From:	Philip Smith
To:	Exhibits HAGLU
Subject:	Fw: Testimony Regarding SB 853 and HB 3058 restricting some Neonicotinoid pesticides and banning Chlorpyrifos
Date:	Tuesday, March 26, 2019 11:44:34 AM

To legislature members reviewing materials,

As a longtime beekeeper (my business here in Eugene since 1997, but keeping bees long before), and a concerned citizen, I'm most strongly urging the passage of SB 853 and HB 3058 banning and or limiting Neonicotinoids and Chlorpyrifos. Both of these chemicals are extremely deadly for not only pollinating insects, but other life forms as well. My late autumn and winter losses started spiking around 2008, when 'neonics' usage became more and more prevalent on farms and residential areas. They bioaccumulate (long half lives) and spread easily through water. My losses the past few years have been devastating, and this is true across the USA. The Europeans and other counties have 'seen the light' because of conducting thorough scientific studies, and banned 'neonics'. Their losses have decreased dramatically, while ours continue to climb. Bayer-Monsanto, the largest makers of 'neonics', try to confuse and divert attention by citing Varroa mites as main cause of bee die-offs. Don't be fooled! While they can be devastating to bee colonies if left untreated, beekeepers in general are fastidious in their controlling mite populations.
Please peruse Gary Rondeau's excellent studies on this matter. This is a life or death matter regarding our precious environment, and again, I'm strongly urging positive action on these matters. There are already practical organic alternatives used with great success regarding pest insects, these deadly chemicals will only hasten overall destruction. Thanks for your consideration.

Philip Smith
Eugene beekeeper

----- Forwarded Message -----
From: Gary Rondeau <gary@asiimaging.com>
To: "haglu.exhibits@oregonlegislature.gov" <haglu.exhibits@oregonlegislature.gov>; Lisa Arkin <larkin@beyondtoxics.org>; Krystal Abrams <kabrams@beyondtoxics.org>
Sent: Tuesday, March 26, 2019, 12:19:51 AM PDT
Subject: Testimony Regarding SB 853 and HB 3058 restricting some Neonicotinoid pesticides and banning Chlorpyrifos

To who it may concern,

I am Gary Rondeau, a beekeeper and a scientist living in Eugene Oregon. I have studied the problem posed by insecticides on honeybees and other invertebrates beginning in about 2010 when I personally started to have trouble keeping my bees alive. I took on the task of identifying the most likely culprits for our bee declines and colony collapse that beekeepers across the country were experiencing. Beekeepers have been dealing with pesticides for many years, so I was at first not convinced that pesticides were the issue. However, the new class of pesticides that were becoming popular, the neonicotinoids, had some problematic properties that raised red flags. The issue that bothered me was what happened if you had low doses of the pesticide present for long periods of time. I looked at various research papers and concluded that this was an issue that needed further attention. I wrote a blog article on the subject that eventually became a published article: https://www.nature.com/articles/srep05566

Delayed and time-cumulative toxicity of imidacloprid in bees, ants and termites
Gary Rondeau , Francisco Sánchez-Bayo , Henk A. Tennekes , Axel Decourtye , Ricardo Ramírez-Romero & Nicolas Desneux

Scientific Reports volume4, Article number: 5566 (2014)

The article has been cited many times and I like to think of it as a chink in the armor that allowed the

European Union to effectively ban the neonicotinoid pesticides throughout Europe.

In the process of learning about pesticides I have come to a much better understanding of their biological mechanisms and their environmental shortcomings. This has resulted in two blog articles that are not overly technical which I believe would benefit decision makers to understand the issues at hand. The links are here:

https://squashpractice.com/2014/06/15/the-mechanisms-of-neuro-toxic-pesticides/

https://squashpractice.com/2017/12/03/threshold-mechanisms-in-acetylcholine-pathway-insecticides-and-environmental-safety/

The point I wish to stress in the second article is that a key means to ensure environmental safety for chemical pesticides is that they exhibit a strong "threshold" type of non-linear dose-response action. Pesticides that exhibit strong threshold action include the organophosphate and carbamate classes of chemicals. Strong threshold action means that low residual doses of these chemicals are relatively benign. In contrast, chemicals without a strong threshold action begin to sicken target and non-target organisms at sub lethal doses and can pose unacceptable environmental risks at almost undetectable levels when organisms are continuously exposed to these nerve toxins.

Finally, recent studies have shown that the neonicotinoids not only attack synaptic nervous system receptors, but that these same receptors are commonly present on insect immune cells. These studies have provided the mechanism for what has been observed in the field, that colonies exposed to low levels of neonicotinoids often succumb to a pathogens, often multiple pathogen species when colony collapse occurs. I reference several of these studies in the articles linked above.

The neonicotinoids are a very dangerous environmental hazard. They are likely a significant factor in the widely reported insect apocalypse where large fractions of the wild insect populations have disappeared. The neonics are water soluble so they move when it rains, eventually finding their way to the oceans. We need to stop using them immediately and hope that some of the lost insect diversity will recover.

Below are copies of the linked articles from my blog.

Thank you for your consideration.

Gary Rondeau, Ph.D.

1025 Elkay Drive,

Eugene, OR 97402

The Mechanisms of Neuro-toxic Pesticides

, 2014Beekeeping, Ideas, Pesticides, Popular, Toxics

ɔf Neuro-toxic Pesticides"

es have become part of the chemical landscape that we all live in. To be able to make bout the use and regulation of these chemicals, it's important to understand how they odern pesticides are chemicals that interfere in some way with the nervous system. The chemical interaction with the nervous system function can shed light on the effectiveness on its physiological effects at residual levels. We will start by looking at how some of the the nervous system work, because it will be disruption of those processes that lead to toxic look at the mode of action for three major classes of pesticides and how they specifically function. In a future article we will look at how the specific mechanisms of action can lationships.

n Function – Neurons, action potentials, sodium and potassium ons channels, and ion pumps

of insects and humans share many common features, starting with the basic structure of ations on the same theme in different parts of the organism. Terminal branches can attach neurons at synapses, or through motor synapses to muscle cells. Individual neurons are x, interacting networks by the synaptic connections. Information processing involves from many neurons and generating an output. When the summed stimulus is high enough, rate an electrical pulse that is sent along the axon and which will, in turn, stimulate neurons connected through synapses to the axon branch terminals.

s accomplished by way of “action potentials”, which are short electro-chemical pulse that on axon. The short pulse-like nature of the nerve signals are generated and maintained by d” ion channels and ion pumps. Ion pumps use the cellular energy store, ATP, to move n ions across the cell membrane, setting up a concentration gradient across the membrane sting potential” of about -70mV from the inside to the outside of the nerve cell. Once this d, then merely opening ion channels in the cell wall allows the sodium or potassium ions the membrane and move the potential closer to zero. Nature’s trick, that turns this process tion processing network, is to open the ion channels which depolarize the neuron with a ion associated with the membrane potential. Once the membrane potential rises from its “threshold” the voltage gated channels open, steepening the rising edge into the action . The figure below is a nice schematic of the ‘anatomy’ of the action potential.

)07. DDT, pyrethrins, pyrethroids and insect sodium channels.

/ way of the action potentials, which propagate along the axons and terminate at the everal ways the action potential can be interact with cellular structures. We will etylcholine mediated synaptic response because this is the target of several pesticide

se Function – acetylcholine-mediated transmission

is a molecular neurotransmitter that conveys information across the synapse. In the ic steps of the interaction are illustrated. Action potentials, those pulses of neural activity, es containing ACh to release the ACh molecules into the synaptic cleft, the junction vo cells. The ACh quickly diffuses across the narrow junction region and is captured by ors (AChRs) that are part of ion channel molecules. The AChRs that have captured an the ion channel and allow Na+ ions to enter the post-synaptic neuron. The binding is the ion channels rapidly open and close as the ACh molecules latch and unlatch from the nwhile, another ACh receptor is also present in the synaptic junction called (AChE). This molecule is an enzyme which rapidly breaks apart the acetylcholine into effectively ridding the synaptic cleft of the neurotransmitter almost as fast as it is made of all of this chemical activity is that the AChRs, as an ensemble, are open only for a few g this time, ions flood into the post-synaptic dendrite, depressing the potential in the down ng it more likely to generate its own action potential.

ssion leaves out many details. There are many more specialized molecules that are part of en molecules that are specific for one important function also are involved in unrelated ls can be specialized and synaptic details can vary. Nevertheless, the basic picture we are ss much of the animal kingdom. These same basic process happen in the nervous systems alike. Now let us move on to discuss ways to interrupt these normal processes for

rgeting axonal voltage-gated ion channels

f insecticides target the voltage gated ion channels shown in our cartoon. The DDT, dieldrin, chlordane) and pyrethroids (e.g. deltamethrin) act by opening these nnels. The molecules hold open the channels and allow ions into the axon that n. In the depolarized state the neuron is non functional, characterized by paralysis. In state and paralysis there is a range where the depolarization of the neuron is only partial. n leaves the neuron susceptible to “false triggering”. A small stimulus that would an action potential will produce one more easily as the resting potential gradually climbs ired to launch an action potential. Organisms in this state typically exhibit twitching and ents as the uncontrolled nerve impulses trigger muscles to move.

ne molecular scale. As organic molecules interact with one another, they can latch onto y loosely or with tenacity depending upon the exact shape of the molecules involved and happens. Binding that occurs via the covalent sharing of electrons is usually very strong, t and irreversible. In contrast, many biological molecules interact through polar or Van t are much weaker. Such interactions may last for a fleeting amount of time before pull them apart. Weak binding is reversible and can be characterized by a dissociation es to break the bond due to random and thermal fluctuations.

esticide chemicals, stronger bonds mean the insecticide is spending more time at the ency is higher. Frequently it is just how tenacious the binding that determine the potency

known as cytochrome P450 enzymes are always on the lookout for foreign chemicals break down into smaller parts in the process of metabolizing and eliminating unwanted ithin a few hours much of a foreign chemical will be metabolized and eliminated from the olecules are not as easily digested by the cytochrome P450s so once toxins are bound to ey are more immune to detoxification.

rgeting the acetylcholine pathway

sses of pesticides that disrupt the acetylcholine pathway. We will start by looking at the
se they have the simplest mechanism, similar to the “direct action” of the pyrethroids

ind strongly to the AChRs. Binding causes he ion channels to open so Na+ ions can flow ike the normal acetylcholine response where the channel is only open for about a e neonicotinoid binds the receptors never close. Hence, it takes only a relatively few open y depolarize the neuron. If the ion pumps cannot keep up with the leakage through the ChRs the cell will depolarize. Partial depolarization will make the neuron more excitable; ion leads to paralysis.

e complicated with acetylcholinesterase inhibitors such as the organophosphate and For these chemicals, the insecticide does not directly bind to neuronal receptors that open the chemicals bind to the acetylcholinesterase (AChE) enzymes which rid the synaptic neurotransmitter that is released with normal activity. However, without the AChE to e ACh continues to bind with AChR ion channels. The figure below shows schematically nese AChE inhibitors.

n

s bind to the acetylcholinesterace (AChE) sites in the synaptic junction, preventing the
Ch for being removed and recycled from the junction. The acetylcholine continues to
eping their channels open thereby depolarizing the post synaptic neuron. Again,
 begin with an over-excitable nervous system, characterized by uncontrolled twitching,

lasses of neurotoxins we have looked at.

ng the most potent biological chemicals known. The chemicals are targeted to interact r molecules that are crucial for nervous system function. This means that very few are required to have a large biological effect. Chemicals used as pesticides need to rget species while remaining benign to non-target organisms and humans. However, much nery is shared across the animal kingdom, so differentiating between target and non-target nge. Often only space and time are used to separate target and non-targets creatures from The environmental effects of pesticide chemicals depends upon the success of various rmful exposure to non-target species. In many cases dilution is the solution, but as and residential uses of potent chemicals become even more widespread, minute residual evitable. Next time we will see why this is more likely to be a problem with some classes an others.

anisms in acetylcholine pathway insecticides and environmental safety

Threshold mechanisms in acetylcholine pathway insecticides and environmental safety

3, 2017Beekeeping, Ideas, Pesticides, Toxics

ms in acetylcholine pathway insecticides and environmental safety"

d at some of the basic principles of nervous system function and how chemicals from sses disrupt normal function. This time we will look in detail about what we can expect characterization of acetylcholine pathway insecticides based upon their mode of action and vous system. This will get a little more technical than usual. The casual reader may want ations but think about the explanations.

esticides function by disrupting the synaptic acetylcholine pathway.

sticides and the carbamates block the enzyme acetylcholinesterase (**AChE**) such that the urotransmitter, acetylcholine (**ACh**), is not broken down and recycled. up in the synaptic junction and over-stimulates the acetylcholine receptors (**AChR**) on the ane.

ct directly by bonding strongly to the nicotinic acetylcholine receptors (**nAChR**) in a en the receptor ion channel.

icals, the **AChE** inhibitors and the **nAChR** agonists, produce excessive numbers of ne receptors on the post synaptic membrane, which gives rise to a reduction in the post ntial and a propensity to generate action potentials in the post synaptic neuron. Acute en the general level of neural stimulation is sufficient to disrupt the normal physiological sustain life. Clinically, insects and animals poisoned with either class of chemicals are r control, exhibit uncontrolled twitching, eventual paralysis, and death.

nsidering a single synapse and come up with a relationship for the post synaptic tion of the fractional lethal chemical level. We will also consider implications of disruption for an entire neural network. Finally we will seek to understand the cations of threshold versus non-threshold action with these chemicals.

o-chemical function

is governed by neuronal generated "action potentials", rapid electrical potential changes ong the neural axons and terminate in the branching tree of dendrites at synapses where lease of neurotransmitter into the synaptic cleft. The neurotransmitters rapidly diffuse unction and attach to receptors on the post-synaptic membrane. These transiently bound permeability of the membrane and allow ion currents to flow across the membrane, thus ular electrical potential in the post-synaptic neuron.

fast transients that last 1-3 milliseconds. Diffusion time of **ACh** across the junction is microseconds, and the decay of synaptic free-circulating **ACh** is normally around one he response of the excitatory post-synaptic potential is slightly slower, typically lasting lliseconds.(1) This allows the post-synaptic neuron to be the summing junction from s, doing some kind of dynamic averaging that determines whether or not the downstream its own action potential. We argue that changing the decay time of **ACh** in the synaptic tly to stimulation that will produce an action potential in the downstream neuron. he decay time is likely to double the likelihood of the downstream neuron generating its because the amount of post-synaptic charge transfer will be proportional to the length of n the **AChR** receptors, and this open time is within the typical averaging period of the

terase Inhibitors – Consider a single synapse

, produced by a single action potential in the downstream neuron can be written as

ncentration of **AChR**s, is the concentration of **ACh** released by the action potential,
constant and is the lifetime of **ACh** in the synaptic junction.

tylcholinesterase inhibitors act is by reducing the number of **AChE**molecules available to on of **ACh** in the synaptic junction. It is reasonable to expect that decreasing the number nolecules will proportionally increase the time it takes for **ACh** molecules to be degraded. raction, , of the **AChE** is bound with inhibitor, then we estimate the ACh lifetime, , in **E** inhibitor as

otential neither nor are affected by the **AChE** inhibitor, so we can express the function of the fraction of inhibited **AChE** as

tually the excess stimulus is lethal which we designate as occurring at .

ard01

at happens as the fraction of bound **AChE** increases. The stimulus enhancement rapidly the **AChE** becomes unavailable to catalyze the destruction of **ACh**.

you can show that the fraction of excess stimulation at the sub lethal limit compared to on can be expressed as is the sub-lethal exposure as a fraction of the lethal level, and is the excess

l with the small dose .

al stimulus level is five times the normal background level of neuronal activity, then 80% e bound. If we ask what happens with an exposure that is 10% of the lethal level, (8% n the increase in simulation is only 1.6% of the increase needed for lethality. In the mulus increase is less-than-linear with exposure, with this “safe residual” effect strongest approaches 1.

e shown that **AChE** inhibition levels need to be 60% to 90% (2), depending upon the , to be lethal. This is more or less in accord with this model where lethality requires most rs to be out of commission, and would suggest that toxicity suppression for residual levels for these chemicals.

Dynamics – Consider the complete network

e nervous system as an ensemble of neurons with average properties. Specifically we are ylcholine pathway, so we define several global average quantities and relationships ylcholine activates receptor sites on the post synaptic membrane that stimulate the post e can express this globally averaged stimulus, , as

onality constant, is the average concentration of synaptic acetylcholine, and is acetylcholine receptor sites. (Unlike the previous section, here is an averaged

n, whereas in Equation [1] described the total release of **ACh** caused by a typical etylcholine is release into the synaptic junction by action potentials from stimulated iickly degraded by acetylcholinesterase receptors located in the synaptic cleft. We can hip as

efficiency of the averaged stimulus at generating additional **ACh** due to stimulus-induced is the concentration of **AChE** that degrades **ACh** and is a constant involving the

destruction of **ACh**. Combining [6] and [7] and defining , we get ferential equation is

te, is

must be negative or acetylcholine concentration will grow without bounds,

conditions, the concentration of **AChE** must be sufficient to prevent runaway growth of
on due to **ACh**'s ability to generally stimulate the neural network. Here we are not
y other neurotransmitters, both agonists and inhibitors, that are included in the network,
ng external inputs. However, conditions that place the entire network in a rough dynamic
network's ability to involve multiple neurons for information processing. Hence, one
e inequality [11] is only weakly maintained, at least in some portions of the neural
ould lead to a network that would more optimal for information processing .

network with AChE Inhibitors

what happens when we add **AChE** inhibitors and to this picture. The effect of
bition will be to reduce the natural concentration **AChE**, , to an available active

{E0} (1-f)

on of bound **AChE** receptors. Substituting [12] into [11] and solving for , we find that
bition fraction that will result in uncontrolled growth of the ACh concentration.

his the threshold level at which AChE pesticides produce a lethal effect.

ure on OP poisoning, one comes across the notion of "cholinergic crisis" which suggests condition (3). Although experimentally it is found that relatively large fractions of the ted to cause lethality, this network effect may play the role of the coup de grâce at the .

Receptor Agonists – Neonicotinoids

ceptor agonists such as the neonicotinoids will directly stimulate the post synaptic neuron. tsynaptic stimulation, , due to the neonicotinoid as

le-receptor ion current stimulation, is the **nAChR** concentration and is the fraction ith agonist. When only a few receptors are bound with agonist, the cell's ion pumps will resting potential of the neuron. However, ion pumps are a slow energy-intensive o an open **nAChR**channel, as a rough estimate, an ion pump will only generate $\sim 10^{-5}$ as another way, for each open **nAChR** there needs to be ~ 10^{5} ion pump channels in action meostasis. A normal functioning **nAChR** would remain activated only for a few so much less pumping is required to recover from normal activity because of the low

l mechanisms are present for this class of chemical. Instead, the excess stimulation is to the amount of bound receptors, which is itself proportional to insecticide dose. If we ise like we did for equation [5] we discover that in the residual limit where ,

is proportional to the residual dose.

for residual levels of these chemicals

f the post-synaptic neuron must be eventually be rectified by metabolic processes that inst the gradient to return the neuron to its normal resting potential. Chemicals that aptic stimulation beyond the natural level will require proportionately more metabolic euron to its resting potential. For the **AChE** inhibitors the excess stimulation is only ynapse is stimulated by the action potential and **ACh** is present. If we wish to find an ulation of the post synaptic neuron, we need to multiply the instantaneous excess naptic duty cycle, . We can rewrite equation [5] for the averaged excess stimulation for f **AChE** inhibitor, as

.

ls, the stimulation is constant, with duty cycle equal to one when doing the time

emical pesticides are applied in the field at rates that are designed to produce a lethal effect hen we can compare the relative effects of residual levels of the chemicals

ome small fraction of the lethal level, by normalizing to an application rate where

re the subscripts and refer to the organophosphate or neonicotinoid classes of ly. With these assumptions, combining [16] and [17],

on suggests that for similar residual levels of the two classes of chemicals, the
roduce a much larger average post-synaptic stimulation. We can make estimates for the
ased upon observed average firing frequency, ~1 Hz, and typical action potential duration,

(1-f_L) = 0.5

the threshold term , then taken together the neonicotinoid chemicals will

more averaged post-synaptic stimulation than would similar residual levels of
ticides. For sub lethal doses of the pesticides, where nervous system function is not
e primary physiological effect one would expect to see would be a much higher metabolic
s exposed to low levels of neonicotinoids.

ive Effects

ne the movement of the pesticide from its initial application, its interaction with target or
, and its eventual dilution and degradation can have dramatic consequences in terms of
ic effect and latent residual toxic effect.(5) An effective and safe pesticide should strongly
nism yet remain benign to similar species that are *not* the target organisms. The best way
ifferentiation from initial application compared to residual pollutant is to use chemicals
llowing properties:

de in the environment.
sociate at targeted biological binding sites.
threshold action.

turn. Persistent chemical pollutants have been the bane of the pesticide industry since
cetylcholine path insecticides are as bad as the organochlorines, but there is still quite a
nembers of this group. The neonicotinoids are said to have around a 1 year soil life, but
hat to be an optimistic number. Where the chemicals have been used for many years, the
continue to increase. Since the neonicotinoids are water soluble, this suggests that what
dation is merely dilution and migration. Instead of the chemical disappearing, we find

m the source of the application. (6,7,8) Chemicals that are persistent in the environment harvested and target insects are gone can only have deleterious consequences for s. The severity of the consequences depends on the final two properties.

s that bind to targeted receptors can have a wide range of receptor affinity and binding that bind transiently (like the **ACh** molecule itself to **AChR**s) will remain in quasi with the extracellular fluid and will bind to target molecules at a rate that is proportional of the chemical. However, some insecticide chemicals are designed to bind tenaciously to sites. In these cases, the molecules will become trapped at the target site even after most been rid from the organism's body by metabolic processes. In cases with very strong an expect accumulation over time of molecules at the target sites as long as there is any to the chemical. How serious a problem this will be for non-target organisms depends on ether the chemical works with a threshold action or not.

esticide Classes

c pesticides have been widely used for more than 70 years. During that time several s have been developed to target specific neurological receptors. The chart below lists es, includes a common example or two from each class and shows typical properties of the typical chemicals in the table above in light of the requirements we identified as esticide. Note that the organochlorines failed badly because they were so persistent in the oint they have been almost universally banned. They were largely replaced by the th which we've continue to have an uneasy coexistence for the last half-century. Under heir potent effects on humans and other vertebrates, many of the organophosphate g forced into retirement. The replacement has been the neonicotinoids, which have the ecificity to invertebrate **nAChR** receptors making the chemicals less toxic to humans and nfortunately, the neonicotinoids fail with regard to all three of the properties for safe and

you can see that the safest chemicals are the carbamates. Typically it takes more chemical neonicotinoids, organophosphates, and carbamates) to kill the target insect, but the emical in the environment is short. It is metabolized relatively quickly, and acts reversibly tors. Finally, it is also an **AChE** inhibitor that has a strong threshold of action effect. e neonicotinoids at the top of the chart. It takes much less neonicotinoid chemical to kill, to its tenacious persistence on the target receptor sites. The chemicals do not degrade very nment so they will continue to accumulate on target and non-target organism synaptic he initial application. And finally, the neonicotinoids produce toxic effects at residual e **AChE** inhibitors. All of the tricks we have in the playbook to segregate between target s fail with the neonicotinoids.

f threshold action for toxicity scaling

e acetylcholine growth rate provides a clear qualitative turning point for the organism. It how such a runaway event can lead to death. Hence, if you wish to model the toxicity nd with such a distinct threshold action, all you have to do is follow the movement of toxin the threshold is reached. This will naturally give you Haber's rule for substances that most of the organophosphate insecticides. For insecticides that don't accumulate on rbamates, one would expect threshold action without a significant time dependence. Once ons reached levels where chemical equilibrium at receptor sites resulted it enough nge the sign of the **ACh** growth rate, the threshold condition would be reached. However, centrations of acetylcholinesterase inhibitors, the molecules disable a few AChE sites and e the synaptic response, but otherwise remain largely benign to the organism. For this e is a very large change in toxic effect with concentration. Despite the continued and concerns with organophosphate pesticides, it should be recognized that they may be nentally safer because of their strong threshold action than the newer neonicotinoids.

ls where there is no distinct threshold condition, the situation is more complicated. The to dead is not accompanied by a convenient mathematical marker like the change in sign pecially at the residual limit, we are left to speculate on the physiological impact of om the toxic chemical. Single molecules will open ion channels and begin to depolarize mal state of affairs would be countered by energy-burning processes in the organism to ion. This is the definition of stress. It is likely that the residual-level stresses to non-target illes' heal for the neonicotinoid insecticides. Very low concentrations of these pesticides switch on compensatory physiological processes that are poorly understood, but likely ple was the discovery that very low levels of the neonicotinoid clothianidin reduced the honeybees to the point where deformed wing virus could replicate. Low levels of the inhibitor chlorpyriphos, the molecules of which in our understanding would be rather o a few of the **AChE** sites, showed no such immune suppression effect.(9) The fact s are involved in less well studied immune system and cellular signaling functions adds to ıg these pathways will have unintended consequences.(10,11)

residual levels, **AChE** inhibitors are really doing nothing. A small fraction of e out of commission, but even that effect is only apparent when the neuron fires and there way. During the neuron's quiet state the pesticide molecules are benign. Contrast this appens on the postsynaptic membrane with a few neonicotinoid molecules. Single ules hold open **nAChR** channels that will tend to depolarize the neuron. This happens n is in an un-stimulated state. However, given the persistent depolarization by the open Instead the cell must muster energetic processes in an attempt to restore the neuron's may still function.

of immune response as mentioned above, there are likely other detrimental effects from esponse required by residual neonicotinoid poisoning. Trade-offs between energy tain neurological function and more normal activities such as powering flight muscles the observed effects of chronic low level exposure. (12) Another study shows epi-genetic orid-exposed honeybee larva that that strongly affects genes involving metabolism. (13) hat low level neonicotinoid exposure presents, such as impaired navigation, poor learning t time, and immunological impairment may be better understood from the perspective of caused by open nAChR channels than by direct neurological impairment.

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