

Pyrethrins and Pyrethroids

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Pyrethrins are among the most widely used class of pesticides in the United States. Natural pyrethrins (agents from pyrethrum) were among the earliest pesticides discovered by agriculturists. It is believed that they were extracted from dried pyrethrum and chrysanthemum flowers (*Chrysanthemum cinerariaefolium*, *C. coccineum*) as early as the first century by the Chinese (Klaassen 1996). In the 1960s the demand for pyrethrin pesticides outstripped the amount of pyrethrum pyrethrins being produced leading to the development of synthetic pyrethroids to meet the increased demand and to reduce costs. Synthetic pyrethroids first became available to consumers in the 1980s. By 1982 synthetic pyrethroids accounted for more than 30% of the pesticide market (Klaassen 1996). This article will explore currently available pyrethrins and pyrethroids and discuss their toxicity and potential hazards regarding human health.

A misconception about current pyrethrin formulations is that they are “organic” or “natural” because they are extracted from flowers. It is also a misconception that they are less toxic or dangerous than other types of pesticides because they originate from pyrethrum or chrysanthemums. This conception is false because pyrethrins are very effective at killing or disabling many species of insects. Pyrethrum-based pyrethrins can pose a serious threat to human health and to the environment if misapplied or misused. It is also a misconception that Pyrethrins, either Pyrethrin I or II or synthetic pyrethroids, rapidly disappear. Pyrethrin residuals last for weeks to months. Synergist chemicals added to pyrethrin formulations last for months to years.

Pyrethrins I and II are esters of Chrysanthemic acid and Pyrethric Acid, respectively, and are found in pyrethrum flowers (Klaassen 1996). Pyrethrin I is a chrysanthemum monocarboxylic acid pyrethrolone ester. Common pyrethrin I chemicals include Pyrethrin I, Cinerin I and Jasmolin I. Pyrethrin II is chrysanthemum dicarboxylic acid monomethyl ester pyrethrolone ester. Common Pyrethrin II chemicals include Pyrethrin II, Cinerin II and Jasmolin II.

Pyrethrum-based pyrethrins and synthetic pyrethroids are divided into two pyrethroid categories regarding their toxic effects, called the Type I "T" Syndrome and the Type II "CS" Syndrome. Both pyrethrin I and pyrethrin II are members of the Type I pyrethroid ester insecticide series of compounds exhibiting the "T" syndrome. Type I "T" pyrethroids are contact poisons that

produce restlessness, incoordination, prostration, hyperexcitement, aggressiveness, body tremors and paralysis in both insects and mammals (Klaassen 1996). Type I "T" pyrethroids do not contain an alpha cyano group (R-C=O,O-R), as do Type II "CS" pyrethroids. Type I pyrethroids include:

<u>Chemical Name</u>	<u>Typical Product or Trade Name</u>
Pyrethrin I,II	ULD BP 300, ULD BP 100, PT 565 aerosol, Total Release, CB-80
Allethrin	(synthetic Cinerin I,II, Jasmolin I,II and Pyrethrin I,II)
Bifenthrin	Talstar
Phenothrin (Sumithrin)	Anvil 10 + 10 ULV; Anvil 2 + 2 ULV
Permethrin	Premise, Dragnet
Resmethrin	Scourge, SBP-1382

Type II "CS" syndrome synthetic pyrethroids contain an alpha cyano group (RC=O,C=CN,R). These pyrethroids have a powerful capacity to disable or "knockdown" many insect species. Type II "CS" pyrethroids are used in household, veterinary and agricultural pesticides (Klaassen 1996). Type II pyrethroids have a higher insecticide activity meaning that they are more toxic to insects than type I pyrethroids. Type II "CS" pyrethroids generally have a higher toxicity to mammals and humans than Type I "T" pyrethroids (Berger-Preiss 1997). Studies have shown that Type II "CS" pyrethroids are active gastrointestinal poisons, and that they may cause damage to the central nervous system producing writhing, salivation, incoordination, dermal tingling, convulsions and seizures in insects and mammals as reported by Klaassen (19). Type II "CS" pyrethroids include:

<u>Chemical Name</u>	<u>Typical Product or Trade Name</u>
Cypermethrin	Demon WP
Cyfluthrin	Tempo products (WP, Tempo 2), Total Release
Deltamethrin	Butox, K-Orthine, Delta Dust, Delta Guard, Suspend,
Fenvalerate	Pydrin, Sumicidin, Tirade
Fipronil	Termidor

Pyrethroid I "TS" syndrome formulations exhibit both central and peripheral nervous system toxicity in mammals, whereas Type II "CS" formulations primarily act on the central nervous system. Toxicity from the pyrethrum-based pyrethrin I and II is due more to their allergenic properties

than to direct neurotoxicity. Pyrethrum-based pyrethrins have been shown to exhibit significant contact dermatitis and asthma-like attacks, including anaphylactic reactions leading to peripheral vascular collapse.

Pyrethrum pyrethrins and synthetic pyrethroids are stable for a limited time period because they are subject to photochemical degradation. To counteract this photochemical degradation chemical additives, called synergists, are added to increase the potency and enhance the mode of action of pyrethroids. The addition of synergists causes the formulations to be more toxic to insects and potentially to mammals and humans as well as reported by Berger-Preiss (3). Piperonyl butoxide (PBO) and MGK-264 are two synergists commonly added to pyrethroids formulations. PBO tends to have a long residual effect due to its oil-like solubility. PBO has been found on surfaces months to years after application (R. K. Simon (36). Recent research on pyrethroids has found that they have a mode of action similar to chlorinated pesticides such as cyclodienes (chlordane, aldrin, etc). Cyclodiene pesticides were banned in the United States in the 1980s due to their dangerous impact on human health and the environment.

How dangerous are pyrethroids? What is their toxicity? The chart below illustrates typical comparative LD₅₀ values for commonly used Pyrethrins in rats. An LD₅₀ value expresses the quantity (milligrams of pesticide per kilogram of test subject body weight) of the chemical that was fatal to 50 out of 100 test subjects.

Toxicity of Pyrethrins and Pyrethroids

*Rat LD₅₀ (mg/kg)

Type I "T" and "CS" Pyrethroid Compound	Oral	IV
Pyrethrin I,II	900	
Allethrin	680	
Tetramethrin	4640	
Resmethrin	100	7
Phenothrin	10,000	>300
Permethrin	2000	>135
Cypermethrin	500	6-9
Fenvalerate	450	20
Deltamethrin	31	2

*IV- *intra venous*

In viewing the chart it is important to note that the toxicity of pyrethrin and pyrethroid compounds varies greatly. Some compounds, such as d-phenothrin, have a much higher LD₅₀ level than other compounds, such as

deltamethrin and resmethrin, which have a markedly higher toxicity. Pyrethrins I/II are more toxic to the rat than d-phenothrin (Sumithrin) and permethrin, commonly used for interior pest and termite control.

Currently there have been more studies of the effects of acute exposure to pyrethrins in humans than studies of chronic, long term exposure to pyrethrins Berger-Preiss 1997 (3). A recent study of acute exposure indicates that humans experienced damage to the central and peripheral nervous systems resulting in headaches, fatigue, lack of concentration, muscle spasms, and impaired vision, hearing and taste Chen et. al., 1991 (7). This study found that persons with acute exposure to pyrethrins experienced abnormalities of the skin and mucous membranes, gastrointestinal tract, respiratory tract, heart and circulatory system and other health effects such as weight loss, fatigue and swollen lymph nodes (Chen et.al., 1991).

Pyrethrins and pyrethroid formulations have been made potentially more toxic and have increased life-spans (longer degradation times) since the development of synthetic pyrethroids and the addition of synergists to pyrethroid formulations. Piperonyl butoxide and MGK-264 are specific synergists that increase the toxicity of pyrethroid ingredients by decreasing the rate of the metabolism of pyrethroids and by adhering to surface residues due to oil type solubility.

Acute exposure to pyrethroid formulations has been demonstrated to cause a range of potentially hazardous health effects in humans. The long term effects of chronic exposure are still being researched. Pyrethroids should be used according to label instructions, manufacturers guidelines and extreme care to avoid human exposure since misapplication, and/or mishandling, could lead to exposure and adverse toxic reactions. Use of pyrethroids in fogging machines or in total release foggers (aerosol cans) can produce very dangerous levels of pyrethrins and PBO. Aerosol cans should never be used in tandem or in excess. Aerosol cans should never be used in a bedroom while persons are sleeping. Fogging machines should never be set up in rooms and left running while other pesticides are applied since this leads to misapplication and overapplication, particularly to the build-up of high residual levels on surfaces, furniture, draperies, carpets, clothing and other furnishings.

It is also a misconception that pyrethrins or synthetic pyrethroids, rapidly disappear. This is especially true when products have been stabilized with piperonyl butoxide (PBO) or MGK 264 or similar synergists. Pyrethrin residuals may last for weeks to months when the synergist chemicals have been added to pyrethroid formulations. Synergists such as PBO have been found in buildings for months to years after use (36). Since PBO is an oil, it sticks to surfaces and is

difficult to remove from porous surfaces (wood products like desks, etc.), paper, office products, curtains, carpets, clothing, upholstered furniture, etc.

Review of the Toxicity of Pyrethrins and Pyrethroids.

Chen et. al., (7) conducted an epidemiological study on cotton farmers by studying the acute exposure of farmers who used pyrethroids for crops. The farmers were found to experience damage to their central and peripheral nervous systems resulting in headaches, fatigue, lack of concentration, muscle spasms, and impaired vision, hearing and taste. This study found that persons with acute exposure to pyrethroids experienced abnormalities of the skin and mucous membranes, gastrointestinal tract, respiratory tract, heart and circulatory system and other health effects such as weight loss, fatigue and swollen lymph nodes. Chen et al concluded that for their study participants the main route of exposure to pyrethroids was dermal (skin) contamination ((7), pg 80) with diagnosis based upon abnormal facial sensations and nervous system effects of dizziness, headache, fatigue, nausea and loss of appetite, listlessness and muscular fasciculation.

Abou Donia et al (1) studied Persian Gulf War veterans for many years since it was first recognized that many troops suffered illnesses since returning home from that conflict. Symptoms such as muscle and joint pain, ataxia, chronic fatigue, headache, difficulty with concentration and other symptoms were frequently reported. Abou Donia et al. studied combinations of pyridostigmine bromide, DEET (common mosquito repellent) and permethrin (a Type I synthetic pyrethroid similar to pyrethrins) in rats. Pyrethrins and other pyrethroids are known not to be inhibitors of brain acetylcholinesterase enzyme (AChE), as are organophosphates, where AChE is an essential chemical in the brain and human body that is required for neurological well being and control of neurological systems (central nervous system). The study by Abou Donia et al found that permethrin (pyrethroid) alone caused a significant increase in cortical and cerebral AChE activity or stimulation of the AChE system. The authors found that permethrin alone lead to neurobehavioral deficits and region-specific alternations of AChE and acetylcholine receptors (see pg 312 at PG 3-4). In this study it was noted by Abou Donia that permethrin had been used in the Persian Gulf War by direct application to the soldiers clothing to control sand fleas. The authors further concluded ((1) see pg 313 at PG 1) that permethrin alone or in combination lead to sensorimotor deficits and alteration in the cholinergic system in rats. The authors suggested that this action may play a role in the development of long-term health consequences from pyrethroid exposure.

Berger Preiss (3) et al., conducted a study in a model house to determine the behavior of pyrethroids in homes. The study was developed due to the large

number of home residents who had reported toxic health symptoms after exposure to pyrethroids. Study chemicals included pyrethrum (the precursor or source of Pyrethrins I, II), piperonyl butoxide and other alpha cyano pyrethroids. The authors developed criteria for normal (treated), overdosed (misapplied) and decontaminated homes following application of known amounts of the pesticides. The authors reported in their study the complaints of German citizens in homes treated with pyrethroid formulations. 33.4% ((3) see pg 249, bottom right) reported CNS (central) and PNS (peripheral) nervous system complaints including headaches, dizziness, tiredness, lack of concentration, uneasiness, paraesthesia, muscle fasciculation (spasms), impaired vision, defective hearing and impairment of the sense of taste. Pyrethrin and PBO air levels decreased, after initial application over a one year period with significant increases in air found when the HVAC was operating and the heat was on. The more the area was overdosed (misapplication) the higher the airborne levels. The authors found that it was difficult to reduce levels of pyrethrins and PBO attached to suspended airborne particulates even when decontamination was performed. Aerodynamic diameters of suspended particles ((3) see pg 258, figure 13) peaked in the particle size of 0.25 microns, a particle size that can lead to deep lung penetration and absorption. They found that pyrethrins and PBO were very persistent ((3) see pg 260, PG 4-5) when used indoors ((3) see page 259, PG 3) with up to 10% of the residues still found two years after application. This study illustrated the important fact that applications of pyrethroids and PBO chemicals would not be expected to disappear rapidly as claimed by some pesticide reviewers.

The health effects discussed by Abou Donia (1), Berger-Preiss (2) and others was further studied for mechanisms of action by Blaylock, et al. (5) in mice. Immune system responses were studied in mice at levels that caused no overt toxicity. The authors investigated reports of decreased humoral responses and altered cellular responses induced by the Type II pyrethroids. The authors extended the immune system studies to Type I pyrethroids using permethrin as the Type I chemical. The authors concluded that ((5) see pg 770, Results and Discussion) the immune system “appears to be a sensitive target for permethrin activity”. The study found the ability of T-cells (lymphocytes) to recognize and respond to foreign antigens was affected by a significant reduction in cytotoxic activity versus controls. Natural Killer cell (NK) activity was reduced. Cox (8) reviewed PBO toxicity findings that indicated that PBO caused atrophy of testes in male rats, a decrease in home recognition behavior in offspring of PBO exposed mothers, and reduced immune response in human lymphocytes ((8) see pg 17, Figure 7). The atrophy of testes occurred at all three doses of PBO. PBO was also found to cause nausea, diarrhea and labored breathing. Thyroid glands

were larger in PBO treated rats and adrenal glands were larger in PBO female treated rats with pituitary glands in male rats being smaller in PBO treated rats. The USEPA (1995) classified PBO as a possible human carcinogen based upon liver tumors and cancer found in mice in an industry task force group study.

Catinot et al., (6) studied the mechanism of pyrethroid toxicity by studying the binding of pyrethroids to rat liver homogenates and microsomes. They studied the covalent binding of pyrethrins to endogenous macromolecules (proteins) because this binding was significant in toxicity mechanisms. The pulmonary, liver (hepatic), nephrotoxic (kidney) and carcinogenic effects have been correlated with this covalent binding to proteins. They found that PBO reduced the binding by mixed function oxidases and P-450 liver enzymes to nearly zero with PBO mimicking the effects of carbon monoxide.

A significant case study on a “probable” anaphylactoid reaction to a pyrethrin shampoo was reported by Culver (9) et al., This case study documented the exposure of a 43 year old female who used head lice A-200 Pyrinate (pyrethroid) Liquid shampoo on herself for head lice. She experienced eye puffiness one hour after use and a burning sensation. She was admitted to an emergency room where she was intubated, revived from unconsciousness and admitted with a diagnosis of asthmas and an anaphylactoid reaction. The patient self reported that she was sensitive and had allergies to molds, ragweed, tree pollen and other chemicals. The authors pointed out the need for immune system testing in exposures to pyrethroids and PBO. These authors also reported on a study by Newton and Breslin (28) in which seven patients with a history of asthmas were exposed to products containing 0.3% pyrethrins and 1.5% PBO. All seven patients reported “asthmas-like” chest tightness. Asthmas-like, allergenic properties, pneumonitis, fatigue, chest pain, coughing, shortness of breath, interstitial lung patterns, etc. have reported extensively in the literature as adverse health effects of exposure to pyrethrins.

Exttoxnet (10,11), the USEPA university based system for reporting on pesticide toxicity, reports that inhaling pyrethrum (pyrethrins) can cause asthmatic breathing, sneezing, nasal stuffiness, headache, nausea, incoordination, tremors, convulsions, facial flushing and swelling, burning and itching sensations. Exttoxnet discusses the absorption through the lungs and skin irritation including itching, pricking sensations and local burning sensations.

Exttoxnet (10,11), Casarett & Doull (19) and others discuss the mechanism of action of pyrethroids on the nervous system. Nerve cell membranes work by altering the amount of ions passing through the ion channels causing the membrane to depolarize and release neurotransmitters. Pyrethroids delay the closing of ion channels causing action potentials that are delayed. The synergists (PBO, MGK 264) restrict action of enzymes (liver esterases) that detoxify the

pyrethroids. Binding of PBO to cytochrome P450 enzymes is the proposed mechanism by which this toxicity occurs. Hillebrand (16) et al reported on the toxicity mechanism of the Type I pyrethroids showing that mammalian calcium channels are altered by these chemicals and that blockage of different types of calcium channels underlies some of the chronic effects of low-level pyrethroid poisoning. Mechanisms of action studied by Kakko (18) et al found that exposure to pyrethroids and PBO, maximizing at a 1:4 ratio, caused decreases in ATPase activity in a dose-dependent manner. The study confirmed that changes in the neuronal sodium homeostasis is one of the mechanisms of neurotoxicity in humans due to pyrethroid exposure. Casarett and Doull (19), Chapter 22, Figure 22-20 provide a cellular mechanism showing disturbances of GABA and Ca-Mg-ATPases leading to increased intracellular calcium levels that accompany increased neurotransmitter releases and postsynaptic depolarization at nerve endings. This mechanism of action was supported by the work of Joy (17). Mueller-Mohnssen (24-26) reported on a 5 Step process of acute pyrethroid intoxication starting with instant reaction (hours), sub acute intoxication (weeks), plateau effects (2-4 weeks) and chronic intoxication (long term effects). Mueller-Mohnssen opined that inhalation and dermal absorption were important mechanisms of exposure. A summary of pyrethroids by Moretto and Lotti (23) supported the health effects of Type I "T" pyrethroids and the mechanisms of action reviewed by Casarett and Doull (19) and others.

Studies by Mueller-Mohnssen (24-26) support mechanisms of action that include CNS, PNS and autonomic neurological mechanisms of action with immunological disturbances. Immunosuppression with consecutive opportunistic infections (candida albicans-like or similar) were found. Residual effects for two or more years after exposure included reduced intellectual performance, lowered work endurance, reduction of mental work endurance and personality disorder, visual disturbances, tinnitus, sensomotor-polyneuropathy, particularly in the lower legs, nervous disorders and decreased humoral and cellular immune disorders. Mueller-Mohnssen found that immune system performance decline could lead to pulmonary disorders and obstruction with some of his patients showing development of autoimmune diseases (attack of the immune system on itself). The mechanisms of action studied and reported by Mueller-Mohnssen elucidated a biological mechanisms that explained how and why the reports of acute and chronic health effects such as chronic allergies, lung allergies and skin allergies can be explained.

Animal studies in mice by Prater (30) using the Type I pyrethroid, permethrin, showed dose-related decreases in thymic cellularity, apoptosis (programmed cell death) in CD4 and CD8 thymocytes with severe decreases in

thymocyte subpopulations. These changes suggested chemically induced apoptotic mechanisms for the thymic atrophy.

Prasada Rao (31) found that pyrethroids inhibited brain and liver Mg-ATPases and suggested this as the mechanism of pyrethroid toxicity (similar to Casarett and Doull (19). Ray (33) and Reigart (34) (USEPA "Recognition and Management of Pesticide Poisonings") reviewed and confirmed the toxic manifestations of exposure to pyrethroids. Valentine (38) confirmed that sodium channels in the nervous system were the major sites of pyrethroid action with the predominate effect being modulation of the gating kinetics of the sodium channel leading to repetitive discharges (Type I) and membrane depolarization (Type II) toxicities. Sunderlund (39) et al., summarized and reviewed the mechanisms of action from the perspective of excitatory neurotoxicity. He confirmed the prior reports of voltage-sensitive sodium channels toxicity and pointed out that different pyrethroids can vary in how this response occurs. He also pointed out that the toxicity of a pyrethroid formulation is not simply additive (addition of the individual component toxicities), but synergistic. This is important in considering the risks of exposure to homeowners since most Total Release Foggers or aerosol cans used by homeowners contain one or more pyrethroid and frequently PBO and/or MGK 264 synergists. Commercial pest control operators frequently use more than one pyrethroid pesticide when applications are made inside of homes and other buildings. The potential for synergistic, dangerous toxic reactions is great in these cases.

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