CENTER FOR FOOD SAFETY

May 4, 2020

OPP Docket
Environmental Protection Agency Docket Center (28221T)
1200 Pennsylvania Ave. NW.
Washington, DC 20460-0001

RE: Center for Food Safety's comments to EPA on the Proposed Interim Registration Review Decisions for Several Neonicotinoid Pesticides: Imidacloprid, Clothianidin, Thiamethoxam, Acetamiprid and Dinotefuran

Docket IDs:
EPA-HQ-OPP-2008-0844: Imidacloprid
EPA-HQ-OPP-2011-0865: Clothianidin
EPA-HQ-OPP-2011-0581: Thiamethoxam
EPA-HQ-OPP-2011-0920: Dinotefuran
EPA-HQ-OPP-2012-0329: Acetamiprid

Center for Food Safety appreciates the opportunity to comment on EPA's proposed interim registration review decisions for the above-named neonicotinoid insecticides.

HUMAN HEALTH ASSESSMENT

Common Mechanism of Toxicity Demands Cumulative Risk Assessment

These five neonicotinoids operate by disrupting neural transmission in the central nervous system of invertebrates. By binding to nicotinic acetylcholine receptors (nAChRs) in the brain, neonicotinoids continuously stimulate neurons, resulting in death as well as sublethal effects (Simon-Delso et al. 2015). Neonicotinoids are more highly toxic to invertebrates than vertebrates because the former have have a larger number of nAChRs with high affinity to these insecticides. Neonicotinoids target primarily the nAChR subtype $\alpha 4\beta 2$ in insects and mammals, and mammalian toxicity correlates with agonist action and binding affinity at these receptors, their primary target in the brain (Tomizawa and Casida 2005).

This shared mechanism of toxicity demands cumulative risk assessment of these neonicotinoids, as required under the Food Quality Protection Act. EPA provides no explanation for its failure to conduct a cumulative assessment, beyond noting that it has not made an official finding as to the fact that neonicotinoids share a common mechanism of toxicity to humans (e.g. EPA Imidacloprid 2020, p. 17). EPA refused to make this finding despite abundant evidence, even in registrant-sponsored animal feeding studies conducted for the human health assessment, that neurotoxicity is the most prominent and consistent class of

adverse effects of all five neonicotinoids. For instance, imidacloprid via oral administration induces tremors, decreased motor activity and similar effects in multiple studies on rats and dogs (EPA 6/22/17, p. 3). Clothianidin induces decreased arousal, motor activity and acoustic startle response; tremors; and other neurotoxic effects in various animal studies (EPA 9/7/17, p. 13). Thiamethoxam triggers developmental neuorological effects in rats, including reduced brain size and weight (EPA 12/5/17, pp. 5-6). Neurotoxic effects induced by acetamiprid include decreases in locomotor activity, alertness, reactivity, spontaneous activity, rearing, muscle tone and grip strength; tremors; and depressed reflexes in rat, mouse and/or rabbit studies (EPA 12/15/17, pp. 17-18). Dinotefuran likewise induced declines in motor activity, grip strength, and brain weight in animal studies (EPA 9/12/17, p. 5).

EPA refuses to officially affirm a common mechanism of human toxicity between any of these neonicotinoids despite acknowledging the fact. EPA states that neurotoxicity is among the classes of adverse effects "commonly observed in mammalian toxicity studies of neonicotinoids" (EPA 9/7/17, p. 12). Still more explicitly, EPA affirms that neonicotinoids have a neurotoxic mode of action both for insect pests and humans: "Dinotefuran is a neonicotinoid and has a pesticidal and mammalian neurotoxic mode of action. Consistent with this mode of action, changes in motor activity were seen in acute neurotoxicity (ACN) and subchronic neurotoxicity (SCN) studies" (EPA 9/12/17, p. 20). EPA also notes that dinotefuran induced "changes in motor activity which are consistent with effects on the nicotinic cholinergic nervous system [nicotinyl acetylcholine receptors, as noted above] seen after repeat dosing" (EPA 9/12/17, p. 5).

Four of the five neonicotinoids belong to a common subclass – the nitroguanidines – while the fifth, acetamiprid, is a closely related cyanoamidine-substituted neonicotinoid (Tomizawa and Casida 2005, Figure 1). EPA "made a programmatic decision to align the registration review schedule for all four nitroguanidine-substituted neonicotinoids (clothianidin, dinotefuran, imidacloprid and thiamethoxam)" (EPA 1/16/20), and subsequently added acetamiprid to the group. This decision makes no sense if, as EPA tacitly assumes, entirely separate risk assessments for each of them is adequate to the task of ensuring human and environmental safety.

Independent scientists have assessed cumulative dietary exposure to neonicotinoids on the basis of their common mechanism of toxicity, employing relative potency factors to permit expression of the cumulative toxicity in imidacloprid-equivalent units (Lu et al. 2018; Zhang et al. 2019). EPA has used this method to assess the toxicity of related groups of compounds, such as dioxins (Staskal et al. 2010). Because cumulative exposure to neonicotinoids would be considerably higher than exposure to any single compound of its class, EPA has underestimated both human exposure to and the health risks of neonicotinoids. To take one example, EPA's estimated dietary exposure to imidacloprid alone is nearly equal to the acute safety threshold (population-adjusted dose, or aPAD) for infants (84%) and toddlers (93%) (EPA 6/22/17, p. 23, Table 5.4.4). Cumulative exposure to all five neonicotinoids would almost certainly exceed the acute safety threshold for these vulnerable groups.

EPA should abstain from any final registration review decision until it has completed a thorough cumulative risk assessment of neonicotinoids.

Safety Factor to Protect Infants and Children

EPA is required by the Food Quality Protection Act (FQPA) to apply "an additional tenfold margin of safety" to account for "the special susceptibility of infants and children," and in particular the "potential for pre- and postnatal toxicity…," and reduce or eliminate it only if "reliable data" demonstrate it is not needed. According to EPA policy, the 10x FQPA safety factor is to be applied when the young exhibit increased susceptibility to a pesticide (i.e. effects not seen in adult animals) or increased sensitivity (the effects occur at lower doses or increased severity in the young) (EPA 2002, p. 30).

Based purely on registrant studies, EPA found increased susceptibility or sensitivity to neurotoxic harms in young test animals versus adult animals for four of the five neonicotinoids at issue here: imidacloprid ("evidence of an increased quantitative susceptility" in the rat," EPA 6/22/17, p. 14); clothianidin (same, EPA 9/7/17, p. 13); thiamethoxam (same, EPA 12/5/17, p. 6); and acetamiprid ("increased qualitative susceptibility," EPA 12/15/17, p. 17-18).

Despite these findings, the clear mandate of the Food Quality Protection Act, and EPA's policy prescriptions regarding implementation of the FQPA, EPA rejected the default 10x safety factor for all five neonicotinoids.

EPA should abstain from any final registration review decision until it has correctly applied the FQPA 10x safety factor to arrive at reference doses that reflect the increased toxicity of these insecticides to the young.

Independent Studies Reveal Greater Mammalian Sensitivity to Neonicotinoids Than Registrant Studies

Kara et al. (2015) administered via gavage 0.5, 2 or 8 mg/kg/day imidacloprid to infant and adult Wistar rats for 3 months. Learning activities were diminished significantly at 2 and 8 mg/kg/day doses in infant rats, but only at 8 mg/kg/day in adult rats. This study's NOAEL for infant rats of 0.5 mg/kg/day is 16-fold lower than the 8.0 mg/kg/day NOAEL (acute and chronic) based on a subchronic dog study conducted by Bayer AG in 1990.[1] This study supports an oral reference dose of 0.005 mg/kg/day (vs. EPA's 0.08 mg/kg/day), and also provides further support for retaining the 10x FQPA safety factor, given the greater sensitivity of infant vs. adult rats.

Burke et al. (2018) infused 0.5 mg/kg/day imidacloprid into pregnant CD-1 mice via an implanted osmotic minipump from gestation day (GD) 4 to post-natal (PN) day 21. Imidacloprid accumulated in livers and brains of maternal mice, and was found in trace levels in offspring. Offspring exhibited a number of neurobehavioral impacts: elevated motor activity, enhanced

[1] Ruf J. 1990. NTN 33893 Technical: Subchronic Toxicity Study on Dogs in Oral Administration (Thirteen-Week Feeding Study). Lab Project Number: 18732: 100176. Unpublished study prepared by Bayer AG. 305 p. MRID 42256328.

social dominance, reduced depressive behavior, and a diminution in social aggression compared to controls. Adult male offspring had reduced weight. Maternal animals had significantly reduced fecundity (roughly 8 vs. 13 pups per mother for treatment vs. control groups). Transient exposure to imidacloprid over the developmental period induced long-lasting changes in behavior and brain function in mice. Based on Burke et al. (2018), the LOAEL for imidacloprid is 0.5 mg/kg/day. This study also supports application of the FQPA 10x safety factory.

ENVIRONMENTAL ASSESSMENT

Cumulative Toxicity

As with human health, EPA must assess neonicotinoids cumulatively, in view of their common mechanism of toxicity to insects and other non-target organisms (Xerces 2016), and their frequent co-occurrence (e.g. Krupke et al. 2012). Maloney et al. (2018) reported roughly concentration-additive toxicity of various neonicotinoid mixtures to the aquatic insect *Chironomus dilutus*, with mild synergism for thiamethoxam-imidacloprid. EPA must also assess the additive or synergistic toxicity of neonicotinoids together with co-occurring formulation additives ad other pesticides (Xerces 2016). To give an idea of the scope of the problem, Sanchez-Bayo and Goka (2014) report that in various studies, a total of 161 pesticides have been found in bee hives: 124 in pollen, 95 in wax and 77 in honey or nectar.

For instance, neonicotinoids are strongly synergized by inhibitors of CPY450 detoxification enzymes, such as piperonyl butoxide, a common "inert ingredient" in over 2,500 pesticide formulations (Tomizawa and Casida 2005; Cross et al. 2017). Imidacloprid exhibits synergy in concert with the adjuvant nonylphenyl polyethoxylate, R-11, towards the crustacean *Ceriodaphnia dubia* (Chen et al. 2010). A wide range of other formulation additives and surfactants, such as organosilicone surfactants, make pesticides more toxic and can also be toxic in their own rights (Mullin 2015, Chen et al. 2018). This is problematic, because regulatory toxicity tests on the active ingredient alone will often underestimate real-world formulation toxicity. For this reason, Zhu et al. (2017) tested the toxicity to honey bee of the imidacloprid formulation Advise 2FL in binary combinations with seven other pesticides they commonly encounter, and found synergistic toxicity between imidacloprid/Advise and Domark/tetraconazole, Transform/sulfoxaflor, and Vydate/oxamyl, with mortality significantly increased by 20%, 15% and 26%, respectively. Tsevtkov et al. (2017) found that both clothianidin and thiamethoxam were twice as acutely toxic to honey bee workers with co-exposure to field-realistic levels of the fungicide boscalid.

Neonicotinoids have frequently been found to synergize with ergosterol biosynthesis inhibitor (EIB) fungicides (reviewed in Wood and Goulson 2017). Thompson et al. (2014) exposed honey bees to sprayed fungicides at realistic, worst-case scenario concentrations and various neonicotinoids. They found mild synergism on a contact basis between thiamethoxam and tebuconazole (synergism ratio of 2.6) and on an oral basis between clothianidin and tebuconazole (synergism ratio of 1.9), with synergism ratio equivalent to the LD_{50} of the

neonicotinoid divided by that of the neonicotinoids plus fungicide mixture. Similarly, Sgolastra et al. (2016) found synergism in three bee species (*A. millifera* [honey bee], *B. terrestris* [buff tailed bumble] and *O. bicornis* [red mason bee]) exposed to LD_{10} doses of clothinadin and a non-lethal dose of the fungicide propiconazole, in the form of increased mortality for the mixture.

These are just a few of many studies that have arrived at similar findings, though because most assess only binary mixtures and pollinators are exposed to far more complex combinations of multiple pesticides, the reported results are likely to substantially underestimate the degree to which neonicotinoids are synergized by co-exposure to other pesticides. Yet EPA makes no attempt to assess the increased risks posed by neonicotinoids upon co-exposure with other pesticides.

Declines in Insect Populations Worldwide Coincide with Rise of Neonicotinoids

Massive declines in insect and pollinator populations worldwide

There have been many reports of declines in various insect species over the years (Dirzo et al. 2014), for instance the over 80% reduction in the migratory monarch butterfly populations since the mid-1990s in North America (Pleasants 2015). However, recently there has been great interest in charting trends in overall insect abundance as a more relevant marker of ecosystem health. For instance, researchers in Gerrmany documented an astounding 76% decline in flying insect biomass in 63 German nature reserves from 1989 to 2016 (Hallmann et al. 2017). They posit agricultural intensification, including pesticide use, as one potential cause, noting that most of the preserves are surrounded by cropland that may serve as an ecological traps or sinks for insects whose origins are in the natural areas. Sanchez-Bayo and Wyckhuys (2019) review 73 historical reports of insect declines around the world, and find that *Lepidoptera* (moths and butterflies), *Hymenoptera* (bees and wasps) and dung beetles have been most impacted among terrestrial insects. They predict extinction of 40% of remaining insect species in the next few decades, and regard habitat loss to agriculture and urbanization as well as pollution, particularly from pesticides and fertilizers, as major drivers. A recent meta-analysis of studies across the world finds a roughly 9% reduction in terrestrial insect abundance per decade, a trend driven largely by findings in North America and parts of Europe (van Klink et al. 2020).

Rise in insecticidal toxicity due to neonicotinoid seed treatments

In the U.S., the toxicity of insecticide use in agriculture has increased dramatically over the past two decades. Researchers found that insect toxic load – a metric that adjusts the amount of insecticides used by their acute potency to honey bees – has increased nine-fold on an oral basis since just 1997 (Douglas et al. 2020). The main driver of this trend is the seed industry's massive deployment of neonicotinoid seed coatings on the seed of field crops (e.g. corn and soybeans) that had previously not been extensively treated with insecticides of any sort (Douglas and Tooker 2015). Because of their extremely high potency as well as extent of usage, by 2012 neonicotinoids alone comprised 98% of oral insect toxic load, equivalent to 16 billion honey bee oral LD_{50} doses per treated hectare (Douglas et al. 2020). The most dramatic increases occurred in the Heartland (121-fold increase) and the Northern Great Plains (53-fold increase), where the majority of corn and soybeans, nearly all (corn) or are grown (Ibid.).

While neonicotinoids are deployed as foliar and soil-applied sprays, seed treatments employing imidacloprid, clothianidin or thiamethoxam comprise roughly three-fourths of total agricultural use of the five neonicotinoid compounds on a weight basis. This is based on EPA's screening level usage analyses for each of the five: 3 million lbs. seed treatment vs. just over 1 million lbs. for foliar and soil-applied sprays, annually, though this is a substantial underestimate thanks in part to lack of data on seed treatments since 2015.[2] Yet EPA has enacted little if any mitigation for this predominant use of neonicotinoids.

Neonicotinoid Exposure Routes

Neonicotinoid dust from treated seeds kills honey bees and other insects

Seeds treated with neonicotinoids (clothianidin, thiamethoxam or imidacloprid) and other pesticides (often fungicides) can stick together, causing uneven plant spacing. Talc or some other lubricant is added to seed boxes to reduce friction and ensure the smooth flow of seed during planting. Some portion of the seed coating is abraded in the seed box and contaminates the talc with high levels of the neonicotinoid. The talc is expelled either with the seed or behind the planter via exhaust fan (Krupke et al. 2012). This seed dust, broadcast across the landscape, has been implicated in numerous bee mortality events since 1999 in Italy, France, Slovenia, German and Canada as well as the U.S.: "[i]n all cases, a great number of dead and dying bees were found near the hive entrance" (Bonmatin et al. 2015).

One study examined the threat of neonicotinoid-laced seed dust to honey bees in Indiana, and found that over 94% of honey bee foragers in the State of Indiana are at risk of exposure to varying levels of neonicotinoid insecticides, including in some cases lethal levels during the planting of corn. They also found that deposition of neonicotinoid residues on non-target lands and waterways occurs on over 42% of the state of Indiana, and that risks to pollinators could be dramatically reduced, with no yield loss, by limiting use of seed treatments to situations where they are actually needed (Krupke et al. 2017).

EPA has not proposed any mitigation to address lethal or sublethal exposure to neonicotinoid-laced seed dust.

Other exposure routes

A major pathway of pollinator exposure to neonicotinoids is the pollen and nectar of crops from treated seed. In a review of 20 studies, Godfray et al. (2014) estimate ***average*** maximum levels of neonicotinoids of 1.9 ppb in the nectar of 6.1 ppb in the pollen of seed-treated crops, values in line with those found in an update to that review (Godfray et al. 2015). Wood and Goulson (2017) report expected residues in several crops (corn, sunflower, rape, cotton) as calculated by

[2] First, the seed treatment figures for each relevant crop that comprise the total are long-term averages (e.g. 2005 to 2013 for thiamethoxam, EPA 1/26/16), and the averages understate usage because the proportion of crop seed, and in the case of corn the rate applied, have increased steadily over that period (Douglas and Tooker 2015). Second, the private sector firm that EPA relies upon for seed treatment usage data stopped collecting it after 2014; and usage of neonicotinoids was trending steadily upward for all major crops (corn, soybeans, cotton and wheat) up until that time, and thanks to inaction on the part of EPA has almost certainly continued to increase since then (Hitaj et al. 2020).

the European Food Safety Authority based on outdoor studies and seed treatment rates authorized in the Europesn Union. Maximum expected residues in pollen ranged up to 37 ppb in corn (clothianidin); 19 ppb in oilseed rape (clothianidin and thiamethoxam); and 4 ppb in sunflower (imidacloprid). See Table 1 below. Guttation droplets (small water droplets exuded by plants) of treated plants contain four to five orders of magnitude (10,000 to 100,000 times) higher neonicotinoid concentrations than those found in nector (Girolami et al. 2009, Wood and Goulson 2017). While the potential for exposure (pollinator visitation of guttation droplets) is uncertain, a honeybee would only need to consume 0.005 ul to receive an LD_{50} dose (Wood and Goulson 2017). Thus, even infrequent visitation could cause considerable harm.

Neonicotinoids are relatively persistent in soil, and the planting of many fields every year to treated seeds (e.g. as in the common corn-soybean in the U.S., with treated seed comprising a majority of each crop) ensures a continual presence in soil (e.g. Xu et al. 2016). Various studies find single digit to 50 ppb concentrations of imidacloprid, clothianidin and/or thiamethoxam in crop fields, with detections even in fields that had not received any treatment in the previous three years (reviewed in Wood and Goulson 2017). EPA does not pay sufficient consideration to this exposure pathway, in part because it is of lesser significance for honey bees, the surrogate for terrestrial invertebrates in EPA's ecotoxicity regulatory scheme. Yet soil contact and/or ingestion is an important exposure pathway for ground-nesting bumblebees and many other terrestrial invertebrates that reside in the soil.

Table 1 Summary of expected residues in pollen and nectar of various neonicotinoid-treated flowering crops calculated by EFSA from the review of outdoor field trials

Crop	Pesticide	Application rates (g a.s./ha)	Residues in pollen (ng/g)		Residues in nectar (ng/g)	
			Minimum	Maximum	Minimum	Maximum
Oilseed rape	Clothianidin	25–80	5.95	19.04	5	16
Sunflower	Clothianidin	27		3.29		0.324
Maize	Clothianidin	25–125	7.38	36.88	*n/a*	*n/a*
Oilseed rape	Imidacloprid	10–52.5	1.56	8.19	1.59	8.35
Sunflower	Imidacloprid	24–35		3.9		1.9
Maize	Imidacloprid	54–268	3.02	15.01	*n/a*	*n/a*
Cotton	Imidacloprid	75–100	3.45	4.6	3.45	4.6
Oilseed rape	Thiamethoxam	8–33.6	4.592	19.29	0.648	2.72
Sunflower	Thiamethoxam	16.4–20.8	2.378	3.02	0.59	0.75
Maize	Thiamethoxam	63–101	13.419	21.513	*n/a*	*n/a*

No nectar values are available for maize as this plant does not produce nectar. Blanks are where no minimum values were stated

Source: Wood and Goulson (2017).

Neonicotinoids have also been detected in the tissues of off-field wild plants. For instance, Krupke et al. (2012) found thiamethoxam (up to 2.9 ppb) and clothianidin (up to 9.4 ppb) in dandelions near a treated corn seed field, while Pecenka and Lundgren (2015) found clothianidin in the leaves of milkweed plants adjacent to treated corn fields. In a field study conducted in the U.K., Botías et al. (2015) placed honey bee colonies near oilseed rape and wheat fields that originated from treated seed. Based on pollen collected in June and August from honey bee foragers returning to the hives, 97% of the total neonicotinoids present in pollen were of wildflower origin, from plants growing in hedges along the field margins.

Remarkably, direct measurements of the neonicotinoid content of pollen and nectar of these wildflowers showed concentrations of the same order as and even greater than that found in treated crops' pollen and nectar. Indeed, others have made similar findings. In a review of studies published since 2013, Wood and Goulson (2017) found:

> "… average levels of neonicotinoids in wild plants range from 1.0 to 7.2 ng/g in whole flower samples, 0.4 to 13.5 ng/g in foliage samples, <0.1 to 1.5 ng/g in nectar samples and <0.04 to 14.8 ng/g in pollen samples. Due to the limited number of studies available, it is difficult to make a comparison with levels in directly treated crop plants. However, they are broadly comparable to the levels found in the treated crop itself."

Neonicotinoids are highly water-soluble and are also frequently found in water bodies, another avenue of exposure to these long-lived compounds (Morrissey et al. 2015, Bonmatin et al. 2015, Wood and Goulson 2017).

Neonicotinoid Effects on Pollinators

A major weakness of EPA's assessment is the failure to evaluate the sublethal effects of neonicotinoids and their interactions with other factors such as disease and pest pressure.

Impacts on growth and reproduction

Whitehorn et al. (2012) simulated exposure of bumblebee colonies to concentrations of imidacloprid in pollen and sugar water realistic for seed treatment use of this neonicotinoid, and found significantly reduced growth rate in the colonies and an 85% reduction in the production of new queens compared to controls. Laycock et al. (2012) found that queenless microcolonies of worker bumble bees subjected to a range of imidacloprid doses delivered in sugar syrup exhibited a dose-dependent decline in fecundity, with realistic doses in the range of 1 ppb reducing brood production by a third. Williams et al. (2015) found that exposure of honey bee queens to field-realistic concentrations of neonicotinoids (bee-collected pollen supplements spiked with 3 ppb thiomethoxam + 1 ppb clothianidin) during development resulted in compromised ovaries and reduced queen success. Tsetkov et al. (2017) quantified the duration and magnitude of exposure to neonicotinoids over four months in Canada's corn-growing region, and then conducted realistic experiments in which honey bee colonies were exposed to clothianidin in an artificial pollen supplement with the concentration time course matching that previously observed. They found increased worker mortality, declines in social immunity (reduced hygienic behavior) and increased queenless over time. James (2019) found that monarch adults fed a field realistic rate of imidacloprid for 22 days suffered nearly 80% mortality by day 22, compared to 20% in untreated controls.

Weakened immunity

There is a large and growing literature demonstrating that neonicotinoid exposure weakens pollinators' defenses against disease pathogens and pests. Alaux et al. (2010) found that honeybees exposed to imidacloprid and the parasitic microsporidia Nosema suffered higher mortality and energetic stress than untreated bees or those exposed to only imidacloprid (IMI) or Nosema. They also found that the IMI-Nosema group had significantly reduced glucose

oxidase activity, which enables bees to sterilize colony and brood food, and hypothesize that IMI and Nosema synergize to render honeybee colonies more susceptible to infection by pathogens. Pettis et al. (2012) exposed honey bee colonies over three brood generations to sublethal doses of imidacloprid, then challenged with Nosema, which produced significantly increased infections versus controls not exposed to imidacloprid.

> "The finding that individual bees with undetectable levels of the target pesticide, after being reared in a sub-lethal pesticide environment within the colony, had higher Nosema infections is significant. Interactions between pesticides and pathogens could be a major contributor to increased mortality of honey bee colonies, including colony collapse disorder, and other pollinator declines worldwide."

Neonicotinoid exposure has also been associated with increased susceptibility to viral disease. For instance, Di Prisco et al. (2013) found that clothianidin negatively modulates NF-xB immune signaling in insects and adversely affects honey bee antiviral defenses controlled by this transcription factor. Clothianidin enhances the transcription of a gene encoding a protein that inhibits activation of NF-xB. Imidacloprid was also found to have this effect. The antiviral suppression led to proliferation of dwarf wing virus.

> "Collectively, our data demonstrate that two neonicotinoid insecticides, each representing one of two alternative structure types in the group of nitroguanidines, actively promote DWV [dwarf wing virus] replication."

A recent study on honey bees collected from a winter apiary in France tested the effects of co-exposure to thiamethoxam and the chronic bee paralysis virus (CBPV). The researchers found that co-exposure did not affect bee survival or their ability to metabolize the thiamethoxam to clothianidin; however they found that co-exposure increased CBPV loads, which reached levels usually found in overt infections, and was associated with down-regulation of vitellogenin and dorsal-1a gene transcription, both of which are involved in immune system pathways.

Sanchez-Bayo et al. (2016) review additional studies on the subject of neonicotinoid exposure and bee diseases. There is also evidence that neonicotinoids weaken plant defenses, for instance to spider mites, by suppressing the expression of plant defense compounds and altering the levels of phytohormones involved in plant defense in cotton, corn and tomato (Szczepaniec et al. 2013).

<u>Other sublethal effects</u>

Neonicotinoid exposure has also been associated with impaired learning, memory and foraging behaviors in various bee species, sublethal effects that are likely contributing to bee declines (reviewed in Wood and Goulson 2017; Godfray et al. 2014, 2015). For one of many examples, Tosi et al. (2017) found that an acute, sublethal dose of thiamethoxam (1.34 ng/bee) triggered excitation and significantly increased flight duration among foragers, while chronic exposure reduced flight duration, distance and velocity.

Neonicotinoid Effects on Other Invertebrates

Douglas et al. (2015) found that slugs feeding on neonicotinoid-treated soybean seeds/seedlings accumulated neonicotinoids in their tissues; and that ground beetles attacking these neonic-laced slugs experienced nervous system impairment, with substantial mortality. They also showed that neonicotinoids suppressed slug predation by ground beetles, and was associated with a significant yield loss relative to an untreated soybean field control. Similarly, Szczepaniec et al. (2011) found that application of imidacloprid to elm trees caused an outbreak of spider mites, an effect mediated by a reduction in the density of the mites' predators due to imidacloprid-induced mortality. Such tritrophic impacts of neonicotinoid use could well be quite common, yet are missed entirely by EPA's regulatory guideline tests. Douglas et al. (2015) also detected neonicotinoid concentrations of 54 and 279 ppb in two earthworms from a thiamethoxam-treated soybean field. While not evidently affected themselves, earthworm predators might take up neonicotinoid residues with their prey, with potential adverse effects.

Neonicotinoid impacts on vertebrates

Neonicotinoids pose a severe acute risk of mortality to birds which consume treated seeds. EPA notes that:

> "The highest risk was identified for small size birds which would need to consume less than a single treated sorghum and wheat seed to exceed the acute level of concern, while with small or medium size birds consuming cotton, sorghum, and wheat seed, a bird would only need to consume 1-4 seeds [two (cotton) or four (sorghum and wheat)] to exceed the acute level of concern." (EPA PIRRD Imidacloprid, p. 23).

Insecticides so toxic that consumption of just one or several treated seeds is sufficient to kill obviously have no place in agriculture. Birds may also be at risk through consumption of neonicotinoid-containing prey, such as slugs or earthworms. Sublethal effects must also be considered. Eng et al. (2017) found that migratory white-crowned sparrows exposed to sublethal doses of imidacloprid suffered significant declines in body fat and mass, and failed to orient properly. A follow-up experiment on the same species revealed similar imidacloprid effects: reduced food consumption, mass, fat and altered likelihood of departure when exposed at a migratory stopover (Eng et al. 2019). A recent study found that the echolocation system of Insectivorous bats might be impaired by exposure to imidacloprid (Wu et al. 2019).

Endocrine-disrupting potential of neonicotinoids

EPA has not yet made any findings regarding the endocrine disruption potential of these five neonicotinoids. Before making any determinations, EPA should consult independent studies on the subject. For instance, three recent studies suggest imidacloprid is an endocrine disruptor, with implications for both human health and wildlife (Yuan et al. 2020, Mikolic et al. 2018, Pandey and Mohanty 2015).

COSTS AND BENEFITS OF NEONICOTINOID USE

EPA as usual conducts a "benefits" rather than a "cost-benefit" assessment of neonicotinoids. Examples of costs not accounted for are the soybean yield reductions attributable to predation of treated soybean seedlings by slugs, whose populations increase thanks to release from control by ground beetles, which are poisoned when they attempt to attack them (Douglas et al. 2015). Growing resistance to neonicotinoids in thrips and other insects is predictable, given their prophylactic use, every year, across hundreds of millions of acres of cropland, and is already leading to a dramatic increase in insecticide use in cotton (Huseth et al. 2018). EPA fails to account for the follow-on costs of this resistance, both increased expenditures on insecticides and environmental harms, which are a direct result of the Agency's blanket approvals for virtually unlimited seed treatment use of neonicotinoid insecticides.

EPA also counts "benefits" in situations where it fails to consider less chemical-intensive and more beneficial alternatives. For instance, a beneficial fungus, *Hirsutella citriformis*, naturally infests and kills the psyllid vector; even better, the dead pysllids remain on citrus leaves for extended periods, spreading the fungus to other psyllids (O'Brian 2013). Another promising biocontrol predator is *Tamarixia radiata*, a parasitic wasp that specializes in killing psyllids (Lopez 2013). For both fungus and wasp, pesticide use for other purposes is an obstacle to their effectiveness. Another neonicotinoid use is for control of the glass-winged sharpshooter, an insect that pierces plants and feeds on their xylem fluids, but which also vectors a plant pathogenic bacterium, Xylella fastidiosa, that infests grapes and other valuable crops in California. Biocontrol options also exist for this pest, but will likely not be pursued diligently as long as there is the easy option of neonicotinoid application (Irvin undated). This failure to develop biocontrol solutions is a clear cost of the neonicotinoid registrations.

On the other hand, the predominant seed treatment use of neonicotinoids provide little or no benefit in terms of yield. EPA itself came to this conclusion for soybeans (EPA 10/15/14), which was recently confirmed by a long list of agronomists from universities across the country (Mourtzinis et al. 2019). A study in Indiana found the same "no yield benefit" of neonicotinoid seed treatments for corn (Krupke et al. 2017).

OTHER REGULATORS SEE AND ACT ON RISKS THAT EPA DISCOUNTS

Canada's Pest Management Regulatory Agency (PMRA) – hardly an enemy of pesticide use – has worked jointly with EPA on assessing neonicotinoids (EPA 1/6/16). On the basis of much the same evidence as EPA, PMRA decided the risks were too great, especially to aquatic invertebrates, and possible mitigation measures ineffective. Despite delays, PMRA is still officially committed to a phase-out. In 2018, the European Food Safety Authority expanded a pre-existing restriction on neonicotinoids to cover all field crops (Stokstad 2018). EPA is thus alone in denying the overwhelming evidence of harm caused by neonicotinoid insecticides to pollinators and other wildlife.

CONCLUSION

EPA is urged to cancel the registrations of the five neonicotinoid insecticides discussed in these comments. At the very least, suspend the use of imidacloprid, thiamethoxam and imidacloprid as seed treatments, particularly for high acreage crops like corn and soybeans.

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References

Alaux, C., J.L. Brunet, C. Dussaubat, F. Mondet, S. Tchamitchan, M. Cousin, J. Brillard, A. Baldy, L.P. Belzunces, Y. Le Conte. 2010. Interactions between Nosema microspores and a neonicotinoid weaken honeybees (Apis mellifera). Environmental Microbiology 12(3): 774-782.

Arnason R (2013). No yield benefit from neonicotinoids: scientist. The Western Producer, May 10, 2013. https://www.producer.com/2013/05/no-yield-benefit-from-neonicotinoids-scientist/.

Bonmatin JM et al. (2015). Environmental fate and exposure; neonicotinoids and fipronil. Environ. Sci. Pollut. Res. 22: 35-67.

Botías C, David A, Horwood J, Abdul-Sada A, Nicholls E, Hill E, Goulson D (2015) Neonicotinoid residues in wildflowers, a poten- tial route of chronic exposure for bees. Environ Sci Technol 49: 12731–12740.

Burke AP et al. (2018). Mammalian Susceptibility to a Neonicotinoid Insecticide after Fetal and Early Postnatal Exposure. Scientific Reports 8: 16639.

Chen J et al. (2018). Are organosilicon surfactants safe for bees or humans? Science of the Total Environment 612: 415-421.

Chen XD et al. (2010). Mixture effects of the nonylphenyl polyethoxylate, R-11 and the insecticide, imidacloprid on population growth rate and other parameters of the crustacean, *Ceriodaphnia dubia*. Ecotoxicology and Environmental Safety 73: 132-137.

Coulon et al. (2019). Influence of chronic exposure to thiamethoxam and chronic bee paralysis virus on winter honey bees. PLoS One 14(8): e0220703.

Cross, A.; Bond, C.; Buhl, K.; Jenkins, J. (2017). Piperonyl Butoxide General Fact Sheet; National Pesticide Information Center, Oregon State University Extension Services. npic.orst.edu/factsheets/pbogen.html.

Di Prisco et al. (2013). Neonicotinoid clothianidin adversely affects insect immunity and promotes replication of a viral pathogen in honey bees. PNAS 110(46): 18466-71.

Douglas MR et al. (2020). County-level analysis revealsa rapidly shifting landscape of insecticide hazard to honey bees. Scientific Reports 10: 797.

Douglas MR & Tooker JF (2015) Large-scale deployment of seed treatments has driven rapid increase in use of neonicotinoid insecticides and preemptive pest management in US field crops. Environmental Science & Technology 49(8): 5088-5097.

Douglas MR, Rohr JR, Tooker JF (2015). Neonicotinoid insecticide travels through a soil food chain, disrupting biological control of non-target pests and decreasing soya bean yield. J Appl Ecol 52: 250–260.

Eng ML et al. (2019). A neonicotinoid insecticide reduces fueling and delays migration in songbirds. Science365: 1177-80.

Eng ML et al. (2017). Imidacloprid and chlorpyrifos insecticides impair migratory ability in a seed-eating songbird. Scientific Reports 7: 15176.

EPA (12/15/17). Acetamiprid: Draft Human Health Risk Assessment for Registration Review, DP Barcode D441937, EPA-HQ-OPP-2012-0329-0025, EPA, December 15, 2017.

EPA (12/5/17). Thiamethoxam: Draft Human Health Risk Assessment for Registration Review, DP Barcode D439309, EPA-HQ-OPP-2011-0581-0096, EPA, December 5, 2017.

EPA (9/12/17). Dinetofuran: Human Health Draft Risk Assessment for Registration Review, DP Barcode D436969, EPA-HQ-OPP-2011-0920-0620, EPA, Sept. 12, 2017.

EPA (9/7/17). Clothianidin: Draft Human Health Risk Assessment in Support of Registration Review, DP Barcode D439294, EPA-HQ-OPP-2011-0865-0243, EPA 9/7/17.

EPA (6/22/17). Imidacloprid: Human Health Draft Risk Assessment for Registration Review. EPA, June 22, 2017.

EPA (1/16/20). Response from the Pesticide Re-evaluation Division to Comments on the Draft Risk Assessments and Benefits Assessments Supporting the Registration Review of the

Nitroguanidine-substituted Neonicotinoid Insecticides. EPA-HQ-OPP-2008-0844-1639, EPA, January 16, 2020.

EPA (6/22/17). Imidacloprid: Human Health Draft Risk Assessment for Registration Review, DP Barcode D437947, EPA-HQ-OPP-2008-0844-1235, EPA, June 22, 2017.

EPA Imidacloprid (2020). Imidacloprid: Proposed Interim Registration Review Decision Case, Number 7605, EPA, January 2020.

EPA (2002). Determination of the appropriate FQPA safety factor(s) in tolerance assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency, February 22, 2002.

Godfray HCJ et al. (2015). A restatement of recent advances in the natural science evidence base concerning neonicotinoid insecticides and insect pollinators. Proceedings of the Royal Society B 282: 20151821.

Godfray HCJ et al. (2014). A restatement of the natural science evidence base concerning neonicotinoid insecticides and insect pollinators. Proceedings of the Royal Society B 281: 20140558.

Hitaj C et al. (2020). Sowing Uncertainty: What We Do and Don't Know about the Planting of Pesticide-Treated Seed. BioScience biaa019, https://doi.org/10.1093/biosci/biaa019

Huseth AS et al. (2018). Insecticide Resistance Signals Negative Consequences of Widespread Neonicotinoid Use on Multiple Field Crops in the U.S. Cotton Belt. Environ. Sci. Technol. 52 (4): 2314-2322.

Irvin N (undated). Biological control of the glassy-winged sharpshooter (*Homalodisca vitripennis*) in California. Applied Biological Control Laboratory, University of California, Riverside. https://biocontrol.ucr.edu/irvin/gwssbiocontrol.html.

James DG (2019). A Neonicotinoid Insecticide at a Rate Found in Nectar Reduces Longevity but Not Oogenesis in Monarch Butterflies, Danaus plexippus (L.). (Lepidoptera: Nymphalidae). Insects 10: 276.

Kara M et al. (2015). Insecticide imidacloprid influences cognitive functions and alters learning performance and related gene expression in a rat model. International Journal of Experimental Pathology 96: 332-337.

Krupke CH et al. (2017). Planting of neonicotinoid-treated maize poses risks for honey bees and other non-target organisms over a wide area without consistent crop yield benefit. Journal of Applied Ecology 54: 1449-58.

Krupke CH et al. (2012). Multiple Routes of Pesticide Exposure for Honey Bees Living Near Agricultural Fields. PLoS One 7(1): e29268.

Laycock I, Lenthall KM, Barratt AT, Cresswell JE (2012) Effects of imidacloprid, a neonicotinoid pesticide, on reproduction in worker bumble bees (Bombus terrestris). Ecotoxicology 21: 1937–1945.

Lopez R (2013). Citrus growers use predator wasp to fight disease threat. Los Angeles Times, August 3, 2013. https://www.latimes.com/business/la-fi-predator-wasp-20130804-dto-htmlstory.html.

Lu C et al. (2018). Neonicotinoid Residues in Fruits and Vegetables: An Integrated Dietary Exposure Assessment Approach. Environ. Sci. Tech. 52(5): 3175-84.

Maloney EM et al. (2018). Can chronic exposure to imidacloprid, clothianidin, and thiamethoxam mixtures exert greater than additive toxicity in *Chironomus dilutus*? Ecotoxicology and Environmental Safety 156: 354-365.

Mikolić, A. and Karačonji, I.B. (2018). Imidacloprid as reproductive toxicant and endocrine disruptor: investigations in laboratory animals. Archives of Industrial Hygiene and Toxicology 69(2): 103-108.

Morrissey CA et al. (2015). Neonicotinoid contamination of global surface waters and associated risk to aquatic invertebrates: A review. Environment International 74: 291-303.

Mourtzinis S et al. (2019). Neonicotinoid seed treatments of soybean provide negligible benefits to US farmers. Scientific Reports 9: 11207.

Mullin CA (2015). Effects of 'inactive' ingredients on bees. Curren Opinion in Insect Science 10: 194-200.

O'Brian D (2013). Helping Citrus Growers Deal With a Nasty Invader. Agricultural Research, USDA's Agricultural Research Service, January 2013. https://agresearchmag.ars.usda.gov/2013/jan/citrus.

Pandey, S.P. and Mohanty, B. (2015). The neonicotinoid pesticide imidacloprid and the dithiocarbamate fungicide mancozeb disrupt the pituitary–thyroid axis of a wildlife bird. Chemosphere 122: 227-234.

Pecenka JR and Lundgren JG (2015). Non-target effects of clothianidin on monarch butterflies. Naturwissenschaften 102(3-4): 19.

Pettis, JS et al (2012). Pesticide exposure in honey bees results in increased levels of the gut pathogen Nosema. Naturwissenschaften 99: 153-158.

Sanchez-Bayo and Wyckhuys (2019). Worldwide decline of the entomofauna: A review of its drivers. Biological Conservation 232: 8-27.

Sánchez-Bayo F, Goulson D, Pennacchio F, Nazzi F, Goka K, Desneux N (2016). Are bee diseases linked to pesticides? A brief review. Environ Int 89-90: 7–11

Sanchez-Bayo and Goka (2014). Pesticide Residues and Bees – A Risk Assessment. PLoS One 9(4): e94482.

Sgolastra F et al. (2016). Synergistic mortality between a neonicotinoid insecticide and an ergosterol-biosynthesis-inhibiting fungicide in three bee species.

Simon-Delso N et al. (2015). Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites. Environ Sci Pollut Res 22: 5-34.

Staskal, D. F.; Birnbaum, L. S.; Haws, L. C. Application of a relative potency factor approach in the assessment of health risks associated with exposure to mixtures of dioxin-like compounds. Princ. Pract. Mixtures Toxicol. 2010, 67–97.

Stokstad E (2018). European Union expands ban of three neonicotinoid pesticides. Science, April 27, 2018. https://www.sciencemag.org/news/2018/04/european-union-expands-ban-three-neonicotinoid-pesticides.

Szczepaniec A et al. (2013). Neonicotinoid Insecticides Alter Induced Defenses and Increase Susceptibility to Spider Mites in Distantly Related Crop Plants. PLoS One 8(5): e2620.

Szczepaniec A et al. (2011). Neonicotinoid Insecticide Imidacloprid Causes Outbreaks of Spider Mites on Elm Trees in Urban Landscapes. PLoS One 6(5): e20018.

Thompson HM, Fryday SL, Harkin S, Milner S. (2014). Potential impacts of synergism in honeybees (*Apis mellifera*) of exposure to neonicotinoids and sprayed fungicides in crops. Apidologie 45(5):545-553.

Tomizawa M and Casida JE (2005). Neonicotinoid Insecticide Toxicology: Mechanisms of Selective Action. Annu. Rev. Pharmacol. Toxicol. 45: 247-68.

Tosi S et al. (2017). A common neonicotinoid pesticide, thiamethoxam, impairs honey bee ight ability. Scientific Reports 7: 1201.

Tsvetkov N et al. (2017). Chronic exposure to neonicotinoids reduces honey bee health near corn crops. Science 356: 1395-97.

Van Klink et al. (2020). Meta-analysis reveals declines in terrestrial but increases in freshwater insect abundances. Science 368: 417-20.

Wood TJ and Goulson D (2017). The environmental risks of neonicotinoid pesticides: a review of the evidence post 2013. Environ. Sci. Pollut. Res. 24: 17285-325.

Xerces (2016). Recommendations to Protect Pollinators from Neonicotinoids: Suggestions for Policy Solutions, Risk Assessment, Research and Mitigation. Xerces Society for Invertebrate Conservation, November 2016. https://xerces.org/sites/default/files/2018-05/NeonicsBeeRecommendations_XercesSociety.pdf.

Xu T et al. (2016). Clothianidin in agricultural soils and uptake into corn pollen and canola nectar after multiyear seed treatment applications. Environmental Toxicology and Chemistry 35(2): 311-321.

Whitehorn PR, O'Connor S, Wackers FL, Goulson D (2012) Neonicotinoid pesticide reduces bumble bee colony growth and queen production. Science 336: 351–352.

Williams GR et al. (2015). Neonicotinoid pesticides severely affect honey bee queens. Scientific Reports 5: 14621.

Wu C-H et al. (2019). Effects of imidacloprid, a neonicotinoid insecticide, on the echolocation system of insectivorous bats. Pesticide Biochemistry and Physiology 163: 94-101.

Yuan, X., Shen, J., Zhang, X., Tu, W., Fu, Z. and Jin, Y. (2020). Imidacloprid disrupts the endocrine system by interacting with androgen receptor in male mice. Science of The Total Environment 708: 135163.

Zhang Q et al. (2019). Dietary risk of neonicotinoid insecticides through fruit and vegetable consumption in school-age children. Environment International 126: 672-681.

Zhu et al. (2017). Synergistic toxicity and physiological impact of imidacloprid alone and binary mixtures with seven representative pesticides on honey bee (Apis mellifera). PLoS One 12(5): e0176837.

July 24, 2017

Comments from Center for Food Safety on the
EPA's Preliminary Pollinator Assessment to
Support the Registration Reviews of Clothianidin and Thiamethoxam, dated Jan. 5, 2017

Clothianidin Docket ID: EPA-HQ-OPP-2011-0865
Clothianidin Document ID: ID: EPA-HQ-OPP-2011-0865
Thiamethoxam Docket ID: EPA-HQ-OPP-2011-0581
Thiamethoxam Document ID: EPA-HQ-OPP-2011-0581-0034

We are pleased to submit this comment on the above-referenced docket on behalf of Center for Food Safety. Center for Food Safety (CFS) is a non-profit membership organization that works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and sustainable agriculture. Our membership has rapidly grown to include over 900,000 people across the country that support organic food and farming, grow organic food, and regularly purchase organic products. CFS and its members are concerned about the impacts of pesticides on biodiversity generally, and on honey bees and other pollinators specifically.

INITIAL COMMENTS:

Unacceptable Delays in the Registration Review Process

The Registration Review process for both of these compounds is behind the schedule to which the agency formally committed. In 2015, EPA announced it would expedite the Registration Reviews for clothianidin and thiamethoxam stating it would complete these initial Risk Assessments by 2016.[1] That did not occur until 2017 and now, with the long delays in opening this public comment period, the commitment to complete all of the Risk Assessments this year has been undone and pushed to 2018.[2] EPA must expedite completion of this process.

Noncompliance with the Endangered Species Act

EPA fails to include any Endangered Species Act (ESA) analysis or compliance despite the existence of endangered and threatened bee species. Illustrative examples of ESA-listed non-*Apis* bees, include: the rusty patched bumble bee (*Bombus affinis*) and seven yellow-faced bees (*Hylaeus anthracinus, H. assimulans, H. facilis, H. hilaris, H. kuakea, H. longiceps, and H. mana*).

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[1] White House Pollinator Health Task Force, National Strategy To Promote The Health Of Honey Bees And Other Pollinators May 19, 2015 https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/Pollinator%20Health%20Strategy%202015.pdf ; Appendix A. U.S. Environmental Protection Agency Pollinator Protection Plan https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/Pollinator-Strategy%20Appendices%202015.pdf.

[2] https://www.epa.gov/pollinator-protection/schedule-review-neonicotinoid-pesticides

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It is essential that EPA act contemporaneously in this Registration Review risk analysis process to also include thorough analyses of foreseeable effects to ESA-listed bee species now. Under the ESA implementing regulation, 50 C.F.R. § 402.14(a), agencies must review their actions at the "earliest possible time". EPA must not delay this ESA-mandated review or else it will be in violation of the law.[3]

FURTHER COMMENTS:

I. The whole colony study underlying the Clothianidin Preliminary Pollinator Assessment was inadequate

a) The Bayer clothianidin Colony Feeding Study submitted in support of the Assessment is not robust, as it was based on just one North Carolina test area over a winter with very high mortality in almost all hives (treated and control) (p. 146). The very high mortality indicates the experiment followed substandard beekeeping practices that should not be accepted by EPA for this critical study. The goal of robust findings regarding possible overwintering chronic effects was defeated by the abnormally high mortality in the control hives that masked possible comparative effects in the treated hives that may appear under more typical overwintering mortality (see p. 12, where the PARA recognizes this).
b) The exposure model excluded any consideration of effects from exposure to pollen and contaminated dust, air, guttation fluid or marginal vegetation to which honey bees are normally exposed. Thus, the exposure model was unrealistic.
c) There is no accounting for any other synergistic effects to which honey bees are normally exposed. Single active ingredients were used, whereas in field exposures synergized mixes are the rule. The revelations of synergistic effects related to several specific clothianidin products should be addressed in the whole colony study for clothianidin.
d) The experiment length was inadequate. It was too short to detect chronic effects that weaken bee colonies. Honey bee experts generally agree that a study for less than one year is inadequate to detect chronic effects.
e) The feeding regime only lasted 6 weeks (from June to August), which is not long enough to assess bees' normal foraging activities in North Carolina, where bees likely could forage from March to October.
f) The researchers did not describe post-mortem observations for the dead hives in detail. When a dead hive was observed, were dead bees found at the bottom of the hive - or did they simply disappear? It is critical to differentiate hives that died from exposure from hives that may have died from other causes, such as Varroa mite. The report did not adequately mention Varroa mite baseline data to be able to assess whether the mites contributed to hive mortalities.
g) The study lacked analysis of chronic effects on queens. As the only fertile females in the hive, effects on queens are critical to understanding viability and productivity of the colony. Queens should have been marked and egg production should have been measured, as well as long-term brood viability. Supersedure of the queen by neonicotinoid stressors and other related effects are now well-documented in several studies published in 2016. However, those effects were not addressed in this study.
h) Finally, the whole colony feeding study suggests a NOAEL of 20 ppb. EPA should review other studies and incident reports that have indicated some clothianidin crop applications result in exposures that exceed that NOAEL. If the Bayer Clothianidin study were to be accepted as valid

[3] The scope of agency actions triggering Section 7 duties is broad, including all activities or programs of any kind authorized, licensed, funded, or carried out by federal agencies, including activities directly or indirectly causing modifications to land, water, or air. 50 C.F.R. § 402.02 (definition of "action"). The potential "effects" of an action that an agency must consider are similarly broad, and include both "direct" and "indirect" effects of the action and all activities "interrelated or interdependent" with that action. Id.

notwithstanding all of the defects outlined above, its findings would indicate that this active ingredient poses unacceptable risks to honey bees in those crop applications. Product registrations allowing those applications should be suspended.

II. The whole colony study underlying the Thiamethoxam Preliminary Pollinator Assessment was inadequate

a) The Syngenta thiamethoxam Colony Feeding Study is not robust, as the findings are based on just one North Carolina test area over a winter with extreme mortality in almost all hives (treated and control). The extreme mortality in almost all hives indicates the experiment followed substandard beekeeping practices that should not be accepted by EPA for this critical study (pp. 163-164).
b) The exposure model excluded any consideration of effects from exposure to pollen and contaminated dust, air, guttation fluid or marginal vegetation to which honey bees are normally exposed. Thus, the exposure model was unrealistic.
c) As with the Bayer clothianidin study, there is no accounting for any synergistic effects to which honey bees are normally exposed. The comment on synergy information that EPA should consider in our comment (c), above, also applies to the Syngenta thiamethoxam study.
d) The experiment length was inadequate. It was too short to detect chronic effects that weaken bee colonies. Honey bee experts generally agree that a study for less than one year is inadequate to detect chronic effects.
e) The feeding regime only lasted 6 weeks (from June through July), which is not long enough to cover bees' normal foraging activities in North Carolina, where bees likely could forage from March to October.
f) The researchers did not describe post-mortem observations for the dead hives in detail. When a dead hive was observed, were dead bees found at the bottom of the hive - or did they simply disappear? It is critical to differentiate hives that died from exposure from hives that may have died from other causes, such as Varroa mite. The report did not adequately mention Varroa mite baseline data to be able to assess whether the mites contributed to colony mortalities.
g) As noted above, for clothianidin, the thiamethoxam study also lacked analysis of chronic effects on queens. Those effects should be addressed.

III. The PPA fails to adequately assess risks to bees from field-realistic exposure

a) The PPA revision should consider critical new published research on the risks of clothianidin and thiamethoxam to honey bees and other pollinators, such as:
    - Woodcock et al., "Country-specific effects of neonicotinoid pesticides on honey bees and wild bees"[4]

        This study evaluated the impacts of neonicotinoid seed coatings on bees using field-realistic exposure levels. The findings confirm what previous studies have also indicated: field exposure to neonicotinoids adversely impacts honey bees, bumble bees, and solitary bees. This is the largest scale field study conducted thus far on the impacts of neonicotinoids and EPA must consider the findings of this research in its final risk assessment.
    - Tsvetkov et al., "Chronic exposure to neonicotinoids reduces honey bee health near corn crops"[5]

        This study indicated that uses of neonicotinoids on corn increased worker mortality and were associated with declines in social immunity and increased

[4] Woodcock, B. A., et al. (2017). Country-specific effects of neonicotinoid pesticides on honey bees and wild bees. *Science, 356*(6345), 1393-1395. http://dx.doi.org/10.1126/science.aaa1190
[5] Tsvetkov, N., et al. (2017). Country-specific effects of neonicotinoid pesticides on honey bees and wild bees. *Science, 356*(6345), 1393-1395. http://dx.doi.org/10.1126/science.aaa1190

queenlessness over time. The researchers also noted the harmful synergistic effects when neonicotinoids are used in combination with other pesticides, notably fungicides. Specifically, the authors found that the acute toxicity of neonicotinoids to honey bees doubled when bees were also exposed to field-realistic levels of the fungicide boscalid.

This research adds to the wealth of existing research indicating that field-realistic exposure to neonicotinoids in or around corn fields can reduce honey bee health. EPA must consider these synergistic impacts in its final risk assessment.

- Krupke et al., "Planting of neonicotinoid-treated maize poses risks for honey bees and other non-target organisms over a wide area without consistent crop yield benefit"[6]

  Researchers measured neonicotinoid dust drift (including for clothianidin and thiamethoxam) during the planting of neonicotinoid-coated corn seeds and found significant risks to honey bees and other non-target organisms over a wide area. Perhaps most alarming, the researchers found that over 94 percent of foraging honey bees throughout the state of Indiana are at risk of exposure to varying levels of neonicotinoid insecticides, including lethal levels, during the planting of neonicotinoid-coated corn seeds. Notably, the researchers also found no benefit of the neonicotinoid seed coatings for crop yield during the study.
- Alford et al., "Translocation of the neonicotinoid seed treatment clothianidin in maize"[7]

  Alford and Krupke conducted a two-year field trial to evaluate concentrations of clothianidin in corn root tissues several weeks after the clothianidin-coated seeds were planted. While their findings suggest the clothianidin seed coatings may provide protection from some early season secondary corn pests, the actual amount of clothianidin that was taken up into the majority of plant tissues throughout the growing season was low overall. These results confirm previous reports that benefits from neonic seed coatings with corn, soybeans, and other crops are inconsistent at best.

b) The PPA also fails to consider additional extensive published research on risks of clothianidin and thiamethoxam to honey bees and other pollinators, including, but not limited to:
   - Baron et al., "General and species-specific impacts of a neonicotinoid insecticide on the ovary development and feeding of wild bumblebee queens"[8]
   - Botías et al, "Quantifying exposure of wild bumblebees to mixtures of agrochemicals in agricultural and urban landscapes"[9]
   - Dance et al., "The combined effects of a monotonous diet and exposure to thiamethoxam on the performance of bumblebee micro-colonies"[10]
   - Fauser et al., "Neonicotinoids override a parasite exposure impact on hibernation success of a key bumblebee pollinator"[11]

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[6] Krupke, C.H., Holland, J.D., Long, E.Y., Eitzer, B.D. (2017). Planting of neonicotinoid-treated maize poses risks for honey bees and other non-target organisms over a wide area without consistent crop yield benefit. *Journal of Applied Ecology.* doi: 10.1111/1365-2664.12924

[7] Alford, A., & Krupke, C.H. (2017). Translocation of the neonicotinoid seed treatment clothianidin in maize. *PLoS ONE, 12*(3). https://doi.org/10.1371/journal.pone.0173836

[8] Baron, G.L., Raine, N.E., & Brown, M.J.F. (2017). General and species-specific impacts of a neonicotinoid insecticide on the ovary development and feeding of wild bumblebee queens. *Proceedings Biological Sciences, 284*(1854). http://doi.org/10.1098/rspb.2017.0123

[9] Botias, C., David, A., Hill, E. M., & Goulson, D. (2017). Quantifying exposure of wild bumblebees to mixtures of agrochemicals in agricultural and urban landscapes. *Environmental Pollution, 222*, 73-82. https://doi.org/10.1016/j.envpol.2017.01.001

[10] Dance, C., Botías, C., & Goulson, D. (2017). The combined effects of a monotonous diet and exposure to thiamethoxam on the performance of bumblebee micro-colonies. *Ecotoxicology and Environmental Safety, 139,* 194-201. http://doi.org/10.1016/j.ecoenv.2017.01.041

- Friol et al, "Can the exposure of Apis mellifera (Hymenoptera, Apiadae) larvae to a field concentration of thiamethoxam affect newly emerged bees?"[12]
- Hernández López et al., "Sublethal pesticide doses negatively affect survival and the cellular responses in American foulbrood-infected honeybee larvae"[13]
- Lentola et al., "Ornamental plants on sale to the public are a significant source of pesticide residues with implications for the health of pollinating insects"[14]
- Mogren et al., "Neonicotinoid-contaminated pollinator strips adjacent to cropland reduce honey bee nutritional status"[15]
- Rinkevich et al., "Influence of Varroa Mite (Varroa destructor) Management Practices on Insecticide Sensitivity in the Honey Bee (Apis mellifera)"[16]
- Samuelson et al., "Effect of acute pesticide exposure on bee spatial working memory using an analogue of the radial-arm maze"[17]
- Sgolastra et al., "Synergistic mortality between a neonicotinoid insecticide and an ergosterol-biosynthesis-inhibiting fungicide in three bee species"[18]
- Silvina et al., "Neonicotinoids transference from the field to the hive by honey bees: Towards a pesticide residues biomonitor"[19]
- Simmons et al., "Chronic exposure to a neonicotinoid increases expression of antimicrobial peptide genes in the bumblebee Bombus impatiens"[20]
- Spurgeon et al., "Chronic oral lethal and sub-lethal toxicities of different binary mixtures of pesticides and contaminants in bees (Apis mellifera, Osmia bicornis and Bombus terrestris)"[21]
- Stoner, "Current Pesticide Risk Assessment Protocols Do Not Adequately Address Differences between Honey Bees (Apis mellifera) and Bumble Bees (Bombus spp.)[22]
- Tosi et al., "Effects of a neonicotinoid pesticide on thermoregulation of African honey bees (Apis mellifera scutellata)"[23]

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[11] Fauser, A., Sandrock, C., Neumann, P., & Sadd, B. M. (2017). Neonicotinoids override a parasite exposure impact on hibernation success of a key bumblebee pollinator. *Ecological Entomology, 42*(3), 306-314. http://doi.org/10.1111/een.12385

[12] Friol, P., Catae, A., Tavares, D., Malaspina, O., & Roat, T. (2017). Can the exposure of Apis mellifera (Hymenoptera, Apiadae) larvae to a field concentration of thiamethoxam affect newly emerged bees? *Chemosphere, 185, 56-66*. http://dx.doi.org/10.1016/j.chemosphere.2017.06.113

[13] Hernández López, J., et al. (2017). Sublethal pesticide doses negatively affect survival and the cellular responses in American foulbrood-infected honeybee larvae. *Scientific Reports, 7*. http://doi.org/10.1038/srep40853

[14] Lentola, A., et al. (2017). Ornamental plants on sale to the public are a significant source of pesticide residues with implications for the health of pollinating insects. https://doi.org/10.1016/j.envpol.2017.03.084

[15] Mogren, C. L., & Lundgren, J. G. (2016). Neonicotinoid-contaminated pollinator strips adjacent to cropland reduce honey bee nutritional status. *Scientific Reports, 6,* 1-10. http://doi.org/10.1038/srep29608

[16] Rinkevich, F. D., Danka, R. G., & Healy, K. B. (2017). Influence of Varroa Mite (*Varroa destructor*) Management Practices on Insecticide Sensitivity in the Honey Bee (*Apis mellifera*). *Insects, 8*(1), 1-12. https://doi.org/10.3390/insects8010009

[17] Samuelson, E. E., Chen-Wishart, Z. P., Gill, R. J., Leadbeater, E. (2016). Effect of acute pesticide exposure on bee spatial working memory using an analogue of the radial-arm maze. *Scientific Reports, 6,* 1-11. http://doi.org/10.1038/srep38957

[18] Sgolastra, F., et al. (2016). Synergistic mortality between a neonicotinoid insecticide and an ergosterol-biosynthesis-inhibiting fungicide in three bee species. *Pest Management Science, 73*(6), 1236-1243. http://doi.org/10.1002/ps.4449

[19] Silvina, N., et al. (2017). Neonicotinoids transference from the field to the hive by honey bees: Towards a pesticide residues biomonitor. *Science of the Total Environment, 581-582*, 25-31. https://doi.org/10.1016/j.scitotenv.2017.01.011

[20] Simmons, W.R., & Angelini, D.R. (2017). Chronic exposure to a neonicotinoid increases expression of antimicrobial peptide genes in the bumblebee *Bombus impatiens*. *Scientific Reports, 7* (44773). http://doi.org/10.1038/srep44773

[21] Spurgeon, D., et al. (2016). Chronic oral lethal and sub-lethal toxicities of different binary mixtures of pesticides and contaminants in bees (*Apis mellifera, Osmia bicornis* and *Bombus terrestris*). *Centre for Ecology & Hydrology,* 1-66. http://doi.org/10.2903/sp.efsa.2016.EN-1076

[22] Stoner, A. (2016). Current Pesticide Risk Assessment Protocols Do Not Adequately Address Differences between Honey Bees (*Apis mellifera*) and Bumble Bees (*Bombus* spp.). *Fronteirs in Environmental Science, 4*(79). http://doi.org/10.3389/fenvs.2016.00079

- Wessler et al., "Non-neuronal acetylcholine involved in reproduction in mammals and honeybees"[24]
- Yasuda et al., "Insecticide Susceptibility in Asian Honey Bees (Apis cerana (Hymenoptera: Apidae)) and Implications for Wild Honey Bees in Asia"[25]

c) We note initially that the PPA's admitted focus on **agricultural uses only** (p. 6), to the exclusion of **approved residential, ornamental, landscaping, tree/forest, structural, and other uses** of clothianidin and thiamethoxam, is highly unfortunate. Those uses are extremely important in some risk scenarios and must be addressed in conjunction with the agricultural uses in order to gather the whole risk picture clothianidin and thiamethoxam present.

d) Other routes of exposure (e.g. soil, surface water, guttation) were not quantitatively considered in the risk assessment even though EPA acknowledges that these routes are potential sources of exposure (p. 7).

e) These points in the Executive Summary (p. 7) indicate that the conclusions are not representative of the real world of risks to honey bees and other pollinators:

> *Exposure Considerations*
>
> *Exposure of bees through direct contact by foliar spray of clothianidin and thiamethoxam (i.e., interception of spray droplets either on or off the treated field) and oral ingestion (e.g., consumption of residues in pollen and/or nectar) represent the primary routes of exposure considered in this assessment. Bees may also be exposed to clothianidin and thiamethoxam through other routes, such as contaminated surface water, plant guttation fluids, honey dew, soil (for ground-nesting bees), and leaves. However, the Agency lacks information to understand the relative importance of these other routes of exposure and/or to quantify potential risks from these other routes, and as such, they are not quantitatively assessed. Exposure of bees to clothianidin and thiamethoxam via drift of abraded seed coat dust, is considered a route of concern given that bee kill incidents have been associated with planting of clothianidin- or thiamethoxam-treated corn.*

That paragraph indicates that PPA's reliability is undercut by its major omissions. The last sentence in particular discounts and avoids an exposure pathway known to have killed or severely weakened tens of thousands of U.S., Canadian, and European bee colonies. Dust and soil contamination not only leads to acute bee kills but also creates chronic contamination through fields and marginal vegetation (weed, wildflowers, clover, willows, and so on) to which bees are attracted. For further explication, see these studies, none of which the PPA cites. All need to be cited and addressed in the revised final PPA:

- Alford et al., "Translocation of the neonicotinoid seed treatment clothianidin in maize"[26]

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[23] Tosi, S., et al. (2016). Effects of a neonicotinoid pesticide on thermoregulation of African honey bees (Apis mellifera scutellata). *Journal of Insect Physiology.* http://doi.org/10.1016/j.jinsphys.2016.08.010

[24] Wessler, I. K., & Kirkpatrick, C. J. (2017). Non-neuronal acetylcholine involved in reproduction in mammals and honeybees. *Journal of neurochemistry.* http://doi.org/10.1111/jnc.13953

[25] Yasuda, M., Sakamoto, Y., Goka, K., Nagamitsu, T., & Taki, H. (2017). Insecticide Susceptibility in Asian Honey Bees (Apis cerana (Hymenoptera: Apidae)) and Implications for Wild Honey Bees in Asia. *Journal of economic entomology, 110*(2). http://doi.org/10.1093/jee/tox032

[26] Alford, 2017.

- Botías et al, "Quantifying exposure of wild bumblebees to mixtures of agrochemicals in agricultural and urban landscapes"[27]
- Botias et al. 2015. "Neonicotinoid residues in wildflowers, a potential route of chronic exposure for bees"[28]
- David et al. 2016. "Widespread contamination of wildflower and bee-collected pollen with complex mixtures of neonicotinoids and fungicides commonly applied to crops"[29]
- Limay-Rios et al. 2015. "Neonicotinoid insecticide residues in soil dust and associated parent soil in fields with a history of seed treatment use on crops in southwestern Ontario"[30]
- Mogren et al., "Neonicotinoid-contaminated pollinator strips adjacent to cropland reduce honey bee nutritional status"[31]

f) The dust-off pathway must be addressed as quantitatively as feasible for the PPA to be an adequate risk assessment, as stated in the EPA's own "Guidance for Assessing Pesticide Risks to Bees*"* (2014). The PPA's failure to do that is mystifying, in light of the effects and the agency guidance. In particular, the PPA's proposal to address risks from neonicotinoid seed coatings through best management practices with industry stakeholders is woefully inadequate. This plan is not described nor is it mandated by EPA in any enforceable way. Hoping that farmers and the seed industry will follow voluntary "best management practices" is not realistic risk mitigation.

g) The assertion that the agency is working on non-mandatory best management practices (BMPs) to address dust-off is evasive. EPA has reiterated that evasion since at least 2013, claiming new technologies will address the risk. To date that has not been the case; there is no mandatory implementation of such technologies—and virtually no voluntary implementation is apparent. The fact that EPA has exempted the clothianidin and thiamethoxam-coated seeds from registration as pesticides under FIFRA (per EPA's past unexplained interpretations) and that clothianidin and thiamethoxam-coated seeds are not subject to mandatory labels or enforcement, are clear obstacles to EPA mandating any effective solution to that risk. EPA needs a clear regulatory path to making dust reduction technologies compulsory, or else it must stop approving the seed coating uses. At minimum, the final risk assessment must fully address the risks.

h) The list of uncertainties beginning on p. 343 is concerning and further indicates that the risk assessment lacks reliability. In particular, the points about "low exposure levels" (p. 346), copied below, undermine the analysis:
   - *Due to low exposures that are below effect levels for honey bees (either at the individual-level or the colony-level), seed treatments of clothianidin or thiamethoxam on canola, corn, cotton, pumpkin, soybean and sunflower are anticipated to pose a low risk for on-field exposures.*

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[27] Botías, C., David, A., Hill, E.M., & Goulson, D. (2017). Quantifying exposure of wild bumblebees to mixtures of agrochemicals in agricultural and urban landscapes. *Environmental Pollution*, *222,* 73-82. https://doi.org/10.1016/j.envpol.2017.01.001

[28] Botías, C, David, A., Horwood, J., Abdul-Sada, A., Nicholls, E., Hill, E., & Goulson, D. (2015). Neonicotinoid residues in wildflowers, a potential route of chronic exposure for bees. *Environmental Science and Technology*, *49*(21), 12731-12740. http://doi.org/10.1021/acs.est.5b03459

[29] David, A., Botías, C., Abdul-Sada, A., Nicholls, E., Rotheray, E.L., Hill, E.M., & Goulson, D. (2016). Widespread contamination of wildflower and bee-collected pollen with complex mixtures of neonicotinoids and fungicides commonly applied to crops*. Environment International*, *88*, 169-178. https://doi.org/10.1016/j.envint.2015.12.011

[30] Limay-Rios, V., Forrero, L.G., Xue, Yingen, Smith, J., Baute, T. Schaafsma, A., 2015. Neonicotinoid insecticide residues in soil dust and associated parent soil in fields with a history of seed treatment use on crops in southwestern Ontario. *Environ Toxicol Chem*. http://doi.org/10.1002/etc.3257

[31] Mogren, C.L. & Ludgren, J.G. (2016). Neonicotinoid-contaminated pollinator strips adjacent to cropland reduce honey bee nutritional status. *Scientific Reports, 6(*29608). http://doi.org/10.1038/srep29608

- *Given the large extent of seed treatment use of clothianidin on corn and thiamethoxam on corn, soybean and cotton, the risk conclusions indicate that the majority of pounds of clothianidin and thiamethoxam applied in the US pose a low on-field risk to honey bees.*
- *According to the USDA's crop attractiveness guidance, these crops are all considered attractive to honey bees, therefore, exposure is of concern on-field. As discussed in the problem formulation, contact-based exposures are not assessed for seed treatments, as it is assumed that bees are not present until after planting; therefore, contact exposures would not reasonably be expected to occur.*

EPA's failure to acknowledge the well-documented risks and numerous exposure pathways from uses of neonicotinoid seed coatings undermines the value of the PPA. Particularly disturbing is the admission that the Agency is aware of exposure routes for the abraded seed dust, but then shirks any responsibility for incorporating these exposure routes into the PPA by instead repeatedly noting its [undescribed] work with stakeholders to address this issue.

EPA itself notes that "when considering the usage data for clothianidin and thiamethoxam (Section 2.4), the majority of the mass applied per year in the US is via seed treatment." In fact, the vast majority of clothianidin is applied to corn alone (1,400,000 lbs/year; 94% of total use). For thiamethoxam, the vast majority is broken down between corn (300,000 lbs/year, 33% of total use), soybeans (300,000 lbs/year, 33% of total use), and cotton (100,000 lbs/year, 11% of total use) (p. 346-347). It is inexcusable that these widely used neonicotinoids lack an adequate risk assessment for their primary use: seed coatings for corn, soybean, and cotton.

i) Clothianidin and thiamethoxam are practically ubiquitous in agricultural areas due to their consistent use and long persistence, leading to chronic effects. As indicated, the seed coatings can abrade and otherwise blow or flow off-site. Limiting the off-field exposure analysis to spray drift may conveniently fit with EPA's existing analytical models, but it ignores extensive off-field pathways associated with the clothianidin and thiamethoxam seed coating application, which represent the main innovation associated with these systemic insecticides. These pathways simply cannot be acknowledged and then immediately discarded in the risk assessment process by stating, "The Agency is working with different stakeholders to identify best management practices and to promote technology-based solutions that reduce this potential route of exposure" (p. 362).

j) With respect to the "Incident Reports," beginning at p. 337, EPA and the beekeeping industry are well aware that many bee kill incidents are not reported. The analysis fails to account for the fact that beekeepers have no reason to report to the system for bee kills resulting from clothianidin and thiamethoxam-coated seeds. Because the seeds themselves are exempted from FIFRA enforcement due to EPA's application of the Treated Article Exemption, there are no mandatory label warnings or use directions, nor is there any required inspection or enforcement by EPA or the State Agencies. In fact, the Agency notes, "Much of the incident information made through phone and email correspondence to EFED does not usually include a thorough investigation of the incident or provide any confirmatory residue data to link a chemical with a particular incident". Furthermore, often times beekeepers feel that they are blamed for the kills, or that the onus is on the beekeeper to prove they are not responsible for the kill. There is also frustration throughout the beekeeping industry that bee kill samples collected at the scene are not analyzed, nor are the pesticide applicators (or those responsible for the pesticide exposure) questioned in the incident reporting process.

With no enforcement, or consequences for farmers who misuse or overuse clothianidin and thiamethoxam-coated seeds, beekeepers will not bother to report their losses via such exposures. With those caveats in mind it still is remarkable that everyday use according to label warnings has led to the numerous severe kill incidents described in Table 5.71 and 5.72.

III. The PPA fails to consider synergistic effects on honey bees and other pollinators

a) Risks to commercial honey bees in particular do not occur in isolation. The bees are transported to fill the nation's pollination needs, and are exposed to many factors. The PPA ignores these "field realistic" scenarios and fails to even mention fungicides as synergistically toxic to honey bees and other pollinators.

b) It is not reasonable for risks of synergistic effects to be ignored in EPA's risk assessment. As noted above, extensive scientific literature indicates that field-relevant toxicity levels for clothianidin and thiamethoxam may be heightened when used in combination with other pesticides, such as fungicides.

c) Five recent studies illustrate synergistic effects; the PPA failed to consider them and must take them into account:

- Brandt et al. 2016., "The neonicotinoids thiacloprid, imidacloprid, and clothianidin affect the immunocompetence of honey bees (*Apis mellifera* L.)"[32]
- Sgolastra et al., "Synergistic mortality between a neonicotinoid insecticide and an ergosterol-biosynthesis-inhibiting fungicide in three bee species"[33]
- Spurgeon et al., "Chronic oral lethal and sub-lethal toxicities of different binary mixtures of pesticides and contaminants in bees (Apis mellifera, Osmia bicornis and Bombus terrestris)"[34]
- Botías et al, "Quantifying exposure of wild bumblebees to mixtures of agrochemicals in agricultural and urban landscapes"[35]
- Tsvetkov et al., "Chronic exposure to neonicotinoids reduces honey bee health near corn crops"[36]

d) The U.S. Government Accountability Office raised concerns about EPA's failure to properly assess risks from pesticide mixtures and synergistic effects. According to the February 2016 GAO report, "EPA officials agreed that such mixtures may pose risks to bees but said that EPA does not have data on commonly used mixtures and does not know how it would identify them". [37] It is unacceptable for EPA officials to claim they are unable to evaluate risks from pesticide mixtures due to a lack of information about common pesticide mixtures. As the GAO report makes clear,

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[32] Brandt, A., Gorenflo, A., Siede, R., Meixner, M., & Büchler, R. (2016). The neonicotinoids thiacloprid, imidacloprid, and clothianidin affect the immunocompetence of honey bees (*Apis mellifera* L.). *Journal of Insect Physiology, 86*, 40–47. doi: https://doi.org/10.1016/j.jinsphys.2016.01.001

[33] Sgolastra, F. et al. (2016). Synergistic mortality between a neonicotinoid insecticide and an ergosterol-biosynthesis-inhibiting fungicide in three bee species. *Pest Management Science, 73,* 1236-1243. http://doi.org/10.1002/ps.4449

[34] Spurgeon, D. et al. (2016). Chronic oral lethal and sub-lethal toxicities of different binary mixtures of pesticides and contaminants in bees (*Apis mellifera*, *Osmia bicornis*and *Bombus terrestris*). *EFSA Journal, 13*(9). http://10.2903/sp.efsa.2016.EN-1076

[35] Botías, 2017.

[36] Tsvetkov, N., et al. (2017). Country-specific effects of neonicotinoid pesticides on honey bees and wild bees. *Science, 356*(6345), 1393-1395. http://dx.doi.org/10.1126/science.aaa1190

[37] United States Government Accountability Office. (2016). Bee Health: USDA and EPA Should Take Additional Actions to Address Threats to Bee Populations. *GAO-16-220*. Retrieved from http://gao.gov/assets/680/675109.pdf

this type of information can be acquired by surveying farmers, pesticide manufacturers, and other stakeholders.

III. Beyond honey bees, the PPA's scope is too narrow

a) The defects outlined above, for the PPA's assessment of honey bees, are magnified with respect to the more vulnerable bumblebees, solitary bees, and other pollinators that the PPA fails to address (as described on p. 12). By wrongly choosing to use the honey bee as a "reasonable" surrogate for other bee species, the PPA ignores many peer-reviewed studies that show impacts to native bees and butterflies from clothianidin and thiamethoxam.

b) The GAO has also called on EPA to improve the scope of its risk assessments and to develop a plan for evaluating pesticide risks to a range of bee species, beyond honey bees. As noted in the GAO's report, it would be prudent for EPA to develop testing models and guidelines for other types of bees, such as solitary bees and bumblebees. The GAO also recommends that EPA "direct the Office of Pesticide Programs to develop a plan for obtaining data from pesticide registrants on the effects of pesticides on non-honey bee species, including other managed or wild, native bees."

c) EPA must consider the significant life cycle and other differences between honey bees, bumble bees, and especially solitary bees. For instance, according to one 2016 study, "Unlike honeybees, bumble bees live in colonies for only a few months each year. Assessing the sublethal effects of systemic insecticides only on the colony level is appropriate for honey bees, but for bumble bees, this approach addresses just part of their annual lifecycle. Queens are solitary from the time they leave their home colonies in fall until they produce their first workers the following year. Queens forage for pollen and nectar, and are thus exposed to more risk of direct pesticide exposure than honey bee queens". EPA acknowledges the "differences in bee life history" (p. 344) but fails to incorporate these significant differences into the PPA.

d) Further, the PPA disregards the substantial risks to bumblebees and other native bees from the use of clothianidin and thiamethoxam seed coatings and soil treatments. When assessing potential risks through seed/soil treatments, the agency only analyzes risks from oral exposure through pollen from treated crops. In fact, because of this significant omission, the agency wrongly concludes, "Exposure of honey bees to clothianidin and thiamethoxam via soil applications are not expected to result in substantial spray drift to adjacent sites. Therefore, off-field risk from soil treatments are assumed to be low". By only considering spray drift and oral exposure routes, EPA completely disregards the significant contact exposure pathways for ground-nesting bees (70 percent of all bee species are ground nesting), yet ground-nesting species will come into contact with residues of clothianidin and thiamethoxam present in the soil.

e) The PPA fails to acknowledge the importance of non-*Apis* pollinators to tomato crop systems. The final risk assessment must assess risks to the full suite of pollinators—and take into account economic as well as environmental damage. A revised PPA should also consider all of the analytical defects outlined above for honey bees, such as the lack of consideration of synergistic effects, for the non-Apis pollinators. There are many other non-bee pollinators, including, but not limited to, monarch butterflies and bats, that the PPA failed to consider at all. This is

unacceptable, particularly as new research indicates that other comparable neonicotinoids threaten monarch larvae.[38]

REQUESTED ACTIONS:

The EPA should:

1. Expedite completion of the final risk assessments and the overall Registration Reviews for clothianidin and thiamethoxam, which are now at least two and likely three years behind the schedule to which EPA had committed.

2. Conduct full ESA Sec. 7 compliance now, contemporaneous with the risk assessments in the Registration Review process, rather than afterwards which would violate the ESA.

3. The high residue levels of clothianidin and thiamethoxam and high risks that EPA identified with respect to cucurbit vegetables, citrus, stone and berry fruits, and oilseed indicate the need to promptly suspend clothianidin and thiamethoxam products with respect to these uses.

4. In view of the: a) high overall risks as stated in this comment; b) the PPA's admitted gaps and substantial analytical uncertainties; c) additionally taking into account the other weaknesses, omissions, and gaps in the PPA described in this comment; d) in order to conserve ESA-listed endangered and threatened wild pollinators, as well as non-listed pollinators; and e) taking a precautionary approach to preserving honey bees and the livelihoods of the nation's essential commercial beekeepers, the risks are high enough to also promptly suspend all outdoor uses of clothianidin and thiamethoxam where pollinators may be exposed. The EPA must take protective actions consistent with the agency's fundamental mission.

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[38] Pecanka, J.R. & Lundren, J.G. (2015). Non-target effects of clothianidin on monarch butterflies. *The Science of Nature, 102* (19). http://doi.org/10.1007/s00114-015-1270-y

CENTER FOR FOOD SAFETY

October 25, 2021

OPP Docket
Environmental Protection Agency
Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Ave. NW.
Washington, DC 20460-0001

RE: Docket EPA-HQ-OPP-2021-0575
Comments on draft Biological Evaluations for the neonicotinoid insecticides clothianidin, imidacloprid and thiamethoxam

Center for Food Safety (CFS) appreciates the opportunity to comment on the EPA's draft Biological Evaluations (BE's) of the neonicotinoid insecticides clothianidin, imidacloprid and thiamethoxam.

These comments will focus on EPA's discussion of seed treatment uses of these insecticides, which was deficient in many ways. We have attached our comments on the proposed interim registration review decisions for five neonicotinoid insecticides that includes the three at issue here and contains additional analysis relevant to these BE's (CFS 2020).

EPA fails to provide any information on the usage of these insecticides as coatings on the seeds of numerous crops, despite the fact that seed treatments are by far their predominant use. Nor does EPA provide any quantitative analysis of environmental exposure to or the associated risk to any listed organism ensuing from seed treatment uses. Finally, to the extent that EPA addresses seed treatments at all, the discussion is filled with false premises, arbitrary choices, and misdirection away from those uses that are of most concern. It misrepresents and mischaracterizes rather than enlightens.

Seed Treatment Usage Data

The first issue is also the simplest. As detailed below, the vast majority of thiamethoxam and clothianidin, and at least half of imidacloprid, are coated onto seeds prior to planting rather than sprayed or deployed as soil drenches. Yet EPA entirely excludes seed treatments in reporting usage, and moreover falsely characterizes the "minus seed treatment" usage as ***total agricultural use***. These blatant errors give the Services and the public the false impression that agricultural neonicotinoid use is many times less than it in fact is, and ***must be corrected*** in the final Biological Evaluations.

In reading EPA's draft BE's, one would have no clue that virtually all of the corn and the majority of soybean seed – the two most widely planted crops in the U.S. – are treated with a

neonicotinoid insecticide; nor that "[f]rom 2000 to 2012, virtually all neonicotinoids applied to maize, soybeans, and wheat were applied as seed treatments" (Douglas and Tooker 2015). Nor would one realize that seed treatments are a major use on dozens of other major and minor crops, unless one were to happen upon a single page buried deep in one of the innumerable attachments and appendices to the BEs, where EPA notes that thiomethoxam, clothianidin and imidacloprid are registered for seed treatment uses on an incredible 102, 61 and 39 crops, respectively (Thiomethoxam BE, App. 4-5, p. 20; Clothianidin BE, App. 4-5, p. 20; Imidacloprid BE, App. 4-5, p. 25).

The easiest way to see the magnitude of EPA's misrepresentations is to compare its statements on "total agricultural use" under Section 4.2: Usage Data of Chapter 1 of each draft BE (p. 1-3 in each) with the best available information on total agricultural use, including seed treatment use, of these neonicotinoids as reported by the U.S. Geological Survey (USGS). For instance, EPA states: "Between 2014 and 2018, the national annual total agricultural usage averaged approximately 180,000 pounds of thiamethoxam over 3.1 million acres (including foliar and soil applications)." (Thiamethoxam BE, Chap. 1-3). This statement is false. In fact, the best available estimate of total agricultural use is 1,432,000 lbs./year, eight-fold more. ***Total agricultural use of clothianidin is over 70-fold more than EPA reports.*** (see table below). Thus, the "total agricultural use" of the three neonicotinoids combined, as reported by EPA, represents just 16%, or one-sixth, of actual use.

Insecticide	EPA "Total Ag'l Use" Excludes Seed Treatments (lbs/year)	USGS Total Ag'l Use 2014 Includes Seed Treatments (lbs/year)	% Total = Seed Treatment
Thiamethoxam	180,000	1,432,000	87%
Clothianidin	50,000	3,700,000	99%
Imidacloprid	891,400	2,000,000	55%
TOTALS	1,121,400	7,132,000	84%

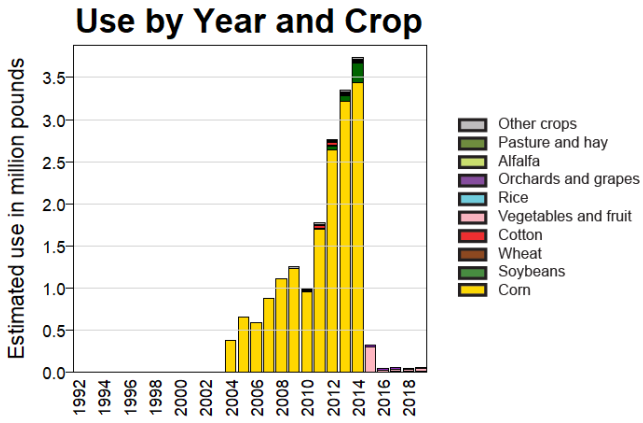
Sources: EPA figures from Section 4.2: Usage Data, Chapter 1 of each draft BE; USGS figures from visual inspection of "Use by Year and Crop" graph, 2014 Epest-Low, for each neonicotinoid, at https://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php. % Total = Seed Treatment is the quotient of (USGS Total minus EPA Total)/USGS Total.

EPA's pretext for excluding seed treatments is that reliable data are hard to come by. For instance: "Quantitative seed treatment usage data are difficult to obtain due to the complexities of capturing this usage information from growers (where seed treatment typically occurs)." (Thiomethoxam BE, App. 4-5, p. 20). This statement is misleading in two ways. First, EPA has at least a decade's worth of reliable data on total agricultural use of neonicotinoids, including seed treatments, that the Agency is conveniently ignoring here. The Agency's Biological and Economics Analysis Division (BEAD) reported total agricultural use, including breakouts of seed treatment uses for major crops including corn, cotton, soybean, potatoes, sorghum, sugar beets and wheat, in Screening Level Usage Estimate (SLUA) reports (EPA 12/30/15, 1/26/16 and 3/14/17). In fact, these SLUA's also give percent area treated estimates for both seed treatment and other uses over the 2005 to 2015 period.

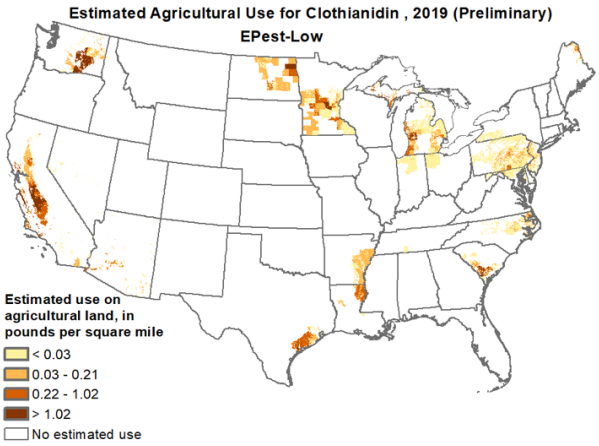
Second, contrary to EPA, growers do not typically treat their own seeds. For the two largest uses, corn and soybeans, practically all seed is treated off-farm – by the seed dealer or the seed dealer's supplier (Douglas and Tooker 2015, Figure 2). This is likely true for many

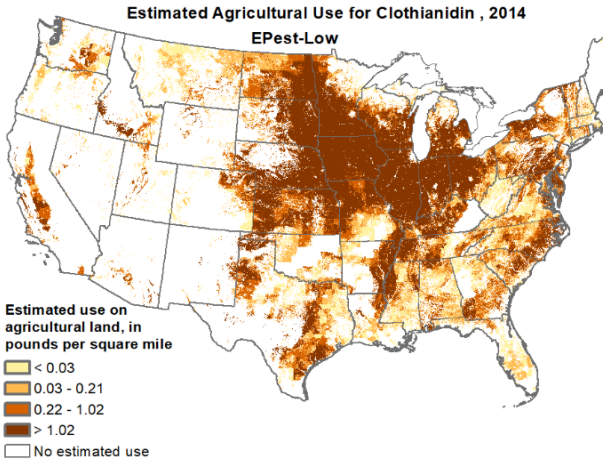
other crop seeds as well. If EPA were really interested in obtaining seed treatment usage data, it could require the neonicotinoid manufacturers, and/or the seed and chemical dealers who distribute their seed and pesticide products, to supply such information as a condition of the registrations. Regardless, the information on seed treatments that EPA does possess constitutes the best available scientific and commercial data on this predominant use of the neonicotinoids at issue here, and must be used.

Seed treatment use of the neonicotinoids (and other pesticides) was reported through 2014 by the U.S. Geological Survey, which relies upon data supplied by the private firm Kynetec (Douglas and Tooker 2005). For unexplained reasons, Kynetec, whose biggest customers for their pesticide usage data reporting services are major pesticide firms, decided to stop collecting seed treatment data after 2014. This coincided with a flurry of scientific papers reporting on both seed treatment uses and the many adverse effects of neonicotinoids. As of 2014, neonicotinoid seed treatment use was rising on major crops, and with corn in particular the average amount used per seed was rising (Ibid.). Thus, there is every reason to believe seed treatment uses are at least as great today as they were in 2014, and most likely considerably higher.



Beginning 2015, the provider of the surveyed pesticide data used to derive the county-level use estimates discontinued making estimates for seed treatment application of pesticides because of complexity and uncertainty. Pesticide use estimates prior to 2015 include estimates with seed treatment application.

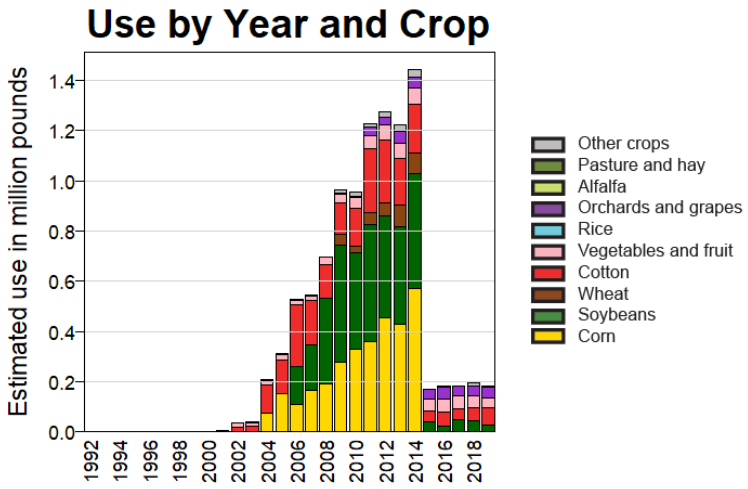


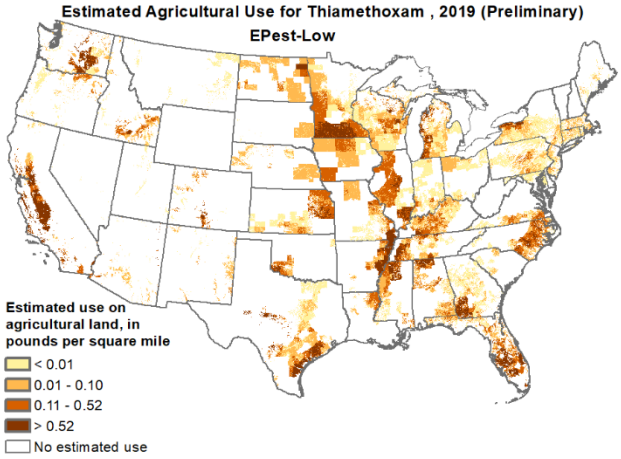


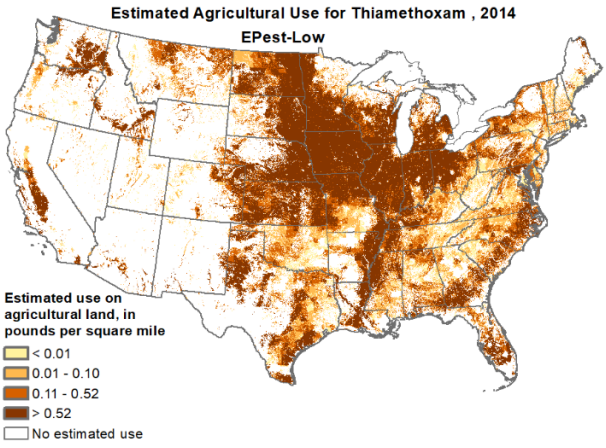
Source: https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2019&map=CLOTHIANIDIN&hilo=L&disp=Clothianidin

The graphics above display clothianidin use rising dramatically on corn from 2004 through 2014, and soybean use rising from 2012 to 2014, when Kynetec stopped reporting seed treatments. The 2019 map represents roughly speaking EPA's assessment of 50,000 lbs/year clothinanidin use, which excludes seed treatments, while the 2014 map represents the best available information on actual agricultural use, which includes seed treatments.

The graphics below display the same for thiamethoxam. For both pesticides, the difference in color intensity between the 2014 and 2019 maps represents seed treatment uses, which are concentrated heavily in the Corn Belt, the center of corn and soybean cultivation in the U.S. and the region with the most intensive use of these two major neonicotinoid insecticides. For thiomethoxam, there is also considerable amounts used to treat cotton seed.







Source:https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2014&map=THIAMETHOXAM&hilo=L

Seed treatment "analysis"

In line with EPA's refusal to report seed treatment usage data, the Agency also refused to conduct any sort of meaningful (i.e. quantitative) risk assessment of these uses. To take thiomethoxam as an example, EPA notes that it did not assess seed treatment applications quantitatively, but rather only qualitatively in Appendix 4-5 (Thiomethoam BE, Chapt. 3, Section

3.5.4). In Appendix 4-5, EPA assumes that flowable uses will result in greater aquatic environmental concentrations than seed treatment uses. EPA acknowledges that neonicotinoid seed dust kills bees, but fails to assess the issue because it has not developed methods to do so. This is no excuse. EPA could develop methods to assess this important and deadly exposure route, following the lead of independent researchers (e.g. Krupke et al. 2017), but chooses not to. The bulk of EPA's qualitative consideration of seed treatment uses is an "exploratory spatial analysis to determine where seed treatment usage would be informative" (Thiomethoxam BE, App. 4-5, pp. 20-34).

This "analysis" is not worth the paper it is written on, for several reasons. First, EPA arbitrarily excludes from its "analysis" the crops that represent by far the largest seed treatment uses in terms of pounds – corn and soybeans, to a lesser extent wheat – on the grounds that only neonicotinoid-treated crops that are grown in "geographically specific areas" are of interest, and these large-acreage crops are widely grown and so inappropriate. This is an arbitrary and senseless exclusion criterion; of concern is the amount of neonicotinoid introduced into the environment where listed species may be exposed to it, not whether this occurs on a broad or a "geographically specific" scale.

Second, EPA arbitrarily chooses to focus its "analysis" on minor crop categories rather than major ones – Other Grains and Vegetables and Ground Fruit, primarily.

Third, EPA does not bring into its analysis a single metric of ***how much*** neonicotinoid is used: either on a single seed or on a treated seeds per acre basis; nor does EPA consult available information on what percentage of a given crop seed is treated. For instance, with corn we know that each kernel is treated with from 0.25 to 1.25 milligrams of clothianidin or thiamethoxam (Krupke et al. 2012); this permits calculation of the amount of neonicotinoid on an acre of treated seed (or a range); and we also know that very nearly 100% of corn seed planted in the U.S. is treated with neonicotinioids (Douglas and Tooker 2015). Without metrics of usage to estimate exposure, EPA cannot address the risk question.

In short, this entire discussion of 30 pages or so appears designed to distract attention from the by far major seed treatment uses of neonicotinoids, which occur on corn and soybean seeds, and the impacts that such uses are having on listed species and their critical habitats.

Poultry Litter Applications

EPA conducts a back-of-the-envelope calculation to estimate how much thiamethoxam (similarly for the other two neonicotinoids) is introduced to the environment when poultry litter from poultry houses treated with thiamethoxam for control of flies and darkling beetles is applied to corn fields as a soil amendment (Thiamethoxam BE, Chapter 3, Section 3.5.3). In a bizarre twist, EPA then uses the results of this "poultry litter" scenario in place of and to represent the scenario of planting a field with thiomethoxam-treated corn seed (Ibid., Section 3.5.4). Elsewhere, we learn that less than 500 pounds of thiomethoxam is applied to poultry houses annually (Thiomethoxam BE, Chapter 1, Section 4.2), while roughly 600,000 lbs. of thiomethoxam are applied to the nation's corn seeds (see thiomethoxam graph above).

Similarly, EPA substitutes an assessment of clothianidin in poultry litter for one of clothianidin on corn seeds, the latter of which amounts to over 3 million lbs. of the insecticide (Clothianidin BE, Chapter 3, Sections 3.5.4 & 3.5.5), and similarly for imidacloprid (Imidacloprid BE, Chapter 3, Sections 3.5.5 & 3.5.6).

Exposure Through Pollen and Nectar and Other Plant Tissues

Nowhere did we find a discussion by EPA of exposure of listed organisms to thiamethoxam, clothianidin or imidacloprid in the nectar, pollen or other parts of plants systemically intoxicated with these insecticides from seed treatments. It does not appear that EPA conducted any sort of risk assessment for this route of exposure, either. The mismatch between the independent scientific literature, where hundreds of publications have addressed every aspect of seed treatment use of neonicotinoids – from levels found in various plant tissues, both those whose seeds are directly treated as well as field-edge plants; to toxicity thresholds for all manner of pollinators, insects and other organisms; to risk assessments – to EPA's dismissal of this exposure route could not be more striking.

We have attached comments submitted to EPA for the interim registration review decisions for five neonicotinoids, including the three at issue here, for further analysis that is relevant to these draft Biological Evaluations

Conclusion

We urge EPA to correct the blatant errors in reporting the usage of these neonicotinoids, as discussed above. EPA should also quantitatively assess seed treatment uses of these neonicotinoids, taking account of independent scientific literature on their prevalence, environmental concentrations, lethal and sublethal toxicity threshold for various organisms, and their persistence especially in the soil, which could give rise to accumulating levels over seasons.

The results of such a re-assessment might well lead to some NLAA determinations changing to LAA's, or to the strength of evidence increasing for some LAA determinations. Regardless, these assessments are designed to provide both the public and the expert wildlife Services with accurate, credible information on these highly toxic insecticides, and as currently written the draft BE's grossly misrepresent the use of thiomethoxam, clothianidin and imidacloprid in U.S. agriculture.

Bill Freese, Science Director
Center for Food Safety

References

CFS (2020). Center for Food Safety's comments to EPA on the Proposed Interim Registration Review Decisions for Several Neonicotinoid Pesticides: Imidacloprid, Clothianidin, Thiamethoxam, Acetamiprid and Dinotefuran. Center for Food Safety, May 4, 2020.
EPA-HQ-OPP-2008-0844: Imidacloprid
EPA-HQ-OPP-2011-0865: Clothianidin
EPA-HQ-OPP-2011-0581: Thiamethoxam
EPA-HQ-OPP-2011-0920: Dinotefuran
EPA-HQ-OPP-2012-0329: Acetamiprid

Douglas MR and Tooker JF (2015). Large-Scale Deployment of Seed Treatments Has Driven Rapid Increase in Use of Neonicotinoid Insecticides and Preemptive Pest Management in U.S. Field Crops. Environmental Science & Technology 49(8): 5088-97.

EPA (3/14/17). Screening Level Usage Analysis (SLUA) or Imidaclopid (129099), Biological and Economics Analysis Division, EPA, March 14, 2017. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0844-1609.

EPA (1/26/16). Screening Level Usage Analysis (SLUA) for Thiamethoxam (060109). Biological and Economics Analysis Division, EPA, January 26, 2016. https://www.regulations.gov/document/EPA-HQ-OPP-2011-0581-0358.

EPA (12/30/15). Screening Level Estimates of Agricultural Uses of Clothianidin (044309): Reporting Time: 2005-2014. Biological and Economics Analysis Division, EPA, December 30, 2015. https://www.regulations.gov/document/EPA-HQ-OPP-2011-0865-1176.

Krupke CH et al. (2017). Planting of neonicotinoid-treated maize poses risks for honey bees and other non-target organisms over a wide area without consistent crop yield benefit. Journal of Applied Ecology 54: 1449-1458.

Krupke CH et al. (2012). Multiple Routes of Pesticide Exposure for Honey Bees Living Near Agricultural Fields. PLOS One 7(1): e29268.