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Letter to the editor "The resilience of the beehive"

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ABSTRACT

A recent quantitative weight of evidence (QWoE) assessment of higher tier studies on the toxicity and risks of neonicotinoids in honeybees by Solomon and Stephenson reported a colony-level no-observed-adverse effect concentration (NOAEC) of 25 µg/kg (ppb) for imidacloprid and clothianidin. The toxicity of these insecticides to honeybees is however known to be reinforced with chronic exposure, and extrapolation of time-to lethal-effect toxicity plots compiled from published studies indicate that an imidacloprid level of 0.25 ppb, i.e. one-hundredth of the reported colony NOAEC, would kill a large proportion of bees nearing the end of their life. This huge discrepancy points to the impressive resilience of beehives in counteracting lethal effects of neonicotinoids, as long as the colony remains otherwise healthy with a productive queen that is able to maintain the colony population. The explicit connection between innate immunity loss and the neonicotinoids leading to infestation with a wide variety of pathogens appears to be the decisive factor that ultimately bring down stressed colonies.

Drs Solomon and Stephenson have performed a quantitative weight of evidence (QWoE) assessment of higher tier studies on the toxicity and risks of the neonicotinoids imidacloprid (Stephenson and Solomon 2017a), clothianidin (Solomon and Stephenson 2017a), and thiamethoxam (Stephenson and Solomon 2017b) in honeybees. The focus of their QWoE analysis was on responses of honeybees to neonicotinoids under more realistic semi-field and field conditions. Toxicity data for higher-tier assessment were provided in whole-hive feeding-exposure studies conducted over a period of 42 days. For imidacloprid and clothianidin, the authors report a colony-level no-observed-adverse effect concentration (NOAEC) of 25 µg/kg (henceforth ppb) syrup, equivalent to an oral no-observed-adverse effect-dose (NOAED) of 7.3 ng/bee/day for all responses measured. For thiamethoxam, an NOAEC of 29.5 ppb syrup, equivalent to an NOAED of 8.6 ng/bee/day, for all responses measured is reported. The authors conclude that these neonicotinoids, as currently used as a seed treatment and with good agricultural practices, do not present a significant risk to honeybees at the level of the colony. I dispute this conclusion. I suggest they have merely demonstrated the impressive resilience of beehives in counteracting lethal effects of neonicotinoids.

In their assessment of the risks from imidacloprid on bees, the EFSA (2013) considered toxic endpoints for acute (3.7 ng/bee) and chronic exposure (20 ppb) that represent a rough consensus of the toxicity studies reported in the literature (see review by Blacquière et al. 2012). However, they cautioned that there are no guidelines for chronic and sublethal exposure testing in bees, and expressed concern regarding the uncertainty about the biological significance of such exposures.

Neonicotinoid insecticides are based on the natural toxin nicotine (Yamamoto et al. 1995), and are of particular concern because they bind virtually irreversibly to the nicotinic-acetylcholine receptors in the insect's nervous system (Abbink 1991). Damage can accumulate, and therefore the toxic effects can be reinforced with chronic exposure (Tennekes 2010). Simple accumulation of a level of toxic exposure **c** to a toxic threshold would appear as directly proportional to time **t**, and such dose–response relationships are known as Haber's rule (Tennekes and Sánchez-Bayo 2013):

$$\mathbf{c.t} = \mathbf{constant} \quad (1)$$

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Reinforcement of toxic effects with chronic exposure can be interpreted as coming from damaging secondary physiological effects that develop over time (Tennekes and Sánchez-Bayo 2013). Observations by many authors show that the longer the exposure time, the less amount of total chemical is needed to kill the insects; in other words, the LD50s decrease with exposure time (Sánchez-Bayo 2009; Tennekes and Sánchez-Bayo 2013). Whether it is enhanced, cumulative, or delayed toxicity, all these terms describe this situation when the power-law scaling exponent of time is greater than 1. Using published toxicity data for imidacloprid for several insect species, time-to-lethal-effect toxicity plots have been constructed and temporal power-law scaling curves have been fitted to the data (Rondeau et al. 2014). The level of toxic exposure to imidacloprid that results in 50% mortality after time **t** was found to scale as $\mathbf{t}^{1.7}$ for ants, from $\mathbf{t}^{1.6}$ to $\mathbf{t}^{5}$ for honeybees, and from $\mathbf{t}^{1.46}$ to $\mathbf{t}^{2.9}$ for termites (Rondeau et al. 2014). This dose–response relationship is known as the Druckrey–Küpfmüller equation, which was first established for carcinogenic nitrosamines (Druckrey et al. 1963):

$$\mathbf{c}.\mathbf{t}^{\mathbf{n}} = \mathbf{constant} \qquad (2)$$

with $n > 1$

Extrapolating the toxicity scaling for honeybees to the lifespan of winter bees suggested that imidacloprid in honey at 0.25 ppb would be lethal to a large proportion of bees nearing the end of their life (Rondeau et al. 2014). *This lethal concentration is two orders of magnitude lower than the colony level NOAEC for imidacloprid used by Solomon and Stephenson in their risk analysis*. Moreover, in view of the similarity of the dose–response relationship with that of carcinogenic nitrosamines, a threshold of toxicity may not even exist, so the discrepancies could even be much greater.

How can these conflicting data between be reconciled? In my view, the evidence points to the resilience of the beehive. Colony health may not suffer significantly due to mortality of older bees as long as the colony remains otherwise healthy with a productive queen that is able to maintain the colony population. Worker losses do occur, and declining homing rates can be accurately measured using radio-frequency identification (RFID) tags (Feltham, Park, and Goulson 2014; Henry et al. 2012; Ohashi, D'Souza, and Thomson 2010). It is well known that colonies can compensate for the losses of worker bees. Indeed, full colony field studies on neonicotinoid treated crops show not much difference in performance between the insecticide treated and non-treated colonies (Faucon et al. 2005; Stadler, Martinez Gines, and Buteler 2003). Also, a field study investigating imidacloprid-treated maize found the level of contamination in stored honey was between 0.05 ppb and 0.5 ppb, and yet mortality rates in apiaries were inversely correlated with the surface of maize fields treated but not with imidacloprid (Nguyen et al. 2009). Additionally, risk analysis studies and reviews of neonicotinoid use have downplayed the importance of the neonicotinoids on honeybee losses, especially as the sole agent (Blacquière et al. 2012; Cresswell 2011; Staveley et al. 2014).

However, the explicit connection between innate immunity loss and the neonicotinoids (Di Prisco et al. 2013) was not known or considered in these studies. The potential for accumulation of neonicotinoids at receptor sites to the level where loss of innate immunity occurs may be far more detrimental to a beehive than direct poisoning.

It is generally accepted that multiple pathogens ultimately bring down stressed colonies (Cornman et al. 2012; VanEngelsdorp et al. 2010). Cornman et al. (2012) found that colony collapse disorder (CCD) colonies were more likely to have higher levels of a wide variety of pathogens than weak, but non-CCD colonies. Not only were the levels of pathogens higher, but multiple agents were frequently found in combinations not typical of non-CCD colonies. It appears that the immune system in the CCD colonies has gone awry, and some authors hypothesize this is the case not only for honey bees and bumblebees but possibly for all insectivores (e.g., freshwater fish, birds, bats, amphibians, reptiles) directly or indirectly exposed to neonicotinoids and known to be in steep decline (Mason et al. 2013).

Could it be a few parts per billion of insecticide that makes the difference? The Di Prisco et al (2013) study showed that both imidacloprid and clothianidin adversely affect insect immunity and

promote replication of a viral pathogen, DWV, in honey bees at exposure levels 1 ppb or less with exposure of 1–3 days. The potential for accumulation of neonicotinoids at receptor sites to the level where loss of innate immunity has been demonstrated may explain the connection between neonicotinoids and CCD, and the decline of insectivores. For solitary insects, however, a far wider array of toxic effects may lead to their demise (Rundlöf et al 2015; Woodcock et al. 2016) because there is no resilient hive to counteract the losses.

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