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ChemicalWatch Factsheet

Synthetic Pyrethroids

Pesticide products containing synthetic pyrethroids are neurotoxic chemicals that can have long-term adverse effects, contribute to behavioral issues, cause disruption of the endocrine system (the body's message system), and cause respiratory distress. Despite all this, these chemicals are often described by the industry groups that produce or use them as "safe as chrysanthemum flowers." Synthetic pyrethroids are chemically designed to have higher toxicity than natural chrysanthemum extracts like pyrethrum and pyrethrin. They also have longer breakdown times and are frequently formulated with synergists, further increasing potency and compromising the human body's ability to detoxify the pesticide. As the use of organophosphate insecticides has declined, particularly in residential settings, the use of synthetic pyrethroids has significantly increased.

What are Synthetic Pyrethroids? Synthetic pyrethroids are synthesized analogues of naturally occurring pyrethrum, the oleo resin extract of dried chrysanthemum flowers. Roughly 50% of pyrethrum extract contains pyrethrins, ketoalcoholic esters of chrysanthemic and pyrethroic acids that have insecticidal properties. Pyrethrins are strongly lipophilic and able to rapidly penetrate many insects and paralyze their nervous system (Reigart and Roberts, 2013). Pyrethrum is the total extract from the flowers, while pyrethrins are a mixture of six structurally related esters formed by a combination of two acids (chrysanthemic acid and pyrethric acid) and three alcohols (pyrethrolone, cinerolone, and jasmolone). While toxicologically similar to synthetic pyrethroids, pyrethrins are extremely sensitive to light, heat and moisture. As a result, they have very short breakdown times. In direct sunlight, half-lives can be measured in hours (NPIC, 2014). Synthetic pyrethroids, however, were developed to capture the insecticidal activity of natural pyrethrins and increase their stability under light. This results in longer breakdown times and increased risk of nontarget exposure.

Natural pyrethrum and pyrethrins are approved for use in organic production. Both pyrethins and synthetic pyrethroids are registered by the U.S. Environmental Protection Agency as pesticides to manage unwanted insects in homes, landscapes, and agricultural settings. The U.S. Food and Drug Administration (FDA) allows use of these compounds for head lice. Various formulations of these pesticides, such as pressurized "bug bombs," are combined with other chemicals, known as synergists, to increase potency and persistence in the environment.

ChemicalWATCH Summary Stats

CAS Registry Number: 8003-34-7

Uses: Broad-spectrum insecticide, primarily used for pest control (e.g., insect sprays/repellents, pet shampoo, flea/lice shampoo)

Toxicity Rating: Toxic

Signal Words: CAUTION, WARNING, DANGER

Health Effects: Neurotoxic, Endocrine Disruption, Carcinogenicity, Reproductive effects, Developmental/Learning Disabilities

Environmental Effects: Toxic to birds, mammals, fish, and non-target invertebrates (terrestrial and aquatic); pest resistance

Synthetic Pyrethroids and Health Effects
Synthetic pyrethroids interfere with the proper

functioning of the brain and nervous system primarily through damage to the sodium channels of nerve cells. By prolonging the sodium current, synthetic pyrethroids cause nerves to discharge repeatedly, resulting in hyperexcitability in poisoned animals (ATSDR, 2003).

Two groups of pyrethroids with distinctive poisoning symptoms include type I (first generation) and type II (second generation). The two groups are distinguishable by an alpha-cyano group in the molecular structure, as type two pyrethroids contain an alpha-cyano group, while type one pyrethroids do not. Type I pyrethroids (e.g., permethrin, cismethrin) exert neurotoxicity via interference with sodium channel function in the central nervous system. Type II pyrethroids (e.g., deltamethrin, fenvalerate, cypermethrin, bifenthrin) can adversely affect ion-channel targets such as chloride, in addition to sodium channels (Werner, 2008). Overall, type I pyrethroids are less toxic to mammals than type II pyrethroids (Rehman et al., 2014).

Synthetic pyrethroids are not easily absorbed through inhalation or by the skin, but exposure can result in irritation and sensitization, and long-term effects. Acute toxicity, calculated by the LD_{50}—the dose it takes to kill 50% of a target organism, ranges from low to high, depending on the specific formulation. Low acute toxicity is attributed to two factors: limited absorption of some pyrethroids, and rapid biodegradation by mammalian liver enzymes (ester hydrolysis and oxidation). Insects, without this liver function, exhibit greater susceptibility to the chemicals (Reigart and Roberts, 2013).

Signs and symptoms of poisoning by pyrethroids may take several forms. Acute exposure can cause dizziness, headache, and nausea that can persist for several hours. Larger exposures may result in muscle twitching, reduced energy, and changes in awareness. Skin exposure may cause sensations of numbness, itching, burning, stinging or tingling, or warmth (ATSDR, 2003). With orally ingested doses, nervous system symptoms may occur, which include excitation and convulsions leading to paralysis, accompanied by muscular fibrillation and diarrhea. Inhalation exposures can result in sneezing, nasal stuffiness, headache, nausea, incoordination, tremors, convulsions, facial flushing and swelling, and burning and itching sensations. Because of similarities to natural pyrethrum, synthetic pyrethroids may act as dermal and respiratory allergens. Exposure to pyrethroids has resulted in contact dermatitis and asthma-like reactions, including both allergic and nonallergic wheeze (Hoppin, 2017). Persons, especially children, with a history of allergies or asthma, are particularly sensitive, and a strong cross-reactivity with ragweed pollen has been recognized. While severe anaphylactic (allergic) reactions with peripheral vascular collapse and respiratory difficulty are rare, when occurring, such exposure can result in death due to respiratory failure (Rehman et al., 2014). Studies suggest pyrethroid metabolites may negatively affect the endocrine system, as well as cause oxidative stress and potential immunotoxicity through cellular effects (Greene et al., 2021).

Children's Health and Synthetic Pyrethroids

Children are more susceptible than adults to pesticide exposure, and the synthetic pyrethroids are a stark example of this scientific fact—given children's small body size relative to exposure and the vulnerability of their developing organ systems. This is particularly troubling in light of

published data finding children are increasingly exposed to synthetic pyrethroids as restrictions around the home use of organophosphate insecticides have been adopted (Trunnelle et al., 2014).

Links to developmental problems are most notable in the scientific literature. Living near a field where pyrethroids were applied during a woman's third trimester corresponded with an 87% increased risk of having a child with autism (Shelton et al. 2014). Children whose mothers were highly exposed to synthetic pyrethroids during pregnancy are three times more likely to have mental delay compared to children whose mothers experienced lower levels of exposure (Horton et al., 2011). Exposure during pregnancy, and high levels of the pyrethroid metabolite cis-DCCA is associated with internalizing disorders in children up to six years old, while high levels of a different synthetic pyrethroid metabolite, 3-PBA, is associated with externalizing disorders, such as behavioral and impulse-control issues (Viel et al., 2017). Pregnancy exposures and higher concentrations of pyrethroid breakdown products in maternal urine samples correspond with a 98% increase in the odds of their children having ADHD scores in the 90th percentile at ages 2-4, a strong predictor for an ADHD diagnosis (Dalsager et al., 2019). Similar findings have been documented for older children, aged 6-11. For every tenfold increase in urinary levels of pyrethroid metabolites, children are twice as likely to score high on parent-reported behavioral problems, such as inattention and hyperactivity (Oulhote and Bouchard, 2013).

Despite these concerning data on the risks posed by high levels of synthetic pyrethroid exposure to pregnant mothers and young children, EPA in 2019 lowered the protective safety factor for synthetic pyrethroids from 3x to 1x for children under six years of age (EPA, 2019). As a result, allowed label application rates of synthetic pyrethroid products are tripled, placing children at greater risk.

Endocrine Disruption and Chronic Disease

Many synthetic pyrethroids have been found to act as endocrine disruptors, by either blocking, mimicking, or synergizing hormones through direct receptor interactions, or indirectly through upstream signaling pathways. There is evidence that pyrethroid metabolites have more endocrine disrupting activity than their parent compounds, dependent on the optical isomer present (Brander et al. 2016). Research has demonstrated that the estrogenic effects of certain pyrethroids increase the levels of estrogen in breast cancer cells (Go et al., 1999). Because increased cell division enhances the chances for the formation of a malignant tumor in the breast, artificial hormones, like those found in pyrethroids, may increase breast cancer risk (PCBR, 1996). Moreover, pyrethroid insecticides exhibit the highest affinities for multiple breast cancer proteins (Montes-Grajales, 2020).

There is evidence that ambient pesticide exposure to those living or working near agricultural pyrethroid pesticide applications can induce chronic neurological issues, like Alzheimer's disease, and psychological disorders, in addition to disruption of the central nervous system that induces various cancers (Furlong et al., 2020). Environmental exposures to pyrethroids

insecticides are associated with an increased risk of mortality from all causes and specific causes, including cardiovascular disease and cancer (Bao et al., 2020). Some pyrethroids are classified as human carcinogens by EPA.

Pyrethroids and the Environment

While the development of synthetic pyrethroids was heralded with claims of selective toxicity to insects, both pyrethroids and pyrethrins are extremely toxic to aquatic organisms, including fish such as the bluegill and lake trout, with LC_{50} (lethal air concentration for 50% of the test population) values less than 1.0 parts per billion. These levels are similar to those for mosquito, blackfly, and tsetse fly larvae, often the actual targets of a pyrethroid application. Lobster, shrimp, mayfly nymphs and zooplankton are the most susceptible nontarget aquatic organisms (Antwi and Reddy, 2015; Mueller-Beilschmidt, 1990).

The nonlethal effects of pyrethroids on fish include damage to the gills and behavioral changes. Since aquatic organisms lack enzymes that can hydrolyze (breakdown) pyrethroids, oxidative stress is the primary mechanism of toxicity among fish and aquatic organisms. Many pyrethroids induce reactive oxygen species (ROS) production in the gills, liver, and muscle of fish, which leads to histological changes, such as lipid peroxidation and alterations in the expression and activity of antioxidant enzymes (Ullah et al, 2019; Yang et al., 2020).

Pyrethroids are moderately toxic to birds, with most LD_{50} values greater than 1000 mg/ kg. Birds can also be indirectly affected by pyrethroids, because of the threat to their food supply. Waterfowl and small insectivorous birds are the most susceptible (Basak et al., 2021). Moreover, wild birds can encounter pyrethroids mainly in urban areas, increasing the number of unhatched eggs (Corcellas, 2017).

Both beneficial insects and “pests” are affected by pyrethroid applications. Many wild bees who forage on flowers in pyrethroid treated areas have seen reductions in colony size, and other beneficial insects (e.g., beetles, grubs, worms) encountering pyrethroid residues in soil have a high mortality rate (Larson, 2014). In some cases, predator insects may be susceptible to a lower dose than the target insect, disrupting the predator-prey relationship.

Synthetic pyrethroid use can induce trophic cascades in aquatic ecosystems. By killing off larval aquatic macroinvertebrates, like mayflies, stoneflies, and caddisflies who eat periphyton (attached algae), their use can result in algae blooms. The endocrine-disrupting properties of many synthetic pyrethroids can also cause aquatic organisms to speed up their metamorphosis, emerging smaller and earlier than usual, resulting in less food for amphibians, reptiles, and birds who rely on these insects as a food source (Rodgers et al. 2016).

Pyrethroids Residues / Persistence

Synthetic pyrethroids are designed to break down more slowly than naturally-occurring pyrethrins. While pyrethrins, extremely sensitive to light, heat, and moisture, break down in a

few hours, synthetic pyrethroids are stable and persist in the environment much longer. Generally, synthetic pyrethroids will break down faster in direct sunlight. However, in areas with limited sunlight or other disturbances, pyrethroids can last much longer. After an initial single application, some synthetic pyrethroids have been shown to persist in homes for over a year (Nakagawa et al., 2017). Metabolites of pyrethroids mainly consist of 3-phenoxybenzoic acid (3-PBA), 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA), *cis*-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxylic acid (TFA), and 2-phenoxybenzoic acid (2-PBA) (Chen et al., 2021). Although 3-PBA is frequently present in the human body, the metabolit is also found in waterways (i.e.., rivers, streams, and ground and surface water), along with d 3-(2,2-dichlorovinyl)-2,2-dimethylycycl opropanecarboxylic acid [DCCA] (Tang et al., 2018). Pyrethroids and their metabolites in these waterways can absorb into sediment, increasing the half-life in soil compared to water mediums. Additionally, environmental degradation of pyrethroids can produce metabolites that may have biologic significance as these chemicals have the ability to interact with steroid hormone receptors, indicating endocrine problems (Tyler et al., 2000).

Pyrethroids Resistance

Continuous use of pyrethroid insecticides has led to certain target insects developing resistance to the chemical from repeated exposure. Target insects frequently exposed to pyrethroids can develop resistance through target site gene mutations and insecticide detoxification via enzymes (Harris, 2010). These insects can be disease vectors, which, lacking an effective management strategy, expose people and animals to transmissible diseases like malaria (Churcher, 2016).

Synergists

Both pyrethroids and pyrethrins are often formulated with oils or petroleum distillates and packaged in combination with synergists, such as piperonyl butoxide (PBO) and n-octyl bicycloheptene dicarboximide. Synergists are added to increase the potency of the pesticide. A range of products from repellents to foggers, pediculicides (lice killers), and garden sprays contain these synergists. Many formulations of the synthetic pyrethroids permethrin, resmethrin, and sumithrin (including formulations of Kontrol and Anvil), used in mosquito adulticide spray campaigns, contain the synergist PBO.

PBO functions as a synergist by slowing the breakdown of toxic chemicals in insects. The first step in the breakdown of many types of chemicals in insects is oxidization by a group of microsomal enzymes called P450 mono-oxygenases, located in the liver. PBO inhibits the activity of these enzymes, and thus prevents the metabolism of many types of molecules, including insecticides. This keeps the pesticide in its toxic form for longer periods of time, increasing the amount of damage it can do to the insect. A heavy dose of PBO makes an organism temporarily vulnerable to a variety of toxic chemicals that would be easily tolerated otherwise (EPA, 2005; Scott et al., 2000). Symptoms of PBO poisoning include anorexia, vomiting, diarrhea, intestinal inflammation, pulmonary hemorrhage, and mild central nervous system depression. Repeated contact may cause slight skin irritation (Breathnach, 1999).

Chronic toxicity studies have shown increased liver and kidney weights, even at the lowest

doses, 30 mg/kg/day, in addition to centrilobular degeneration in the liver. Moreover, chronic exposure induces changes in red blood cells, white blood cells, and hemoglobin levels, as well as, biochemical changes related to liver, kidney functions, and protein metabolism (Yavuz et al., 2015). PBO disrupts a biological signaling system that is critical for brain development. The disruption of this pathway, according to scientific research, may be the reason that such profound developmental effects are seen in children exposed to end use products containing PBO and synthetic pyrethroids (Wang et al., 2012). EPA considers the synergist to be a possible human carcinogen (EPA, 2005).

SPECIFIC SYNTHETIC PYRETHROIDS

Bifenthrin (Talstar™, Brigade™, Capture™)

EPA registers bifenthrin for residential and commercial use, with the chemical being the most used for outdoor residential areas in 2016. Bifenthrin is used to control insect pests like ants, cockroaches, termites, flies, mosquitos, and ticks, both indoor and outdoor, as well as uses in pet products as an insect repellent (U.S. EPA, 2020). In addition, EPA has registered bifenthrin for use on greenhouse ornamentals and cotton.

Studies show bifenthrin to be relatively insoluble in water, putting aquatic life at greater risk (Sardiña et al., 2019). Its half-life in soil can range anywhere from seven days to eight months, depending on the soil type and the amount of air in the soil (ETN, Bifenthrin, 1995; Mukherjee et al., 2020). Moreover, bifenthrin persistence in water is dependent upon pH level, as a higher pH has an association with the lowest persistence (Meena et al., 2021). Bifenthrin is one of a few synthetic pyrethroids that are relatively stable in direct sunlight (U.S. EPA, 2010). EPA has classified products containing bifenthrin as acute toxicity category II (I = most toxic, IV = least toxic), and the word WARNING must appear on all product labels.

Bifenthrin is moderately toxic to mammals when ingested (oral rat LD_{50}=54 to 70 mg/kg), and like all pyrethroids affects the central nervous system. Symptoms of poisoning include incoordination, tremor, salivation, vomiting, diarrhea, and irritability to sound and touch (ETN Bifenthrin, 1995; Buchweitz et al., 2019). Although bifenthrin does not cause inflammation or irritation on human skin, it can cause a tingling sensation, lasting about 12 hours. A study on laboratory mice shows that bifenthrin causes gene mutation in white blood cells. The chemical is also genotoxic and causes chromosomal somatic mutations among human peripheral blood cells through oxidative stress (ETN, Bifenthrin, 1995; Kizilet and Uysal, 2022). EPA classifies bifenthrin as a Class C (possible human) carcinogen (EPA, 1997; EPA, 2021). Of concern in the environment, bifenthrin is very highly toxic to fish, crustaceans, other aquatic animals and bees, and is moderately toxic to birds. Scientists are particularly concerned about possible bioaccumulation in fish, as bifenthrin binds well to organic material and has the potential to accumulate in fish and animal tissue (Assessment, 2012). Although bifenthrin can negatively affect wildlife in an acute manner, the sublethal toxicity of the chemical and its metabolites remain a concern as exposure can induce chronic health risks, including developmental delays, endocrine disruption, and immunotoxicity among wildlife (Yang, 2018). Moreover, research

finds growing resistance to bifenthrin among various pest populations in as little as two years, with some specific effects on enzyme inhibition (Herron et el., 2001; Julio et al., 2017).

Cypermethrin (Ammo™, Cymbush™, Demon™)

Cypermethrin is one of a handful of light-stable synthetic pyrethroids (Raj et al., 2014). The chemical is registered to control cockroaches, fleas and other indoor pests in homes, restaurants, hospitals, schools, and food processing plants, and also in agriculture to control pests on cotton, fruits, and vegetables. Approximately 300,000 pounds of active ingredient are used to treat 6.2 million acres of cropland annually. Soybeans, cotton, corn, oranges, and alfalfa account for about 70 percent of the usage in total pounds applied and 75% in total acres treated. Food handling establishments use approximately 3,000 lbs of cypermethrin, in 2013, and professional pest management companies use over approximately 300,000 lbs of cypermethrin for control of various nuisance and public health pests both in and around residential and commercial building (U.S. EPA, 2021). Compared to other pyrethroids, cypermethrin is relatively stable, with a half-life of 8-16 days in direct sunlight, breaking down quickly in ultraviolet (UV) light. In soil and water, studies have shown the half-life between four and eight weeks (Whangchai et al., 2021). Cypermethrin has considerable persistence in the home (e.g., up to or over three months), increasing the risk of exposure to these products. (Wright et al., 1993, Nakagawa et al., 2017).

EPA classifies cypermethrin as a class C (possible human) carcinogen (EPA, 1997; Whangchai et al., 2021). Studies in laboratory animals have shown exposure to cypermethrin to cause reproductive effects, including abnormal sperm and disruption of sex hormones (Cox, 1996; Li et al., 2013).

Cypermethrin is moderately toxic (oral male rat LD_{50}= 87 to 326 mg/kg, dermal rat LD_{50}=1600 mg/kg) and like all pyrethroids, affects the central nervous system, especially dopaminergic neurodegeneration (ETN, Cypermethrin, 1996; Kumar et al., 2012). It is an acute toxicity category II pyrethroid known to adversely affect exposed organisms (Farag, 2021). Depending on the specific product formulation, EPA classifies pesticides containing cypermethrin as toxicity category II or III (I=most toxic, IV=least toxic) and must display the word WARNING or CAUTION on the labels. Symptoms of cypermethrin poisoning in humans include numbness, burning, loss of bladder control, vomiting, incoordination, seizures, coma, and death (Whangchai et al., 2021). In California, cypermethrin is the fourth most common cause of pesticide-related illness in pest control operators.

Cypermethrin should not be applied near water because it is very toxic to fish and other aquatic organisms, particularly aquatic invertebrates such as insects and crustaceans.

Deltamethrin (Butoflin™, Butoss™, Crackdown™)

First registered in 1994, deltamethrin is a type II (neurotoxicity through ion-channels) pyrethroid insecticide that kills insects on contact and through ingestion. It works by paralyzing the insect's nervous system, therefore giving a quick knock-down effect. It is used commonly to control caterpillars on apples, pears, and hops, and for the control of aphids, mealy bugs, scale

insects, and whiteflies on glasshouse cucumbers, tomatoes, peppers, potted plants, and ornamentals (ETN, Deltamethrin, 1995). It is also registered for use on livestock and for public health uses.

Deltamethrin's half-life can last anywhere between 5.7- 209 days and changes based on soil chemistry, temperature, water content and the amount of organic matter in the soil. On plant surfaces deltamethrin has a half-life of 5.9-17 days, putting bees and other pollinators at risk (Johnson et al., 2010). Deltamethrin is persistent in the environment, binding tightly to soil particles. Most deltamethrin products persist from one to two weeks in the environment, with shorter times in direct sunlight (ETN, Deltamethrin, 1995; Mukherjee et al., 2020). Depending on the product formulation, deltamethrin pesticides may range in toxicity from EPA toxicity category I to category III, bearing the words DANGER-POISON, WARNING or CAUTION on the label (PANNA, 2000). Deltamethrin products may be classified as General Use or Restricted Use (only for certified applicator use).

Deltamethrin produces different signs of poisoning than other pyrethroids. When exposed to deltamethrin, mammals exhibit typical type II motor symptoms, which include a writhing syndrome in rodents, as well as copious salivation. The acute oral LD_{50} in male rats has been reported as low as 128 mg/kg to greater than 5,000 mg/kg depending on the carrier and conditions of the study (ETN, Deltamethrin, 1995; Manna, 2006). In rodents, liver and bone marrow damage occur via oxidative stress from exposure (Nieradko-Iwanicka, 2015). Some studies have shown deltamethrin to cause skin irritation as type II pyrethroids cause paresthesia, which is characterized by transient burning, tingling, itching sensation of the exposed skin (Rehman et al., 2014). Especially characteristic of deltamethrin poisoning are rolling convulsions. The sequence of the signs of poisoning is clearly defined, progressing from chewing, salivation, and pawing to rolling convulsions, tonic seizures, and death (ETN, Deltamethrin, 1995; Rehman et al., 2014).

In humans, symptoms of poisoning include ataxia, convulsions leading to muscle fibrillation and paralysis, dermatitis, edema, diarrhea, dyspnea, headache, hepatic microsomal enzyme induction, irritability, peripheral vascular collapse, rhinorrhea, serum alkaline phosphatase elevation, tremors, vomiting and death due to respiratory failure (Rehman et al., 2014). Deltamethrin is a suspected endocrine disruptor and has neurotoxic properties that impact the central nervous system (Pitzer et al., 2021).

Deltamethrin does not readily dissolve in water, so the chemical is toxic to fish, aquatic organisms, and amphibians.

Fenvalerate (Esfenvalerate, Sumifly™, Sumiflower™)

Fenvalerate is registered for use on a wide array of crops including cotton, soybeans, corn, vegetables, apples, peaches, pears, and nuts, as well as a termiticide and insect repellent. During the late 1980's, fenvalerate received national press coverage due to over 200 dog and cat poisonings, including 26 deaths, following the use of Blockade™, a product containing

fenvalerate in combination with DEET, a common insect repellent (Parmar et al., 2017). Fenvalerate is one of the most persistent synthetic pyrethroids in the environment—half-lives of fenvalerate ranges from 15 days to three months in soil, 21 days in water, and 2-4 weeks on vegetation. Upon chronic exposure, the chemical is suspected to cause endocrine disruption that can induce uterine fibroids through molecular mechanisms rather than binding to estrogen receptors (PANNA, 2000; Gao et al., 2010). Fenvalerate is moderately toxic with symptoms of poisoning through direct contact including, dizziness, respiratory issues (asthma-like), burning and itching (which is worsened by sweating and washing), blurred vision (a strong eye irritant), tightness in the chest, and convulsions (Reham et al., 2014). When ingested by laboratory animals, symptoms of poisoning include muscle incoordination, tremors, convulsions, nerve damage, and weight loss, while in severe cases of intentional poisoning; convulsive attacks, disturbance of consciousness, dyspnea, cyanosis, and pulmonary edema mainly occur (Reham et al., 2014).

EPA classifies fenvalerate products as category II (I = most toxic, IV = least toxic), and includes the word WARNING on all product labels. Some formulations are Restricted Use Pesticides and may only be purchased or applied by certified applicators or persons under the direct supervision of a certified applicator.

Although countries, including Sweden, have banned the chemical for use in forestry following health related complaints from workers, it remains in use in the U.S. Studies have found that immediate application of vitamin E to exposed areas can lessen the painful effects (Rehma et al., 2014). Fenvalerate is extremely toxic to bees and fish and is slightly toxic to birds and mammals, but pyrethroids produce neurotoxicity in mammals at high doses (acute toxicity), which are dangerous in mammalian tissue (Parmar et al., 2017).

Flumetherin (Flumethrin Technical, Pnr1427 Insecticide™, Bayvarol Strips™, Bayticol™, Seresto®)

Flumethrin is a synthetic pyrethroid ectoparasiticide applied topically to cattle, sheep, and other farm livestock for the control of ticks, lice and mites, and sheep keds. Additionally, strips impregnated with flumethrin are hung in beehives for the treatment of varroa in honey bees. Flumethrin has no uses on crops.

Registered in 2012, Flumethrin receives an EPA acute toxicity category rating of II (I = most toxic, IV = least toxic), and carries CAUTION or DANGER on its label, depending on the formulation. The chemical may be fatal if inhaled, swallowed, or absorbed through the skin. The chemical can cause skin and eye irritation, resulting in lesions and conjunctivitis, respectively (Campbell, 2019). Like most pyrethroids, flumethrin induces neurological problems, such as seizures and learning disabilities in children, and gastrointestinal distress. Studies find this chemical to be an endocrine disruptor that induces apoptosis and cytotoxicity at high concentrations, and estrogenic effects at low concentrations (Kara-Ertekin, 2021). According to an evaluation by the Food and Agriculture Organization (FAO), repeated oral exposure on rats and rabbit during a 1-to-26-week period resulted in a reduction in adult body weight, and developmental toxicity for both mother and offspring, while long-term effects (> one year) via

oral exposure resulted in skin lesions (FAO, 2019).

Flumethrin is extremely toxic to fish and other aquatic organisms, with long lasting effects. Bees can be exposed to the chemical through hive treatments involving flumethrin strips.

Permethrin (Pounce™, Torpedo™, Dragnet™)
Current permethrin uses include lice treatments and urban/suburban $_{pest}$ control. Permethrin resembles pyrethrins chemically, but is chlorinated to increase its stability. The chemical is a type I (neurotoxicity through sodium channels) pyrethroid with four isomeric forms, two cis and two trans of technical permethrin. Although the acute toxicity of the mixture (oral rat LD_{50} > 5000 mg/kg, oral mouse LD_{50} = 500) is less than that of natural pyrethrins, the cis-isomer is considerably more toxic (oral mouse LD_{50} = 100), and in rats the metabolites of the cis-isomer are more persistent biologically. (The cis and trans isomers differ in the spatial arrangement of the atoms.) Product formulations of permethrin can vary greatly in isomeric content (Jin et al., 2012). Compared to other pyrethroids, permethrin is very stable, even when exposed to ultraviolet light. Permethrin strongly binds to soil and other organic particles, with half-lives in soil of up to 43 days (Toynton, 2009). However, when used as a termiticide, permethrin can persist for more than 3.8 years (Nakagawa et al., 2020).

Based on studies demonstrating carcinogenicity, EPA ranked permethrin as class B—likely carcinogenic to humans—in 2007, but currently categorizes the chemical as class C— suggestive evidence of carcinogenic potential (U.S. EPA, 2007; U.S. EPA, 2021). Many studies attribute the oxidative stress from permethrin exposure to neurotoxicity, immunotoxicity, cardiotoxicity, hepatotoxicity, reproductive, genotoxic, and haematotoxic (harmful to red blood cells) effects, digestive system toxicity, and cytotoxicity in humans and animals (Wang et al., 2016). Other studies have shown effects on the immune system, enlarged livers and, at high doses, decreased female fertility, and endocrine disruption. Permethrin is extremely toxic to aquatic life, bees, and other wildlife and should not be applied in crops or weeds where foraging may occur (ETN, Permethrin, 1996; Wang et al., 2016).

Permethrin receives an EPA toxicity category rating of II or III (I = most toxic, IV = least toxic), and carries either the word WARNING or CAUTION on its label, depending on the formulation. While it is not extremely, acutely toxic to humans, there are numerous reports of paresthesia and transient skin, eye, and respiratory irritation (Javed et al., 2015). Like all pyrethroids, permethrin is a central nervous system poison. Workers and researchers report tingling in face and hands, and some report allergic reactions.

Resmethrin (Scourge™, Raid Flying Insect Killer™)
Resmethrin is used for control of flying and crawling insects in homes, greenhouses, processing plants, commercial kitchens, airplanes and for public mosquito control. In laboratory animals, chronic toxicity studies have shown hypertrophy of the liver, proliferative hyperplasia, and benign and cancerous liver tumors. EPA classifies resmethrin as class B—likely to be

carcinogenic in humans—based on laboratory studies (EPA, 2021). Additionally, EPA reviewers noted slight, but significant, increases in the number of offspring born dead and decreased viability, which they thought might be secondary to transplacental toxicity, as well as induced germ cell-specific apoptosis, indicating reproductive toxicity (Park et al.,2021). Resmethrin is a suspected endocrine disruptor (PANNA, 2000; De Guise et al., 2005). Studies find resmethrin is neurotoxic, with a case demonstrating a fatality (brain dead) in a child who ingested the chemical (Huang et al., 2021).

Resmethrin is type I pyrethroid and considered slightly, acutely toxic to humans and rated EPA toxicity category I, II, and III, bearing the words DANGER, WARNING, or CAUTION on its label (Jackson et al., 2008). The oral rat LD_{50} is about 2500 mg/kg. Although resmethrin has a very short half-life (under an hour in direct sunlight), it persists much longer in soil with a half-life of 30 days (ETN, Resmethrin, 1996; Jackson et al., 2008). Photooxidation breaks down resmethrin to several metabolites in the environment, including (+)-*trans*-chrysanthemic acid, which is more toxic to mice compared to the parent compound (Jackson et al., 2008). Resmethrin breaks down into a smelly byproduct, phenylacetic acid, which binds strongly to textiles and dissipates slowly, smelling of urine (Singh et al., 2022).

Resmethrin is absorbed rapidly and distributed to all tissues, including the brain. Although skin absorption is low, contact with the chemical acts as an allergen, with some individuals manifesting allergic-like responses, including dermatitis, asthma, runny nose, and watery eyes, after initial contact. Moreover, oral exposure (inhalation) of the chemical readily absorbs into gastrointestinal tract and into the blood stream (Javed et al., 2015).

Resmethrin is extremely toxic to fish, aquatic life, bees, and other nontarget species (Dai et al., 2010; Oberhauser et al., 2009). Because of its toxicity to fish, resmethrin was a Restricted Use Pesticide available for use only by certified pesticide applicators. However, resmethrin registrants voluntarily canceled all of the restricted resmethrin products. After December 31, 2015, resmethrin registrants could no longer sell and distribute resmethrin products. However, any products purchased before the date can still be used (EPA, 2022).

Lambda-Cyhalothrin (Dovetail™, Hallmark™, Seal Z™, Warrior™, Jackpot 2™) Registered in 1989, Lambda-cyhalothrin is a type II synthetic pyrethroid used to control termites, and has uses on pet bedding, livestock, wood treatments, vegetables, wheat and other grains, stone fruits, tree nuts, tobacco, tree plantations, and nurseries (U.S. EPA, 2016). Lambda-cyhalothrin is highly toxic and has a category II EPA toxicity rating, bearing the word WARNING or DANGER on its label. It may be fatal if swallowed or inhaled. Acute exposure to the chemical can cause skin and respiratory irritation and sensitization, dizziness, headache, nausea, tremors, convulsions, coma, and death (Waltz, 2014).

Like other pyrethroids, this chemical is neurotoxic. In epidemiologic studies, continuous exposure to lambda-cyhalothrin results in more intense neurological and behavioral changes in rats due to inhibition of dopamine uptake and release (Ansari et al., 2012). Lambda-cyhalothrin promotes genotoxicity and cytotoxicity in animal studies, as chronic exposure suppresses both

humoral and cell-meditated immune responses (suppresses immune system) in a dose-dependent manner, suggesting an alteration in immune function (Morgan and Osman, 2007; ,2012). Similar genotoxicity and cytotoxicity occur in human lymphocyte cells from DNA damage after chronic exposure. Studies on human cells reveal that lambda-cyhalothrin exposure induces oxidative stress in erythrocyte cells, a type of red blood cell (Naravaneni and Jamil, 2005; Deeba et al., 2017). Chronic exposure to lambda-cyhalothrin can also increase breast cancer risk, as exposure promotes MCF-7 human breast cancer cell (Zhao et al., 2008; Waltz, 2014). Studies suggest lambda-cyhalothrin to have endocrine disrupting properties, resulting in sex specific effects on the male reproductive system, such as impaired sperm, and impacts on hormone regulation in the thyroid that induces changes in weight (Waltz 2014).

Cyhalothrins are slightly toxic or practically nontoxic to birds upon acute exposures (U.S. EPA, 2016). Like all insecticides, this chemical is highly toxic to bees and other beneficial pollinators. However, target insect pests, like the predatory lady beetle *Eriopis connexa* and the disease (e.g., malaria) carrying mosquito *Anopheles funestus,* are developing resistance to lambda-cyhalothrin through repeated exposure (Rodrigues, 2013; Samb et al., 2016).

Due to the propensity of lambda-cyhalothrin to adsorb organic matter, including soils, plants, and tissue of organisms, the chemical is not mobile. Moreover, the stability in aquatic environments and fish allows the chemical to accumulate in these ecosystems, resulting in toxicity to aquatic invertebrates and fish (He et al., 2008; Watts, 2014).

Sumithrin (Anvil™, d-Phenothrin) Sumithrin, also known as d-Phenothrin or phenothrin, has been registered for use since 1975 to control adult mosquitoes and as an insecticide in transport vehicles, commercial, industrial, and institutional nonfood areas, homes, gardens, greenhouses, and on pets. Studies have shown that sumithrin is an endocrine disruptor, demonstrating significant estrogenicity and increases the level of estrogen in breast cancer cell, suggesting that sumithrin may increase the risk of breast cancer (Go et al., 1999; Montes-Montes-Grajales and Olivero-Verbel, 2020).

Chemically, sumithrin is an ester of chrysanthemic acid and alcohol. It is a combination of two cis and two trans isomers. The chemical is a type I pyrethroid with four isomeric forms, two cis and two trans of technical XXXX. Sumithrin degrades rapidly, with a half-life of 1-2 days under dry, sunny conditions. Under flooded conditions, the half-life increases to 2-4 weeks for the trans isomer and 1-2 months for the cis isomer (Jackson et al., 2011). In grain silos, with no sunlight and little air circulation, most of the product remains after one year (WHO, 1990; Singh et al., 2022).

Sumithrin is slightly toxic and is rated EPA acute toxicity category IV, bearing the word CAUTION on its label. However, like other pyrethroids, sumithrin is neurotoxic. The oral rat LD_{50} is greater than 5,000 mg/kg, and the LC_{50} for inhalation is greater than 1210 mg/m3. Symptoms of acute sumithrin poisoning include hyperexcitability, prostration, slow respiration, salivation, tremor, ataxia, and paralysis (Singh et al., 2022). Animals exposed to a toxic dose of sumithrin had inflammatory reaction, hemorrhage, congested blood vessels, necrosis, fibrosis and multiple granuloma lesions in internal organs and proliferation, as well as a decrease in overall body

weight (Hassan, 2017).

Sumithrin is highly toxic to aquatic organisms and nontarget species. However, insects that are resistant to one pyrethroid pesticide are frequently resistant to another, thus, lice, cockroaches, and other insect pests can develop sumithrin resistance in the absence of exposure (Singh et al., 2022).

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