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THE EFFECTS OF PYRETHRINS & PYRETHROIDS ON HUMAN PHYSIOLOGY

Joni Mitchell sang about it. Rachel Carson wrote a renowned book about it. It was banned in the U.S. in the 1970's after it was detected in mothers' milk (Rea 1996). Even if one doesn't know what an "organochlorine pesticide" is, few people are unfamiliar with the letters DDT. There has been a significant amount of attention placed on this particular pesticide in the last forty years, with research conducted on the effects it has on humans, other animals and the environment. Although pesticide research has focused a great deal on organochlorines and organophosphates, products from these classes are not the most prevalently used today. In the U.S. there are over 240 million applications annually of pyrethrins and/or pyrethroids, which is more than any other class of pesticides (Cox 2002). Approximately 440,000 pounds are used worldwide every year (Cox 2002). Despite its extremely high prevalence, little research has been conducted on pyrethrin's effects on non-targeted organisms because they are derived from chrysanthemums and thus thought to be safer. However, in 1991 the Environmental Protection Agency (EPA) summarized calls to poison control centers in the U.S. and discovered that pyrethrin exposures caused over 9000 incidents of poisoning (Blondell 1991 in Cox 2002). Since then, researchers have been looking more closely at the possibility that pyrethrins can cause harm to humans; mostly focusing on the effects they may have on the human neurological system, but also exploring possible risks to other aspects of human physiology.

In order to understand the toxicology of pyrethrins and pyrethroids, it is important to clearly define them. *Pyrethrum* is the oleoresin extract from dried Chrysanthemum cinerariaefolium and

Chrysanthemum cineum flowers (Chemical Watch Factsheet 2000). *Pyrethrins* are the six insecticidally active ingredients derived from pyrethrum (Cox 2002). *Pyrethroids* are synthetic derivatives of pyrethrins, created to increase the toxicity and persistence of the pesticide (Mueller-Beilschmidt 1990).

Pyrethrins and pyrethroids are the ingredients that are used in pesticide products, and although they are chemically and toxicologically similar, there are some structural differences between the two. The insecticidal properties of pyrethrins are derived from the ketoalcohol esters of pyrethrum's chrysanthemic and pyrethroic acids (which are highly lipophilic) (Rea 1996). There are three different alcohols; pyrethrolone, cinerolone, and jasmololone; each yielding its own active ester; pyrethrin, cinerins, and jasmolins, respectfully (Rea 1996). Although indoors the persistence of pyrethrins is significant, they are extremely sensitive to light, heat, and moisture, and when outdoors in direct sunlight their half-lives can be measured in hours (Chemical Watch Factsheet 2000). Therefore, synthetic pyrethroids were created in order to capture the effective insecticidal activity of pyrethrins, while also increasing their stability and persistence in the environment (Chemical Watch Factsheet 2000).

There are different types of pyrethroids, and the toxicity of each is highly dependant on the stereochemistry (the three-dimensional configuration of the molecule) of each isomer (Mueller-Beilschmidt 1990). Most pyrethroids have pairs of geometrically unique isomers, referred to as the *cis* and *trans* isomers (Mueller-Beilschmidt 1990). Cis isomers tend to be more toxic, as are more highly halogenated pyrethroids (those containing chlorine, bromine or fluorine) (Mueller-Beilschmidt 1990).

Pyrethrins are considered to have a low toxicity for mammals, with an LD_{50} level (the amount needed to kill half of the tested population) that varies between several hundred or several

thousand mg/kg of body weight (BW) for rats. However, the toxicity for pyrethroids may be significantly higher than that for pyrethrins (Rea 1996). Despite the toxicity of the particular derivative, pyrethrins and pyrethroids are thought to be much less harmful to mammals than to insects for two reasons. First of all, there is limited absorption in mammals, as the pesticides absorb much more slowly through skin than through insect chitin (Rea 1996). However, pyrethrins and pyrethroids *are* easily absorbed through mammalian lungs (Chemical Watch Factsheet 2000). The other reason that pyrethrins and pyrethroids are thought to be more toxic to insects than to mammals is because insects lack certain hepatic enzymes that are found in mammalian livers. These enzymes carry out rapid biodegradation of pyrethrins through ester hydrolysis (which is the breaking of the pyrethrins' ester double bonds between a carbon and an oxygen atom through esterase action and oxidation) (Rea 1996 and Mueller-Beilschmidt 1990).

However, there is also much debate about whether insects are the only targeted species of these chemicals. Bev Pagan, a geneticist with over 20 years of toxicology experience, feels very strongly that insects are *not* the only susceptible organisms; "there is no pesticide out there that only targets insects. Rather they all target and attack basic physiological processes in insects, that are also found in all other animals...including humans" (Pers. Com. 2002).

It is important to note here that although pyrethrins are well-known for having a quick "knockdown effect" (Rea 1996), sometimes the exposure isn't enough to kill the insects, and it simply leads to impairment or paralysis. For this reason, pyrethrins and pyrethroids are often combined with the synergists piperonyl butoxide or n-octyl bicycloheptene dicarboximide (unknown 2000). These synergists are known to inhibit the hepatic enzymes needed to detoxify the active ingredients in the pesticide, in order to keep the pesticide in the body longer (Chemical Watch Factsheet 2000). These are the same enzymes that set mammals and insects apart and if these

enzymes are inhibited by synergists, the toxicity of the pesticide could be just as great in mammals as in insects.

Although few pyrethrin/pyrethroid exposures lead to fatalities in humans, they can affect physiological processes and create a variety of symptoms. One of the most common symptoms of a pesticide exposure is anxiety and panic (Simpson 2000). Other symptoms include numbness and tingling, headaches, confusion, difficulty concentrating, cognitive impairment, a feeling of "unreality", dizziness, seizures and tremors, respiratory problems, fatigue, and many others (Miller 1995). This raises a major question: what is actually occurring in the body to produce such a myriad of symptoms?

It is important to understand how pyrethrins and pyrethroids kill insects in order to assess the effects they could have on other animals. Pyrethrins and pyrethroids are neurotoxins that target both the neurological enzymes and the nerves themselves. The main strategy that they use to kill insects involves disrupting the sodium current in the nerve cells, causing the nerves to rapidly fire neurotransmitters. Instead of only sending one impulse, the nerve sends a train of impulses in response to a stimulus (Cox 1998).

The sodium channels represent major players in the conduction and transportation of neural impulses. At rest, a neuron is said to be polarized because the gates that allow sodium (a positive ion) to enter are closed, and there's a high level of negative ions on the inside. When the neuron is stimulated, the first sodium channel opens, allowing sodium to enter which makes the nerve slightly more positive. This change in charge initiates the next channel to open to allow in more sodium, which makes the nerve more positive, and so on. An action potential travels the length of the axon to the synaptic end bulb. When it reaches this point, the nerve is now at a positive enough charge to "fire". Calcium channels open and calcium floods in, which releases vesicles containing

neurotransmitters into the synapse. Once the nerve has fired, the sodium gates close, the sodium is actively pumped out, and the nerve repolarizes, ready to fire again with the next new stimulus. This is the normal functioning of a neuron.

Pyrethrin and pyrethroids prolong the sodium current by "slowing or preventing the shutting of the channels" (Tvedten 2000). This causes a constant influx of sodium. Some pyrethrins delay the shutting of the channels, keeping them open long enough for the nerve to fire multiple neurotransmitters. As long as there's enough of a change in charge, the nerve will keep firing. This leads to symptoms such as convulsions, tremors, cyclical thoughts, and anxiety due to the excessive amounts of signals being released at once (Tvedten 2000). Other pyrethrins prevent the channels from closing. If too much sodium enters the nerve it will eventually become inactive, because if a nerve is *too* positive then it will be unable to repolarize and will no longer fire. This causes such symptoms as numbness, ataxia and dizziness (Tvedten 2000).

It is also important to think about the two types of nerves: excitatory and inhibitory. If the sodium current of an excitatory nerve is prolonged, then the result will be hyper-excitability, while over-exciting an inhibitory nerve will result in inhibition of actions or responses. Therefore, disrupting the sodium current can be very damaging, and can have very different ramifications, depending on which nerves are targeted.

Another pyrethrin-induced inhibition of nerve cells was found in a study by researchers from the University of Maryland School of Medicine and the University of Alexandria (Egypt). They found that pyrethrins inhibit the uptake of calcium in rat brain cells (Ramadan 1988 in Cox 2002). Without calcium entering the synaptic end bulb, the vesicles containing neurotransmitters can't be released, and impulses will fail to transmit signals.

Pyrethrins and pyrethroids are fat-soluble pesticides, and therefore they accumulate in fat deposits in the body (Pers. Com. 2002). The highest concentration of fat in the body is in the brain due to the lipid-based myelin sheaths surrounding every nerve cell (Pers. Com. 2002). The myelin sheath serves as an insulator and conductor, protecting the nerve and giving the neural impulses speed and direction. All types of pesticides can degrade the myelin sheath (Pers. Com. 2002). If demyelinization occurs, nerve impulses are either slowed (sometimes to the point of halting), or they misfire because there is no conductor to give them direction.

Pyrethrins and pyrethroids are considered neurotoxins because of their disruption of neurological enzymes. The first enzyme that they have been found to inhibit is ATPase; inhibition of ATPase leads to an increased release of the neurotransmitter acetylcholine (ACh) (Al-Rahji 1990 in Cox 1998). Acetylcholine acts as an excitatory neurotransmitter at some synapses (like the neuromuscular junction), and it also acts as an inhibitory neurotransmitter at other synapses (such as acting on the parasympathetic neurons of the vagus nerve to slow heart rate). Therefore, too much ACh is problematic regardless of the type of transmission, because it will either over-excite certain nerves and lead to convulsions, tremors and repetitive thoughts or over-inhibit them and lead to numbness, poor muscle control and slow heart rate.

In addition to inhibiting ATPase, pyrethrins and pyrethroids have been found to inhibit acetylcholinesterase, the enzyme responsible for breaking down ACh at nerve junctions into acetate and choline portions (Rao 1995 in Cox 1998). "The resulting accumulation of acetylcholine at nerve synapses at parasympathetic and myoneural junctions in the autonomic nervous ganglia, and in the brain, initially overstimulates and later paralyzes neural transmission" (Rea 1996). Therefore, pyrethrins and pyrethroids are destructive to neural transmission, not only because they cause an increase in ACh, but also inhibit the very enzymes needed to break down ACh. Symptoms of too

much ACh in humans are convulsions, nervousness, excess salivation, nausea, vomiting, abdominal cramps, headache, weakness, tremors and noise sensitivities (Simpson 2000).

Gamma aminobutyric acid (GABA) is an amino acid found only in the brain that causes inhibitory postsynaptic potentials by opening the gated chloride channels in the nerve. It is the most common inhibitory neurotransmitter, and pyrethrins and pyrethroids have been found to inhibit the receptor sites for this amino acid (Ramadan 1988 in Cox 2002). When an inhibitory neurotransmitter is inhibited, there is nothing to counterbalance the excitatory neurotransmitters and they will continue to fire. This can result in such symptoms such excitability and convulsions (Ramadan 1988 in Cox 2002).

By affecting both the sodium current of nerve cells and the enzymes needed for proper neurological functioning, pyrethrins and pyrethroids can be very destructive to the nervous system. The over-excitement or over-inhibition of certain nerves each produces its own array of symptoms. However, both effects result in paralysis in insects, eventually leading to death. Since all animals share the same nerve structure and neurological enzymes, organisms other than insects also run the risk of neural effects from this class of pesticides.

Pyrethrins and pyrethroids have also been found to cause other physiological damage. In various studies performed on rats, pyrethrins and pyrethroids were found to inhibit mitochondria, cause peaked blood glucose levels and decreased hemoglobin count, cause degeneration of tubules in the nephron of kidneys, and negatively effect the endocrine system by acting as xenoestrogens (Cox 2002).

The human antioxidant system has also been found to be susceptible to damage by pyrethrins and pyrethroids (Kale 1999). The antioxidant system is responsible for "mitigating the toxic role of Reactive Oxygen Species (ROS)" and includes superoxide dismutase (to dismutate superoxide

anions (O_2^-)) and catalase (to decompose H_2O_2). Other enzymes such as glutathione peroxidase (GSH-PX) and glutathione-S-transferase (GST), and antioxidants such as Vitamin E, ascorbic acid and glutathione, also have a role in combating free radicals in the human body (Kale 1999). GST detoxifies a variety of electrophilic compounds to less toxic forms by combining with -SH groups, such as glutathione (Kale 1999). A decrease in GST activity could result in increased lipid peroxidation, which lowers the functioning of the antioxidant system (Kale 1999).

In a study conducted by M. Kale, et. al. Male rats weighing 150-180 grams were given 0.2 mL doses of two different pyrethroids; cypermethrin (LD_{50}=2500 mg/kg $^{-1}$ body weight (BW)) and fenvalerate (LD_{50}=450 mg/kg $^{-1}$ BW). The rats were sacrificed after 0,1,3,7, and 14 days of pesticide treatment and their organs were examined. The pesticide treatment caused an increase in lipid peroxidation in days 1-7, with improvement by the 14th day. It also caused an increase in superoxide dismutase and catalase. Glutathione levels decreased in the kidneys and the heart and was totally depleted in the liver by day 7, while GST activity decreased in the same organs. Also, the activity of acetylcholinesterase in the liver, kidneys, and heart was "markedly inhibited", with a significantly low recovery rate when exposed to both pyrethroids (Kale 1999).

Compromise to the immune system is also very common with exposures to this class of pesticides. Pesticides can stimulate, suppress, or deregulate the immune system. Most of them can do all three, depending on the concentration and duration of the exposure (Rea & Liang 1991). The most basic change that occurs is proteins altering to become haptens. Pesticides may also alter the bacteriocidal, viricidal and phagocytic ability of neutrophils, decrease the responder plasma cells in the lymph nodes, and/or deregulate the basophil leukocytes which prevents histamine release and phylaxis (Rea & Liang 1991).

The lymphocytes can also be seriously affected by a pyrethrin or pyrethroid exposure. Ingestion of the pyrethroid permethrin was found to reduce the ability of T-lymphocytes to recognize and respond to foreign proteins (Blaylock 1995 in Cox 1998). In a study performed by R.L Blaylock et al, doses of permethrin equivalent to 1/100 of the LD_{50} amount inhibited T-lymphocytes over 40% and also reduced the activity of natural killer cells by almost 40% (Blaylock 1995 in Cox 1998). Similarly, in a study performed at the Environmental Health Centre-Dallas, 107 pesticide-exposed patients were tested and 81% of them had depressed levels of both T-and B-lymphocytes. Their white blood cell count was also significantly lower than that of the control group (5520 vs 7560) (Rea & Liang 1991).

What makes a person vulnerable to a pesticide exposure? What is the reason that one person may suffer physiological damage while another person subjected to the exact same exposure does not? There have been very little studies done on pesticide victims to answer this question, however research has been done on patients with Multiple Chemical Sensitivity (MCS). MCS is a chronic illness in which patients suffer adverse reactions to chemicals, often after exposure to levels below which normally elicit a reaction (Simpson 2000). Since pesticides are not only chemicals, but are also very often the initiating chemical that causes MCS (Simpson 2000), it may be safe to apply the same susceptibility theories to pesticide-exposed patients. The main factor that increases one's chances of suffering physiological damage from pesticides is sex. Women have a larger concentration of body fat than men do, and as mentioned earlier, pesticides are almost always fat-soluble. Women have more adipose tissue for pesticides to be stored in, and when the fat cells are broken down, the pesticides are released back into the body (Simpson 2000). Approximately 80% of patients suffering from chemical sensitivities are women (Simpson 2000).

Beyond sex, there are two major theories attempting to explain what makes a person susceptible to such chemicals as pesticides. The first theory involves the detoxifying threshold of humans. This theory basically states that certain people have a higher threshold for detoxifying chemicals (Mellish 2001). It is assumed that the process for detoxifying a xenobiotic chemical works much like the other stimulus response systems in the body which all function by a dose/response relationship, in which the amount of the stimulus has to fall within a certain range in order for the body to respond to it (Mellish 2001). With hearing for example, sounds below or above a certain frequency are not able to be heard because they do not fall within our hearing threshold range. It is theorized that people with sensitivities to chemicals genetically have a higher threshold for eliciting a detoxifying response to chemicals than the average person does (Mellish 2001). This means that if a sensitive person was exposed to an amount of a pesticide that triggers a normal detoxifying system, their body wouldn't respond because the dosage would be *below* their high detoxifying threshold (Mellish 2001). When levels of xenobiotics fail to trigger one's detoxification system, they remain loose in the system until they can find something to react with (Mellish 2001).

The other theory, which has gained more support, involves a person's detoxifying enzymes. The enzymes responsible for the chemical transformation of such foreign compounds as pesticides are called the cytochrome P450 enzymes (Blakeslee 1997). They are found in virtually all animals, and vary widely in number. Although mammals have about three dozen different C-P450 enzymes, one's specific level of them can also vary greatly due to genetics and polymorphism (Simpson 2000). The C-P450's are found throughout the human body, but are most active in the liver, lungs, skin, gut, and kidneys (Blakeslee 1997). They are involved in the first of the two phases of the detoxification process. During this phase, the enzymes prepare the toxic hydrophobic molecules for the second phase by making them more water-soluble. They do this by adding oxygen atoms, usually

in the form of hydroxyl groups (Blakeslee 1997). Most of the C-P450's exist in low levels until a xenobiotic enters the body, at which time the enzymes' genes are activated and large amounts are produced (Blakeslee 1997). If for some reason, large amounts are unable to be produced, some of the toxic molecules may not be broken down.

During the second phase, another compound (such as sulfate, glutathione or sulfur-containing amino acids) joins to the toxin to make it unreactive and safe for removal through the kidneys (Eaton 2000). Any deficiency or overloading of the necessary C-P450 enzymes or assisting co-factors, would result in insufficient detoxification. As was mentioned earlier, exposure to pyrethroids have been found to decrease levels of glutathione. Also, acute exposures to pesticides could overload the enzymes and result in damage to their future production, possibly weakening the detoxification system permanently. Based on this theory, if someone has an inadequate detoxifying system, they could be much more likely to suffer physiological damage from an exposure to pyrethrins or pyrethroids.

Whether it is because of detoxifying enzymes or detoxifying thresholds, some humans are poisoned by pesticides. Although pyrethrins are natural and thought to be "safe" for humans, there is some significant evidence suggesting that this is not necessarily the case. Pyrethrins and pyrethroids are neurotoxins that don't discriminate between insects and other animals. "Any organism with a sodium channel is at risk of being affected"...now that's a catchy phrase for a product label.

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