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Policy analysis

Bees and pesticide regulation: Lessons from the neonicotinoid experience

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ABSTRACT

Neonicotinoid insecticides have been signaled as an important driver of widespread declines in bee diversity and abundance. Neonicotinoids were registered in the 1990s and by 2010 accounted for one third of the global insecticide market. Following a moratorium in 2013, their use on open-field crops was completely banned in the EU in 2018. Pesticide regulation should be based on solid and updated scientific evidence, whereby products showing unacceptable effects on the environment are not approved. Clearly, pesticide regulation failed to detect the ecological threats posed by neonicotinoids. We argue that at the time neonicotinoids were authorized, risk assessment (RA) protocols were inadequate to detect some of the risks associated with neonicotinoid properties, including high efficacy, long persistence, high systemicity, high mobility, and application versatility. We advocate for the adoption of a more holistic RA approach that should account for: a) temporal and spatial dimensions of pesticide exposure; b) co-exposure to multiple compounds; c) differences among bee species with different life histories in levels of exposure and sensitivity; and d) sublethal effects (mostly ignored in current RA procedures). We also argue that regulatory studies conducted to support pesticide registration should be publicly available, and that pesticide regulation should not be discontinued once a product has been authorized. We should use the knowledge acquired through the neonicotinoid experience as an opportunity to profoundly revise bee RA schemes. These efforts should be initiated promptly; the neonicotinoid story has also taught us that the regulatory system is reluctant to react.

1. Introduction

In her bestseller "Silent Spring" (1962) Rachel Carson wrote "what the public is asked to accept as safe today may turn out tomorrow to be extremely dangerous". More than 50 years after the publication of this milestone book on the environmental risks of pesticides, these words still resound as the neonicotinoid saga unfolds. The introduction of neonicotinoid insecticides in the global market in the early 1990s was heralded by statements about their effectiveness and their limited side effects on beneficial organisms, including bees. Since then, a growing body of scientific evidence has established a link between neonicotinoids and bee declines (Maini et al., 2010; Goulson, 2013; Godfray et al., 2014, 2015; IPBES, 2016; Woodcock et al., 2016a). As a result, the use of neonicotinoids in open-field crops is now banned in the EU and restricted in some areas of the US, Philippines and Canada. Neonicotinoids have a unique combination of properties, including high toxicity, long persistence, high systemicity and high mobility, that make them stand out from other pesticides. Clearly, at the time neonicotinoids were authorized, risk assessment (RA) schemes were inadequate to detect some of the threats associated with these properties. Current RA protocols have incorporated important changes, many of them prompted by studies on neonicotinoids. Nonetheless, we argue that current procedures are still insufficient to assess some of the threats posed by pesticides to bees and other pollinators, and we propose a profound revision of RA schemes.

Agro-chemical pollution has been identified as one of the main factors associated with widespread insect declines (Sanchez-Bayo and Wyckhuys, 2019), including bees and other pollinators (Biesmeijer et al., 2006; Bartomeus et al., 2013; Woodcock et al., 2016a; Grab et al., 2019). About 9% of bee species and 37% of bee populations in Europe are considered to be declining (Nieto et al., 2014). Bees play a key role in ecosystem function and provide an invaluable ecosystem service in

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the form of crop pollination (Klein et al., 2007; Gallai et al., 2009; IPBES, 2016). For these reasons, pollinator protection has become a priority in the policy agenda of many national and supra-national administrations that are designing pollinator initiatives (IPBES, 2016; Pollinator Health Task Force, 2016; Underwood et al., 2017). An improvement of RA regulation would signify a major contribution to the conservation of pollinators and the services they provide. In this study, we discuss the limitations of current RA procedures (with focus on the EU and North America), and provide recommendations to improve the regulatory process based on the knowledge gained from the neonicotinoid experience.

2. Neonicotinoids and bee declines

Following their appearance in the early 1990s neonicotinoids rapidly became the most widely used insecticides worldwide (Jeschke and Nauen, 2008). In 2010 seven major neonicotinoid compounds (imidacloprid, thiamethoxam, clothianidin, dinotefuran, nitenpyram, acetamiprid and thiacloprid) represented about one third of the global insecticide market (Simon-Delso et al., 2015). Several factors contributed to the rapid success of neonicotinoids: i) due to their high efficacy they are applied at low concentrations; ii) they have a long persistence, thus providing protection for long periods (months); iii) due to their systemicity they are readily absorbed and translocated to all plant tissues, thus facilitating the control of a broad spectrum of pests; iv) they have a high application versatility, thus increasing the range of potential exposure routes (Simon-Delso et al., 2015).

Neonicotinoids first came under the spotlight in 1994, when French beekeepers reported abnormal behavior, drastic reductions in honey production and severe colony losses in hives located near sunflower and corn fields sown with neonicotinoid-coated seeds (Gaucho®). Bees were allegedly exposed to residues of the active ingredient via ingestion of pollen and nectar (Maxim and van der Sluijs, 2013). The causal relationship between the so-called “French bee malady” and Gaucho® was rebutted by research linked to the agrochemical industry (Maus et al., 2003). Nonetheless, the French Government applied the precautionary principle and suspended the use of Gaucho® on sunflower (1999) and corn (2004). In subsequent years, following massive honeybee-poisoning events during the sowing of corn fields, other European countries (Italy, Germany, Slovenia) restricted the use of the three most widely used neonicotinoids (imidacloprid, thiamethoxam and clothianidin). Flowers in the surroundings of corn fields were being contaminated with neonicotinoid-loaded dust from the abrasion of the coated seeds generated by the pneumatic sowing machines (Greatti et al., 2003; Krupke et al., 2012). In 2012, a series of pivotal studies showed that, following exposure to realistic neonicotinoid levels, honeybee foragers were less likely to return to the hive (Henry et al., 2012) and bumblebee colonies experienced a reduction in colony growth and queen production (Gill et al., 2012; Whitehorn et al., 2012). These and other studies led to an EU moratorium of imidacloprid, thiamethoxam and clothianidin on bee-attractive and some non-bee attractive crops in 2013 (Auteri et al., 2017). This decision was contested by the agrochemical industry on the grounds that it was mostly based on studies conducted in the laboratory or under controlled conditions. Following a series of field studies (e.g. Pilling et al., 2013; Heimbach et al., 2016; Peters et al., 2016) the agrochemical industry argued that these products were safe under field conditions (Campbell, 2013). However, these studies received strong criticism (Schick et al., 2017; Bailey and Greenwood, 2018). Five years later, a reassessment of the existing evidence by the European Food Safety Authority (EFSA, 2018) which incorporated new field studies (Rundlöf et al., 2015; Woodcock et al., 2017, review in Wood and Goulson, 2017) prompted EU Member States to approve a full ban of these three molecules in outdoors applications.

3. Pesticide regulation and neonicotinoid properties

Before being authorized, pesticides undergo a RA process to assure they do not pose unacceptable risks to the environment. In some EU countries authorization for imidacloprid was obtained in 1991, before the implementation of the European Plant Protection Products Directive 91/414/CEE. Other neonicotinoids were authorized during the late 1990s and early 2000s. During this period, the European Plant Protection Organization (EPPO) worked on the harmonization of test protocols leading to the publication of a bee RA scheme in 1999, subsequently revised in 2010 (EPPO, 2010). These schemes follow a tiered approach. The first tier consists of a battery of cost-effective laboratory assays based on acute exposure and LD_{50} estimates. Products showing significant levels of toxicity are elevated to more environmentally-relevant semi-field and field tests (tiers 2 and 3). The implementation of a standardized RA scheme signified an improvement in our ability to detect pesticide threats to bees within a cost-contained framework. However, the EPPO RA scheme still failed to account for the above-mentioned combination of neonicotinoid properties (EFSA European Food Safety Authority, 2012).

At the time neonicotinoids were registered, RA schemes were designed only for “spray applications” ignoring the evaluation of seed-treated and soil-drenching chemicals and assumed exposure to be restricted to the pesticide application period and to the treated crop (EFSA European Food Safety Authority, 2012). This assumption is suitable for most non-systemic pesticides, but due to the ability of neonicotinoids to translocate to and persist within various plant tissues, bees may be exposed to neonicotinoids via ingestion of contaminated pollen and nectar even when the application was conducted several months before bloom. For the same reasons, neonicotinoid residues are frequently found in weeds growing in field margins and in crops planted after the neonicotinoid application (Goulson, 2013; Botıas et al., 2015; Tsvetkov et al., 2017). Application versatility further hindered the assessment of the threats posed to bees by neonicotinoids. Exposure routes that proved to be highly relevant, such as dust generated during the sowing of coated seed and guttation drops seeped out by vegetation, were totally overlooked during the RA process (EFSA European Food Safety Authority, 2012).

Due to their high toxicity to target pests (Jeschke and Nauen, 2008), neonicotinoids are applied at low concentrations compared to other insecticides. Consequently, they are usually found in pollen and nectar at very low levels, and for many years our ability to detect them was limited by analytical sensitivity. However, even at these low levels, neonicotinoids have been shown to have sublethal effects on bees, including reduced learning ability (Decourtye et al., 2004), impaired orientation (Fischer et al., 2014) and thermoregulation (Tosi et al., 2016; Azpiazu et al., 2019), lowered immune response (Di Prisco et al., 2013) and reproductive output (Laycock et al., 2012) and impaired performance of queens (Williams et al., 2015) and drones (Ciereszko et al., 2017). Unfortunately, the detection of sublethal effects constitutes, to this day, an important gap in RA. It is often argued that sublethal effects can be detected in tiers 2 and 3, but there are two problems with this reasoning. First, products yielding no relevant mortality in tier 1 are not submitted to higher tiers. Second, sublethal effects in general and behavioral effects in particular are difficult to detect in semi-field and field tests using honeybees. Honeybees are highly stressed by confined conditions: oviposition rate declines and workers engage in hive thermoregulation at the expense of foraging. This response and the small size of the foraging area may result in exposure levels being underestimated. In addition, the small size of the colonies used hinders extrapolation to full-size colonies. Field tests are conducted under more realistic conditions with larger colonies. Even then, given the large foraging areas of honeybees and their generalist foraging habits, a good part of the foraging population may not be visiting the treated plots. For this reason, field tests are often confounded by unreliable exposure levels and cross-contamination

between control and treatment hives (EFSA European Food Safety Authority, 2012), and are often afflicted by low statistical power (Cresswell, 2011; Woodcock et al., 2016b). The short duration of the tests in relation to the growth period of the colony further hinders our ability to detect significant and relevant sublethal effects.

Another shortcoming of bee RA schemes is their reliance on single-pesticide tests. This is in contrast to exposure in agricultural environments, where pollen and nectar are often contaminated with assorted combinations of products (David et al., 2016; Tsvetkov et al., 2017), which can cause additive and/or synergistic effects (Sgolastra et al., 2017a, 2018). Although synergism also affects other insecticides, neonicotinoids seem to be particularly prone to interactions with fungicides resulting in enhanced bee toxicity (Berenbaum and Johnson, 2015).

Lastly, current pesticide RA relies on a single species, the western honeybee, *Apis mellifera*. Yet, different bee species have different sensitivities to pesticides, and the limited information available indicates that non-*Apis* bees are more sensitive to neonicotinoids than honeybees (Arena and Sgolastra, 2014). An additional problem associated with relying solely on honeybees is related to the ability of heavily-populated colonies to overcome the loss of large numbers of workers (colony resilience) (Wu-Smart and Spivak, 2016). Conversely, in solitary bees (and to a lesser extent in bumblebees, which go through a solitary phase in spring), negative effects at the individual level have direct consequences on reproductive success (Rundlöf et al., 2015; Woodcock et al., 2017; Sgolastra et al., 2018, 2019) and probability of population extinction (Baron et al., 2017). Possibly for this reason, field studies in neonicotinoid-treated environments have yielded negative population trends for solitary bees and bumblebees but not for honeybees (Rundlöf et al., 2015; Woodcock et al., 2017). As a result, the appropriateness of using honeybees as the only surrogate for more than 20,000 bee species worldwide (most of them solitary) is under discussion (Sgolastra et al., 2019).

4. Towards a holistic bee risk assessment

Pesticide regulation should be based on solid updated scientific evidence, whereby products showing unacceptable negative effects are not approved or promptly removed from the market. In the face of scientific uncertainty, the precautionary principle should prevail. In view of the recent banning by the EU, it is difficult to avoid the conclusion that RA procedures have been inadequate not only in evaluating but also in regulating the ecological impacts of neonicotinoids. We therefore advocate for the adoption of a more holistic pesticide regulation approach accounting for the complexity of the environmental context in which bees live. Some of the measures we propose have already been discussed elsewhere (Sánchez-Bayo and Tennekes, 2017; van der Sluijs et al., 2015; Rortais et al., 2017) and partially addressed by EU and US pesticide regulatory agencies in recent years (EFSA (European Food Safety Authority, 2012, 2013); USEPA, 2014).

RA procedures should account for the temporal and spatial dimensions of exposure, including delayed mortality and the potential cumulative effects of chronic exposure (Sanchez-Bayo and Goka, 2014; Sánchez-Bayo and Tennekes, 2017). The short duration of current RA laboratory and field tests has hindered the detection of delayed mortality resulting from time-reinforced toxicity due to the bioaccumulation of the toxicant in the bee body during sustained exposure even at low concentrations (Rondeau et al., 2014; Simon-Delso et al., 2018; Holder et al., 2018).

RA should also account for the co-occurrence of multiple compounds that can interact among themselves and with other stressors. While it is impossible to test all potential combinations, the mixtures most likely to occur in specific agricultural areas should be considered (Zhu et al., 2017). Importantly, these tests should not be restricted to active ingredients but also include co-formulants employed to increase pesticide efficiency (Mulin, 2015). The active ingredient of the herbicide Roundup® (glyphosate) was correctly assessed as harmless to non-target organisms and human health at the time of registration. However, the co-formulants used in the original product were toxic to frogs (Mann and Bidwell, 1999) and showed carcinogenic effects in human cells (Defarge et al., 2018). It is surprising that to this day even the evaluation of the risk of pesticides on human health is based on bioassays testing single active ingredients!

Tests specifically designed to detect sublethal (Desneux et al., 2007) and long-term effects (Sánchez-Bayo and Tennekes, 2017) are urgently needed. These tests (e.g., time-to-event tests, memory tests based on the proboscis extension reflex) (Newman and McCloskey, 1996; Decourtye et al., 2005) should be implemented in tier 1. Otherwise, the criteria to decide whether compounds are submitted to tiers 2 and 3 should be reconsidered. Substances not yielding lethal effects in tier 1 could still cause sublethal effects and therefore should be tested in tiers 2 and 3. Fecundity, a highly relevant endpoint that is routinely assessed in vertebrate species (EFSA European Food Safety Authority, 2009), can only be measured under field and semi-field conditions in bees.

RA should include other bees besides honeybees. Although differences in pesticide sensitivity among bees can be accounted for using appropriate assessment factors (Chapman et al., 1998; Arena and Sgolastra, 2014), current honeybee RA schemes fail to cover certain exposure routes that are highly relevant to other bees (such as exposure through soil for ground-nesting bees) (Sgolastra et al., 2019; Chan et al., 2019). Even more importantly, risk assessment should take the opportunity afforded by some life history traits of solitary bees and bumblebees to design tier 2 and 3 tests that are more reliable and cost-effective. Adding solitary bees (*Osmia*) and/or bumblebees (*Bombus*) in tiers 2 and 3 would greatly simplify the detection of highly relevant behavioral effects such as reproductive output, as well as the extrapolation from the individual to the population level (Gradish et al., 2019; Sgolastra et al., 2019).

Regulatory studies conducted to support pesticide registration should be publicly available to allow scrutiny by independent parties and to promote transparency in the RA process (Boyd, 2018). Currently this information is protected under the umbrella of commercial confidentiality, even when these studies do not compromise the trade secret.

Finally, pesticide regulation should not be discontinued once a product has been authorized (Milner and Boyd, 2017). Post-registration monitoring is necessary to check whether RA assumptions are met in real conditions and to detect negative effects that may only become apparent when the product is used at a large scale (van der Sluijs et al., 2015) and therefore were not detected or even considered during the evaluation process. Post-registration monitoring could take advantage of the widely distributed network of apiaries. Currently, pesticides are re-evaluated every 10–15 years. Re-evaluation should be flexible enough to facilitate the incorporation of ad-hoc assays as soon as unexpected potential effects are detected.

A holistic approach to pesticide regulation requires that information from different databases, including landscape composition, pesticide use and climate be combined with information on the routes of exposure and sensitivity of the major bee groups to provide risk managers with science-based criteria for developing efficient mitigation measures and/or apply restrictions (Sponsler et al., 2019). Publicly available data on pesticide use at the farm level is an important first step towards this goal. Information gathered through post-registration monitoring and data on pesticide use in a given area could be integrated to define a “landscape dose effect” (Milner and Boyd, 2017). Acceptable pesticide load at landscape scale should be established by the environmental safety agencies, which should also take into account benefits derived from the use of the chemical product in terms of crop protection (van der Sluijs et al., 2015; Sgolastra et al., 2017b). Pesticide use should be based on acceptable landscape dose rather than on market demand. Currently, information on when, where, and how chemicals are applied is not readily available and therefore exposure and co-exposure levels cannot be quantified (Milner and Boyd, 2017).

The neonicotinoid saga has underscored some shortcomings of pesticide regulation. We should take this experience as an opportunity to revise bee RA schemes. At a time when bee declines have been documented in various parts of the world and as new plant protection products are being considered (Siviter et al., 2018; Tosi and Nieh, 2019), this effort should be initiated promptly. The neonicotinoid experience has also taught us that the regulatory system is reluctant to react.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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