, scales, spiders, ticks, tomato fruitworm, wasps, weevil, etc. [1,3,4]. Malathion is regulated by both FDA and U.S. EPA at a maximum amount of 8 parts per million (ppm) as residue on specific crops used for food. Because of its potential toxicity to humans, the EPA requires that an appropriate time lapse be observed between the application time and entry/reentry of a field worker.

4. Uses and environmental exposure

Malathion is an OP insecticide that is used mostly in agriculture and in public health programs to control infestations of insects including ants, aphids, fleas, fruit flies, hornets, mites, mosquitoes, moths, spiders, thrips, ticks, wasps, and weevil. It is also used as pest control for agricultural food and feed crops including blueberries, raspberries, strawberries, limes, cotton, cherries, garlic, greens, dates, and celery [1]. In addition to the use of malathion in plant applications, it is a key component of personal hygiene products used for lice control [10]. Currently, malathion is still used in a large scale in agricultural sector and public health programs all over the world. The estimated average annual total domestic usage of malathion in the USA is approximately 15 million pounds of malathion as an active ingredient [11]. Between late 1970s and 2008, malathion was the primary pesticide used in the USDA Boll Weevil Eradication Program to protect cotton crops in the southern United States [12, 13]. In 1998, malathion and diazinon were applied in some areas of the state of Florida after an outbreak of Mediterranean fruit flies called Medflies. Medfly outbreak resulted in a significant reduction in agricultural yields. To minimize its damage, federal and state authorities implemented the Medfly Eradication Program. Within 5 months of application, 123 people reported symptoms associated with pesticide exposure, such as respiratory distress, gastrointestinal distress, neurological problems, skin reaction, and eye distress [14]. The United States used malathion among the insecticides to control mosquitoes carrying West Nile Virus during the year 2005 [15].

Published research has reported cases of malathion poisoning associated with accidental and/or intentional exposure to malathion. A previous study conducted in Japan reported 10 deaths out of 63 cases of accidental exposure to malathion, as well as 404 deaths out of 480 cases of malathion-associated suicides or homocides [16]. Other accidental death from malathion

toxicity in human population has also been documented [17]. The median lethal dose (LD_{50}) of malathion is estimated to be 2100 mg/kg in man [18].

Exposure to malathion occurs via dermal contact, ingestion, and/or inhalation [6]. Most people are not exposed to malathion in the air that they breathe or on things that they touch, unless they live near areas being sprayed. The people who are at the greatest risk to malathion toxicity are those who are occupationally exposed. These include farm workers, chemical sprayers, and people who work in factories that make malathion or other malathion-containing products. These high-risk groups can be exposed through skin absorption by contacting contaminated products or surfaces, or through lung absorption by inhaling contaminated air. Domestic users of malathion are also at high risk of intoxication related to its application in residential areas near homes and gardens for medflies and mosquitoes control. Exposure to high concentrations of malathion has been associated with severe toxicity and death in some cases. Hence, it has been recommended not to enter or go to the fields sooner than 6 days after malathion spraying [4]. Also, the utilization of personal protective devices such as breathing equipment and special clothings may prevent toxicity and protect against malathion intoxication. A previous study conducted by the U.S. EPA between 1971 and 1991 in 3 states pointed out that malathion was the only chemical detected in twelve groundwater monitoring wells. The highest malathion concentration of 6.17 ppb was reported in Virginia in a county where the land was mainly agricultural and forested.

More recent investigations on the environmental contamination have reported the absence of malathion in groundwater near areas that have been chemically sprayed; indicating a lower risk of malathion toxicity in drinking water collected from groundwater. Symptoms of exposure to malathion include headache, nausea and vomiting, burning eyes, difficulty breathing, and lethargy. Malathion exposure has been associated with metabolic disorders [19], oxidative stress [20], immunotoxicity [21], inflammation [22], and hepatotoxicity [23]. Malathion has also been reported to induce genetic damage in a variety of laboratory studies, including a study of mice fed with malathion-treated grains. In epidemiological studies with human blood cells, DNA damage and oxidative stress have been proposed as a process that could mechanistically link pesticide exposure to a number of health outcomes [2]. According to the U.S. EPA, there is evidence that malathion causes cancer. Experimental studies have pointed out that the commercial grade of malathion insecticide causes breast cancer in laboratory animals. Also, the use of malathion by farmers has been associated with an increased incidence of non-Hodgkin's lymphoma [24].

5. Environmental fate and transport

In general, OPs are transported through the environment in various ways. Malathion released in the atmosphere as a result of its use on agricultural crops and/or residential areas may form droplets that fall on ground covers including plants, animals, soils, water resources, buildings, and/or other structures. Malathion deposited on these platforms may subsequently be transported away through the action of rainfall/precipitation, and wind. It has been reported

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that malathion may remain in the environment for up to few months, but is usually transformed or degraded within a few weeks through the processes of photolysis, hydrolysis, and/or biodegradation by microorganisms. Because malathion is rapidly degraded by soil bacteria, low concentrations are expected to be present in groundwater [4]. Reported half-lives in soil range from 1 to 17 days [25, 26]. In water, malathion breaks down quickly by hydrolysis or by the action of bacteria present in the water. The half-lives of malathion in water were estimated as 1.65 days at pH 8.16, and 17.4 days at pH 6.0 [27]. In air, malathion is broken down by reacting with other chemicals formed naturally in the air by sunlight, to form a more toxic product called malaoxon. A study conducted in the Sierra Nevada Mountains reported very low malathion concentrations in air (< 1 ng/m^3), and concentrations ranging from 64 to 83 ng/L in surface waters between 18 and 2042 altitude. These results led the investigators to speculate that the distribution of malathion was a result of atmospheric transport [28]. If malathion is present on dry soil or on man-made surfaces such as sidewalks, pavements, or playground equipment, it usually does not break down as fast as it would in moist soil.

Published data indicate that malathion may be transported in the air following application to either agricultural or urban/residential areas [28, 29]. Malathion may be transported in the atmosphere as a vapor or adsorbed onto particulate matter [30]. Also, its occurrence in the atmosphere is generally localized. However, in a non-U.S. study of malathion adsorbed to fly ash (particulate matter) [31]. Adsorbed malathion is photodegraded when exposed to irradiation for up to 1.5 hours, but does not degrade when adsorbed to kaolin. The results from this study indicated that malathion adsorbed to kaolin maybe transported over long distances, while that adsorbed to fly ash will be photodegraded and therefore will not be transported far in the atmosphere [30]. Additionally, malathion has been detected in the fog of remote pristine areas, indicating that long-range transport may occur under some conditions [32].

6. Toxicokinetics

6.1. Absorption and distribution

Absorption of malathion occurs through the gastrointestinal tract, the respiratory tract and its primary and slowest absorption pathway, and the skin. Ingestion of contaminated food or water is the predominant route of exposure to malathion for the general population, compared to the inhalation and dermal routes. The predominant route of occupational exposure for the general population is through the dermal contact. Although it is well known that malathion is rapidly absorbed through the gastrointestinal tract and the skin, little is known about its fate from inhalation exposure. Absorbed malathion can be transported by the blood and distributed to many organs and tissues including the liver where it is metabolized to form malaoxon. In biologic systems, malathion and its metabolites have a very low accumulation potential and are eliminated through urine within a few days. Hence, analysis of malathion or its metabolites in urine should be performed within few days after exposure. Their concentrations in tissues and body fluids are important biomarkers of exposure. Currently, there is a scarcity of scientific data regarding the background concentrations of malathion in human tissues [4].

Dermal absorption of malathion is rapid. However, the absorption rate vastly depends on it applied dose and the exposure site [4]. From a study examining the absorption rates of applied malathion on various parts (forearm, axilla (armpit), ball of the foot, abdomen, forehead, and jaw angle) of the skin of male human volunteers, the greatest rate of absorption was found in the armpit followed by the forehead. The armpit and forehead areas respectively showed 4.2 and 3.4 times greater absorption than the forearm skin [33]. In another toxicokinetics study, it was reported that more than 90% of absorbed malathion was eliminated through urine within 24 hours of exposure, by male rats orally exposed to 28 mg/kg malathion, or dermally exposed to 41 mg/kg malathion. The remaining malathion was detected in the feces, blood, intestines, liver, and kidneys [34]. Based on organ weight changes during a two-week inhalation study in rats, other target organs for malathion distribution and toxicity included the liver and the kidney [35].

6.2. Mode of action

OP pesticides including malathion share a common mode of action. They bind to the enzyme acetylcholinesterase (AChE) at nerve endings throughout the bodies of insects and other organisms [36]. AChE plays a key role in the synaptic transmission of nerve impulses. Its inhibition causes the blockage to signal transmission leading to intoxication manifested by restlessness, hyperexcitability, convulsions, paralysis, and death [24]. A similar mode of action has been reported for all OP insecticides [37]. Malaoxon, the toxic metabolite of malathion, is known to illicit a similar effect in mammals. However, the signs and symptoms of malathion toxicity are different in mammals and insects because in mammals AChE is not active in the central nervous system, but rather in nerves that connect with muscles [37]. Malathion is toxic via skin contact, ingestion, and inhalation exposure [6]. Under normal circumstances, AChE binds to the neurotransmitter acetylcholine (ACh) at the nerve junction, effectively ending the stimulation of the next neuron. Resulting effects from malathion toxicity include restlessness, hyperexcitability, convulsions, blurred vision, salivation, difficulty breathing, chest tightness, diarrhea, vomiting, sweating, headaches, and cramps [4, 24]. Intermediate syndrome (delayed neuropathy) has been reported in humans as a result of acute exposure to high amounts of malathion. Symptoms include weakness in several motor cranial nerves, weakness in neck flexors and proximal limb muscles, and respiratory paralysis.

There is evidence that exposure to malathion below the level that causes nervous system effects results in few or no health problems. Toxicity is usually the result of binding of AChE to malaoxon (malathion metabolite) which leads to the accumulation of ACh at the nerve junctions and subsequent overstimulation of the nervous system [36]. Malaoxon, the primary toxic metabolite of malathion, is produced in the liver as a result of a biotransformation process involving an oxidative sulfuration catalyzed by the cytochrome P450 enzyme [38, 39]. Findings from experimental studies have pointed that malaoxon is 22 times more toxic than malathion when exposure is by oral route, and 33 times more potent by all routes of exposure from acute and sub-acute exposure durations [40]. Exposure to multiple OPs can lead to additive toxicity. However, the different OPs vary widely in their potency and how well they are absorbed by the body depending on the route of exposure [36].

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The accumulation of acetylcholine at the nerve junctions as a result of OP binding to the acetylcholinesterase enzyme, phosphorylating its serine hydroxyl group, and deactivating its functional esterase site [9]. The buildup of acetylcholine at the neuromuscular junction also causes a persistent depolarization of the skeletal muscle, leading to fasciculations, tremors, ataxia, weakness, convulsions, and coma. [41]. In the central nervous system, neural transmission is disrupted. Acetylcholinesterase is also contained in the erythrocytes, and is identical to that which is found in the nervous system; however, the function is to control, to a certain extent, permeability of the cell membrane.

Malathion toxicity causes a disruption of the functioning of the cholinergic system, and elicits basic clinical signs and symptoms that are similar in humans and other mammals [4]. Both muscarinic and nicotinic receptors as well as central nervous system receptors are modulated by malathion exposure [36]. Several muscarinic effects such as salivation, lacrimation (production of tears), urination and defecation (the SLUD syndrome), vomiting, dyspnea (shortness of breath), bradycardia (reduced heart rate), abdominal pain, miosis (constriction of the pupils), and anorexia have been documented as a result of malathion interaction with AchE and over excitation of the post-ganglionic parasympathetic receptors in the nervous system [42]. Other clinical signs of toxicity including muscle tremors and rigidity, weakness and loss of limb mobility, and paralysis have been observed as a result of excessive stimulation of nicotinic receptors [40].

In humans, the clinical manifestations of malathion toxicity depend on several factors including the target enzyme and its sensitivity, the site of interaction at the synaptic junction, the dose of malaoxon that interacts with the receptor, and the exposure route [4]. Several muscarinic effects including excessive perspiration, constriction of the pupils, lacrimation, salivation, abdominal cramps, diarrhea, nausea, vomiting, chest tightness and difficulty breathing have been reported in humans [4, 36, 43].

6.3. Metabolism and distribution

From an in vivo study examining the metabolism and distribution of malathion, ten metabolites were found in the urine and feces of rats pre-exposed to radiolabeled malathion. A large amount of radiolabeled compound (80%) was excreted in urine, and was comprised mainly of malathion dicarboxylic acid and of thiomalic acid and malathion mono acids to a lesser extent. Malaoxon, desmethyl malathion, O,O-dimethyl phosphorothioate, monoethyl fumarate, and thiomalic acid concentrations were relatively low [38]. Similar metabolites of malathion were reported in both humans and rats, with the exception of monomethyl and dimethyl phosphate that were detected in humans, and of thiomalic acid and monoethyl fumarate that were found in rats. An experimental study with rats also reported that malathion had low accumulation affinity in tissues, and constituted the majority of residual compounds excreted [44].

It has been pointed that other components in malathion-containing products can enhance its toxic action by deactivating the activity of the carboxyesterase enzymes that catalyze its conversion to malaoxon [45]. These other constituents of malathion compounds are impurities that may result from contamination during manufacturing and/or chemical storage [4]. Through the action of carboxylesterases, both malathion and malaoxon are degraded into

metabolic products that are more water-soluble and less toxic [44]. In humans, carboxylesterases are not found in the blood, but are mainly present in the liver which constitutes the main organ of biotransformation. In rats, they have been found in many organs including the liver, blood serum, and kidney [4]. Secondary metabolic pathways include oxidative desulfuration to malaoxon, hydrolysis to phosphatases, and dealkylation to desmethylmalathion [38].

6.4. Excretion

Orally administered malathion has been reported to be excreted in large amount (80–90% as parent compound) in the urine within the first 24 hours post-exposure[44]. From a toxicokinetics study with radiolabeled malathion, it was reported that ten different metabolites of malathion were detected in the urine of rats. Urinary excretion accounted for about 85–89% of the exposed dose, while fecal excretion accounted for about 4–15% within 72 hours post-exposure[38]. In a study examining the dermal absorption, metabolism, and excretion, malathion was applied to the ventral forearm skin of eight human male volunteers at 4 μg/cm^2. Its excretion was highest at 4–8 hours post-exposure; however, only 8% of its initial dose was found in urine within 120 hour post-exposure [46]. Malathion has been detected in human breast milk [47], although no studies were found that examined the relationship to exposure or if its presence could cause adverse effects in nursing infants.

7. Genotoxicity studies

Malathion has been identified by the National Institute for Occupational safety and Health (NIOSH) as a mutagen, based on a comprehensive review of scientific evidence from many mutagenicity tests including bacteria, fruit flies, mice, hamsters, fish and human cell cultures bioassays conducted in 29 laboratories between 1978 and 1995 [48]. Similar findings have been reported from recent studies, supporting those that were previously reviewed by NIOSH. From an in vivo genotoxicity study, researchers from Assan and North-Eastern Hill Universities (India) demonstrated that oral exposure to malathion induces genetic damage in mice [49]. Other investigators from the Egyptian National Research Center reported that mice fed with malathion-treated wheat developed genetic damage of two different types at all tested doses [50]. Many other investigations have shown that exposure to malathion, its metabolite malaoxon, and its contaminant isomalathion induces genetic damage in human blood lymphocytes [51–53].

8. Carcinogenicity studies

Evidence of the carcinogenic effects of few pesticides in animals and an increase in the risk of developing malignancies in occupationally exposed populations have made necessary studies in exposed workers [54–58]. Several studies have been conducted with rats and mice to determine whether malathion has the potential to cause cancer, with variable results. In April

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2000, U.S. EPA classified malathion as having "suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential by all routes of exposure". This categorization was made considering Cheminova's findings that malathion induces hepatocellular carcinomas in experimental animals at higher doses of exposure. [59].

Recent studies have underscored the need to strengthen EPA's carcinogenicity classification. From a 2001 study conducted by researchers at Columbia University and the Universities of Tarapaca and Concepcion (Chile), malathion exposure significantly increases the incidence rate of breast cancer in rats [60]. Findings from another study demonstrated that the increase in cancer incidence was linked to the damage of an important gene by malathion [61]. In an investigation involving long-term dietary exposures to malathion, researchers observed an increased incidence of liver and nasal/oral tumors in rats and increased incidence of liver tumors in mice [44]. In a two-year dietary study, researchers administered oral doses of 2,359, 739, or 868 mg/kg/day to rats. They found no evidence of an association between tumor incidence and exposure to malathion [10, 62]. The International Agency for Research on Cancer (IARC) concluded in 1987 that the carcinogenic potential of malathion was not classifiable, and placed it in group 3 [63]. Also, an epidemiological study at six Canadian provinces pointed out that the cancer risk of non-Hodgkin's lymphoma was twice in men exposed to malathion compared to healthy men who had not been exposed to malathion [64]. This finding was consistent with the results of previous studies conducted in the United States. [65]. Also, occupational exposure to pesticides has been reported to be associated with an increase risk or incidence of different types of carcinomas such as non-Hodgkin's lymphoma [66], Hodgkin's lymphoma [66], leukemia [57], multiple lymphoma [67], pancreatic cancer [68], gastric cancer [69], lung cancer [70], bladder and colon cancer [71], and gall bladder sarcoma [72].

In addition to its potential genotoxic and carcinogenic effects, malathion has also been reported to have significant adverse effects on different organ systems. Its potential systemic health effects on specific organs include the following:

9. Hematologic effects

At high doses, malathion acts like other OP insecticides to suppress the immune system in certain animal species [73]. A study indicated that malathion usage may affect the hematopoietic system [74]. In addition, the study reported that sublethal doses of malathion exposure caused deleterious effects on hematological parameters of treated animals [75]. Other studies indicated that chronic exposure to malathion significantly decreases RBCs, Hb, and P.C.V% values in treated animals compared to the control group [76]. Furthermore, similar studies demonstrated that high levels of malathion induced DNA abnormalities in exposed persons [77], decreased human immunity [78], and caused non-Hodgkin's lymphoma [79, 80]. Acute malathion treatment resulted in bone marrow failure and plastic anemia [81, 82]. Although acute toxicity study with malathion displays deleterious effects in humans and test animals, chronic toxicity study revealed that a group of volunteers who ingested low dose of malathion over a period of 1.5 months did not show a significant inhibition of their blood cholinesterase activity [16].

10. Neurologic effects

Malathion is a widely used OP insecticide because of its relatively low toxicity to mammals and its high selectivity compared to other OP insecticides. Possible symptoms of acute exposure to high levels of malathion include skin and eye irritation, cramps, nausea, diarrhea, excessive sweating, seizures and even death. Most symptoms tend to resolve within several weeks. According to EPA, there is currently no reliable information on adverse health effects of chronic exposure to malathion [83]. Malathion is usually less toxic. However, its overall toxicity is influenced by its metabolites and other chemical constituents of its chemical formulation. Malathion oxidative metabolism results in the production on malaoxon in mammals, insects, and plants. Being the most hazardous form, malaoxon is 40 times more acutely toxic than malathion [84, 85]. Interestingly, malathion present in the body system will clear up or be eliminated within three to five days [86]. The rapid rate of excretion from human body is facilitated by the action of carboxyesterases that catalyze the biotransformation of malathion and its metabolites to non-toxic and water-soluble products that can be easily eliminated from the body or cells. Arthropods such as insects lack or possess a low level of carboxyesterases. Therefore, insects are highly sensitive to malathion toxicity. Today, malathion is still considered as one of the safest OP insecticides. It was used for large eradication programs against insect infestations in metropolitan areas of Florida, Texas, and California [87].

11. Reproductive and developmental effects

Malathion is known to influence the reproductive function through two mechanisms including its cellular toxic action and its effect on the encephalic regulatory serotoninergic, besides acetylcholinergic which is the main mechanism of the reproductive functions [88]. The enzyme acetylcholinesterase (AChE) is used as a marker for exposure to OPs and carbamates (both inhibit this enzyme, resulting in a general nervous system failure) [89]. Malathion is found to inhibit the release of acetylcholinesterase at the synaptic junction [60]. AChE plays an important role in the control of nerve excitability at post-synaptic sites. Inhibition of liver AChE activity is a useful indicator of OP pesticides poisoning. In addition, many scientific reports indicated that malathion-induced physiological, biochemical, immunological, and histological changes in experimental animals [90–92]. A documented scientific report showed that high doses of malathion induce developmental and reproductive effects in experimental animals [93]. Another report indicated malathion and its metabolites can cross the placenta of mammals and depress cholinesterase activity of the fetus [94]. A 2003 report indicated that malathion reduced sperm count and the number of normal forms in test mice with a maximal effect at 18 days post-injection [95]. Previous studies indicated that administration of malathion caused damage to the Leydig cells and decreased the levels of testosterone [96, 97]. Similar study showed reduction in the number of immature germ cells due to decrease of steroidogenic activity and damage of the Sertoli cells [96]. Another study demonstrated that malathion interferes with the process of spermatogenesis by preventing the maturation in the later post-meiotic stages, which are androgen-dependent [98].

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12. Hepatic effects

There is limited data in the literature regarding the hepatic effects of malathion in agricultural workers. However, recent scientific data have demonstrated that malathion and other pesticides induce liver and kidney histopathological alterations in experimental animals [92, 99–101]. The study conducted showed that malathion intoxication may affect the structures of the liver and kidney showing the presence of fine subcapsular infiltrations, diffused parenchymatous degeneration of single hepatocytes, presence of fine foci constructed of plasmatic cells, and histiocytes located between hepatic plates [102].

13. Regulatory guidelines

Malathion is an OP insecticide that was first registered in 1956, and remains largely in use worldwide. The regulations and recommendations for malathion include the following: The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) allow a maximum amount of 8 parts per million (ppm) of malathion to be present as a residue on specific crops used as foods [10]. The Occupational Safety and Health Administration (OSHA) has established an exposure limit for malathion in the workplace of 15 milligrams per cubic meter (mg/m^3), for an 8-hour workday, 40 hours per week [79]. According to the National Institute for Occupational Safety and Health (NIOSH)'s guidelines, workers should not be exposed to malathion concentrations greater than 10 mg/m^3 during a 10-hour workday, 40 hours per week. NIOSH also recommends that an atmospheric concentration of 250 mg/m^3 malathion be considered as being immediately hazardous to human health and life.

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