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Do novel insecticides pose a threat to beneficial insects?

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Systemic insecticides, such as neonicotinoids, are a major contributor towards beneficial insect declines. This has led to bans and restrictions on neonicotinoid use globally, most noticeably in the European Union, where four commonly used neonicotinoids (imidacloprid, thiamethoxam, clothianidin and thiacloprid) are banned from outside agricultural use. While this might seem like a victory for conservation, restrictions on neonicotinoid use will only benefit insect populations if newly emerging insecticides do not have similar negative impacts on beneficial insects. Flupyradifurone and sulfoxaflor are two novel insecticides that have been registered for use globally, including within the European Union. These novel insecticides differ in their chemical class, but share the same mode of action as neonicotinoids, raising the question as to whether they have similar sub-lethal impacts on beneficial insects. Here, we conducted a systematic literature search of the potential sub-lethal impacts of these novel insecticides on beneficial insects, quantifying these effects with a meta-analysis. We demonstrate that both flupyradifurone and sulfoxaflor have significant sub-lethal impacts on beneficial insects at field-realistic levels of exposure. These results confirm that bans on neonicotinoid use will only protect beneficial insects if paired with significant changes to the agrochemical regulatory process. A failure to modify the regulatory process will result in a continued decline of beneficial insects and the ecosystem services on which global food production relies.

1. Introduction

Beneficial insects, such as bees, wasps and lacewings, provide ecosystem services to both native ecosystems and agriculture. An estimated 35% of global food produced is dependent on pollinators [1] and beneficial insects also aid in biological control, reducing crop pests such as aphids [2]. As such, documented insect declines [3–6] will not only result in a loss of biodiversity, but also threaten agriculture and food security [7–9]. While insect population declines are caused by numerous anthropogenic stressors, agrochemical use is clearly an important driver of these declines [10,11].

Neonicotinoid insecticides are the most commonly used insecticides in the world [12] and are effective at controlling a broad range of unwanted pest species [12]. Neonicotinoids work by targeting the insect nervous system, acting as agonists of nicotinic acetylcholine receptors (NAChRs) and, owing to differences in the binding sites of NAChRs in vertebrates and invertebrates [13], have a reduced risk to humans and vertebrate wildlife [12]. However, as both highly persistent and systemic insecticides, neonicotinoids can contaminate freshwater sources and the nectar and pollen of both treated crops and nearby wildflowers [14–17]. Given their lack of specificity within insects, field-realistic applications of neonicotinoids can have significant sub-lethal impacts on beneficial insects [18–25] with knock-on effects on ecosystem services [26,27]. This has resulted in bans and restriction on neonicotinoid use globally, most notably in the European Union. Importantly, these sub-lethal effects were identified post-licencing and not during the regulatory process. The process by which insecticides are licenced for use is a tiered system, where the first tier involves testing the toxicity of an insecticide (i.e. through LD_{50} experiments). Because this is the only part of the regulatory process that is mandatory [28,29], the sub-lethal impacts of novel insecticides can go undetected [28–30]. Furthermore, toxicity testing is conducted with model species which are not always representative of insect groups more broadly (i.e. *Apis mellifera* representing all pollinators) [31]. Consequently, neonicotinoids could be replaced with other insecticides that are equally as harmful to beneficial insects [32–34].

In this review we: (i) introduce two novel insecticides (flupyradifurone and sulfoxaflor) that could replace neonicotinoids over broad geographical regions and outline the potential risk of exposure for beneficial insects, (ii) review, with a systematic literature search, the potential sub-lethal impacts of these insecticides on beneficial insects, (iii) quantify these effects with a meta-analysis, and (iv) use these insecticides and neonicotinoids as case studies for how the regulatory process could be improved to better safeguard beneficial insects.

2. Flupyradifurone and sulfoxaflor mode of action and routes of exposure

Flupyradifurone and sulfoxaflor are the first butanolide and sulfoximine-based insecticides, respectively, that have been registered for agricultural use [35,36]. Both share the same mode of action as neonicotinoids, targeting NAChRs, but differ in their chemical structure, and specifically in their structural activity relations [13,35–39]. Therefore, despite their similar modes of action, each chemical is classified into a distinct group by the Insecticide Resistance Action Committee (IRAC) (neonicotinoids = group 4A, sulfoxaflor = group 4C, flupyradifurone = group 4D [35,36]). Because flupyradifurone and sulfoxaflor are both effective at targeting pest species that are resistant to neonicotinoids [35,37,40,41], they are likely candidates to replace neonicotinoids in areas where the latter is restricted [42] and in areas with high levels of pest resistance [35,36,43].

Flupyradifurone and sulfoxaflor have both been registered for use globally including in the European Union, where neonicotinoid use is heavily restricted. Both can be applied as spray or seed treatments [35,36], and as systemic insecticides, are expressed throughout the tissue of the treated plant, as well as in the flower's nectar and pollen. Beneficial insects can either be directly exposed during spray treatment, or indirectly exposed via feeding on plant tissue, nectar or pollen. Neonicotinoids are highly persistent in soil and plants, lasting for months and in some cases, years [15]. Similarly, flupyradifurone appears to be relatively persistent in the environment, lasting in the soil for several months [44]. Sulfoxaflor is less persistent, with its half-life in the soil estimated to be between 2 and 3 days [45]. Despite this, beneficial insects appear to be exposed to both flupyradifurone and sulfoxaflor in agricultural environments. For example, nectar and pollen collected by honeybees (*Apis mellifera*) foraging on buckwheat fields that had been sprayed with a recommended concentration of flupyradifurone contained on average 259 and 565 ppb of flupyradifurone, respectively [46], and honeybees foraging on winter-sown oilseed rape treated with both seed and spray applications of flupyradifurone contained up to 4 ppm in the collected nectar [44]. Similarly, honeybees foraging on a cotton crop treated with label recommendations of sulfoxaflor had up to 510 ppb in their collected pollen [47], and other studies have found that concentrations collected by foragers can be much higher (e.g. strawberry pollen = 12 700 ppm to 110 ppb, pumpkin pollen = 162 ppb to 9 ppb) [45]. Sulfoxaflor appears to degrade more quickly in the nectar and pollen of treated crops than neonicotinoids, but still persists for at least 11 days (the longest period that has been tested) [45,47]. Therefore, while we do not have a complete understanding of the residue persistence of flupyradifurone and sulfoxaflor, the existing data suggest that beneficial insects will be exposed to them at relatively high concentrations [44,45,48].

3. The sub-lethal impacts of flupyradifurone and sulfoxaflor on beneficial insects

We conducted a systematic literature search of the potential impacts of flupyradifurone and sulfoxaflor on beneficial insects (methods in the electronic supplementary material). We first reviewed and summarized the literature on bees because they made up the majority of the published research (§§3a–c). We then reviewed the literature on predatory insects (§3d), including wasps, lacewings and beetles. Finally, we extracted and quantified the available data with a meta-analysis (§3e; see the electronic supplementary material for methods and analysis).

(a) Bee mortality

The purpose of this review was to highlight the potential sub-lethal consequences of novel insecticides on beneficial insects, but when reviewing the literature, it quickly became apparent that flupyradifurone can have lethal consequences at field-realistic levels [49–52]. For example, flupyradifurone exposure increased larval mortality at high dosages (0.33 µg bee^{-1} d^{-1} for 6 days) in the Asiatic honeybee (*Apis cerana)*, although no effects were found at a lower dosage (0.033 µg bee^{-1} d^{-1} for 6 days) [50]. However, in a follow-up experiment that used a similar design with western honeybees (*A. mellifera*), larvae fed a lower dosage (an estimated 0.025 µg adult bee^{-1} d^{-1} over 3 days) had higher larval mortality [51], suggesting that *A. mellifera* larvae are more vulnerable to flupyradifurone exposure than *A. cerana*. Furthermore, flupyradifurone exposure, as with other insecticides [53], is more likely to be detrimental when combined with other environmental stressors such as poor nutrition [54], pathogens [53] or other agrochemicals [49,55]. Honeybees (*A. mellifera*) exposed to field-realistic concentrations of flupyradifurone had higher levels of mortality when simultaneously exposed to the fungicide propiconazole [49]. Similarly, exposure to both flupyradifurone and the common fungal parasite *Nosema ceranae* can alter detoxification and immune genes in honeybees and also increase mortality [51]. Therefore, despite flupyradifurone been labelled 'bee safe', field-realistic exposure can increase the risk of honeybee mortality [49,50].

Sulfoxaflor is toxic to bees at high concentrations [56–60], yet the effects on mortality at lower doses may depend on interactions with other environmental variables. Honeybees Bumblebees (*B. terrestris*) and honeybees (*A. mellifera*) fed a sucrose solution containing sulfoxaflor (1 ppm or 3 ppm) over 14 days had mortality rates of 90% and 88%, respectively [56,58]. However, while bees can be exposed to these concentrations in the short-term (acute exposure), the existing data suggest that these concentrations are unlikely to persist over a two-week period [46–48] (see §2). For example, in two semi-field experiments, honeybee (*A. mellifera*) colonies foraging on cucumber and buckwheat flowers sprayed with sulfoxaflor had an initial rise in mortality compared with control colonies, but this dropped as the chemical started to degrade [57,59]. As with flupyradifurone, exposure to sulfoxaflor with other environmental stressors appears to increase bee mortality at field-realistic applications [61]. Bumblebee (*B. terrestris*) larvae reared *in vitro* and chronically exposed to a field-realistic concentration of sulfoxaflor (5 ppb) or inoculated with the common bumblebee parasite *Nosema bombi* did not differ in mortality compared to unexposed controls, but when larvae were simultaneously exposed to both stressors, mortality increased [61]. Given the prevalence of *N. bombi* in some bumblebee populations [62], field-realistic concentrations of sulfoxaflor could significantly increase bumblebee larval mortality.

(b) Bee fitness and reproductive output

A healthy bumblebee or honeybee colony will grow and produce sexuals (gynes and males). Reproductive output is arguably the best measure of colony fitness [32,63,64] but other proxies such as colony growth or larval production are also useful fitness measures [64,65]. As described in §3a, laboratory experiments have demonstrated that flupyradifurone exposure can increase honeybee larval mortality [50,51] and can also reduce adult emergence [51], which could have knock-on effects on colony growth. In one of the first experiments to examine the colony-level impacts of flupyradifurone on beneficial insects, Campbell *et al.* [46] monitored the ‘colony strength’ (growth) of honeybees (*A. mellifera*) foraging on buckwheat crops, that had either been treated with a label-recommended foliar spray of flupyradifurone or untreated control fields. The experimental treatment did not affect any of the measures of colony fitness addressed, including the number of bees, eggs, brood or colony weight. However, this study also highlights the difficulties in conducting these types of field experiments as honeybees returning to the control colonies were also found to be carrying nectar and pollen containing flupyradifurone, suggesting that fields neighbouring the control fields had been treated with it.

Chronic sulfoxaflor exposure appears to have comparable negative impacts on the reproductive output of bumblebee colonies to those observed with neonicotinoids [64,65]. For example, Siviter *et al.* [32] chronically exposed bumblebee (*B. terrestris audax*) colonies to a field-realistic concentration (5 ppb) of sulfoxaflor in sucrose over two weeks, before they were placed in parkland and allowed to forage naturally. The colonies were monitored until the end of their life cycle and compared to unexposed colonies. Sulfoxaflor exposure reduced the number of sexuals produced by 54% and treated colonies also contained fewer workers than control colonies. Interestingly, the drop in worker production did not occur until week 5 of the experiment, when larvae that had been exposed to sulfoxaflor for the longest period of time would be emerging. This implies that sulfoxaflor exposure may impair larval development, resulting in a drop in worker production, and downstream consequences on reproductive output [32]. In a follow-up experiment, chronic sulfoxaflor exposure (5 ppb over 10 days in a sucrose/pollen mixture) did not increase bumblebee larval mortality (*B. terrestris)* although larval growth was impaired [61]. As sulfoxaflor residue levels are generally higher in pollen than nectar [45,48,57], bumblebee larvae could be exposed at higher concentrations of sulfoxaflor than adults [32,61,66]. Microcolonies chronically exposed to 5 ppb of sulfoxaflor showed a 31% and 40% reduction in egg laying and larval production respectively [66], offering a possible mechanism for the fall in reproductive output observed in [32]. Taken together, these results suggest that sulfoxaflor exposure will have significant, sub-lethal impacts on bumblebee colony fitness.

(c) Bee behaviour

While mortality and reproductive output are direct measures of beneficial insect fitness, many of the upstream effects of insecticide exposure could be behavioural as foraging bees need to identify floral resources and learn which offer the highest rewards to maximize their nutritional input [67]. This requires both the physiological mechanisms involved in flight and motor control, but also the cognitive mechanisms involved in perceiving and learning about floral stimuli (e.g. colour, scent) and rewards (e.g. nectar, pollen). After foraging, bees also need to navigate from flower patches back to their natal colony, requiring the use of spatial and olfactory cues. Disruption to behaviours such as these could have knock-on consequences for colony fitness [68]. Flupyradifurone exposure can impair honeybee (*A. mellifera*) sucrose responsiveness and motor function, but only at high dosages [69,70], and honeybee olfactory learning is impaired at field-realistic dosages both when individuals are exposed as larvae or as adults [50,71]. In the first large-scale field study to monitor the impact of flupyradifurone exposure on honeybee foraging, honeybees (*A. mellifera*) were chronically exposed to flupyradifurone for 7 days and foraging was monitored for 40 days with radio frequency identification tags [72]. Honeybees exposed to flupyradifurone began foraging at an earlier age compared to unexposed controls and performed more foraging bouts, that took longer to complete. Neonicotinoid exposure can have a similar effect on bumblebees, increasing the frequency and/or duration of foraging trips [19,73] possibly caused by bees being less efficent at foraging [19,23,73,74]. While effects on foraging efficiency have not been directly tested, acute, field-realistic flupyradifurone exposure (approximately 4 ppm) can impair honeybee (*A. mellifera)* flight: honeybees exposed to flupyradifurone and tested in a flight mill were less likely to complete a successful flight [54]. Interestingly, flight velocity was greater in the flupyradifurone-treated bees, which could be as a result of hyperactivity [49,54], akin to effects observed with neonicotinoid exposure [75]. Thoracic temperature was also lower in exposed bees, suggesting that flupyradifurone may also impair thermoregulation [54].

Sulfoxaflor exposure does not appear to impair bee behaviour, although the available data are currently limited [32,76]. Foraging bees learn about floral scents and use their working memory to remember flowers that they have already visited [18,77]. Neonicotinoid exposure can impair both olfactory learning and working memory [18,77] but acute sulfoxaflor exposure at doses directly comparable to those used with neonicotinoids (5 and 10 ppb) [77,78], did not influence (i) honeybee (*A. mellifera*) or bumblebee (*B. terrestris*) olfactory learning or (ii) bumblebee (*B. terrestris*) working memory [76]. Siviter *et al.* [32] found no long-term impact of chronic sulfoxaflor exposure (5 ppb) on bumblebee foraging performance, although foraging observations were not made during the exposure period [32], so the results are not directly comparable to research with neonicotinoids [19,23]. More recent experiments similarly found no effect of acute sulfoxaflor exposure on locust (*Locusta migratoria*) behaviour [79], suggesting that the lack of behavioural impairment may hold across insects more broadly.

(d) Effect on predatory insects

Most research on flupyradifurone and sulfoxaflor to date has been conducted on the potential impact of these novel insecticides on insect pollinators and specifically bees. However, both flupyradifurone and sulfoxaflor have been suggested for use within an integrated pest management (IPM) approach [35,36]. As such, the impact on predatory insects that aid in pest control, such as wasps and lacewings, needs to be low. To assess the potential impact of insecticides on predatory insects, researchers have conducted bioassays that expose insects at various stages of their life cycle to label-recommended applications of insecticides. Topical flupyradifurone exposure resulted in a 40–60% dose-dependent increase in the mortality of rove beetles (*Dalotia coriaria*) and 100% mortality of insidious flower bugs (*Orius insidiosus*) [80]. Taken together, these studies suggest that the effects of flupyradifurone exposure occur more broadly across insects. However, given the limited number of studies available in beneficial insects, more research is required to determine the breadth of sub-lethal effects of flupyradifurone exposure.

Sulfoxaflor appears to have detrimental effects on broad insect taxa, including in the Hymenoptera, Coleoptera and Hemiptera. For example, sulfoxaflor is toxic to wasps (*Tamarixia radiata*) and ants (*Solenopsis invicta*) at high dosages [81,82]. At field-realistic levels of exposure, sulfoxaflor has also been found to reduce the parasitism capacity of parasitoid wasps (*Trichogramma dendrolimi*, *Trichogramma ostriniae* and *Trichogramma confusum)* and can also increase mortality [83]. Lacewings (*Chrysoperla carnea)* topically exposed to sulfoxaflor at the maximum label recommendations had a significant reduction in fertility when exposed as larvae and an increase in mortality when exposed as adults (56% compared with no mortality in the control treatment) [84]. Ladybird (*Adalia bipunctata*) larvae exposed to the same concentrations had 100% mortality (compared to no mortality in the control group) [84]. Field-realistic applications of sulfoxaflor also has detrimental effects on beetles, including reducing pupation and adult emergence of the harlequin ladybird (*Harmonia axyridis*) [85], increasing adult mortality in *Hippodamia convergens* [86] and reducing the number of predatory beetles (*Coccinellidae*) found in treated crops [86]. Finally, sulfoxaflor exposure at label recommendations caused 96% mortality of the Hemipteran *Orius insidiosus* within 24 h after exposure [86].

(e) Quantifying the impact of flupyradifurone and sulfoxaflor on beneficial insects: a meta-analysis

Of the 26 papers on flupyradifurone and sulfoxaflor that we discuss above, we were able to extract data from 19 (effect sizes: flupyradifurone, $n = 38$, sulfoxaflor $n = 60$, see the electronic supplementary material, table S1 for a full list). We found an overall negative impact of both flupyradifurone and sulfoxaflor on beneficial insects (flupyradifurone, figure 1*a*, Hedges d (d) = −0.53, 95% confidence intervals (CI) = −0.74 to −0.32; sulfoxaflor, figure 1*b*, $d = -1.61$ CI = −2.16 to −1.07).

Flupyradifurone exposure had a significant negative effect on the mortality, fitness and behaviour of beneficial insects (figure 1a, mortality, $d = -0.89$, CI = −1.28 to −0.51; fitness, $d = -0.42$, CI = −0.77 to −0.06; behaviour, $d = -0.20$, CI = −0.38 to −0.02). Importantly, these negative effects held at field-realistic levels (figure 1*a*, field realistic, $d = -0.29$, CI = −0.44 to −0.14). Effects occurred across both pollinators (*Apis*) and predatory insects (*Dalotia*), although the sample size was low for the latter ($n = 3$) and so this result should be treated with caution (figure 1*a*, pollinators, $d = -0.50$, CI = −0.72 to −0.28; predatory insects, $d = -1.23$, CI = −2.01 to −0.44). Sulfoxaflor similarly had a negative effect on beneficial insect mortality and fitness (figure 1*b*, mortality, $d = -2.56$, CI = 4.02 to −1.09; fitness, $d = -0.71$, CI = −0.92 to −0.50), while no effect was observed on behaviour ($d = -0.14$, CI = −0.40 to 0.11). Again, the negative effects on beneficial insects still held at field-realistic concentrations (figure 1*b*, field realistic $d = -0.54$, CI = −0.69 to −0.40), and these effects were consistent across pollinators (*Apis* and *Bombus*) and predatory insects (*Adalia*, *Chrysoperla*, *Chrysopidae*, *Coccinellidae*, *Harmonia*, *Orius*, *Solenopsis*, *Trichogramma*) (figure 1*b*, pollinators, $d = -1.29$, CI = −2.19 to −0.39; predatory insects, $d = -1.27$, CI = −1.57 to −0.86).

4. Changing the regulatory process to better protect beneficial insects

Our review and meta-analysis demonstrate that novel insecticides have significant sub-lethal impacts on beneficial insects, demonstrating that, in its current form, the regulatory process does not safeguard beneficial insects from detrimental effects of agrochemical use. Thus, simply replacing neonicotinoids with novel chemical insecticides is unlikely to reduce negative consequences on beneficial insects. Below we outline three ways in which we believe the agrochemical regulatory process can be changed to better protect beneficial insects.

(a) Mandatory assessments of sub-lethal effects on wild bees

The agrochemical regulatory process is a tiered system that is highly reliant on toxicity assessments in the first tier [28,29]. Toxicity tests are used to determine ‘worst-case’ scenario outcomes. If these tests demonstrate a high potential risk to bees (or other organisms), then further higher tier experiments (tiers 2 and 3) may be conducted [28,29]. Western honeybees (*A. mellifera*) are used as a model species for all bees in tier 1, regardless of their unique biology compared to the approximately 20 000 other species of bee [31,87]. This means that insecticides can be licenced for use without the sub-lethal impacts on wild bees, such as bumblebees and solitary bees, ever being assessed. In this review, we highlighted a range of complex and species-specific sub-lethal effects of insecticide exposure on beneficial insects. While it is impractical to test for every possible sub-lethal effect of novel insecticides, we believe that a few key sub-lethal effects should be measured. The most all-encompassing measure of detrimental effects outside of lethality is fecundity (e.g. number of eggs, larvae, pupae, workers and/or sexuals

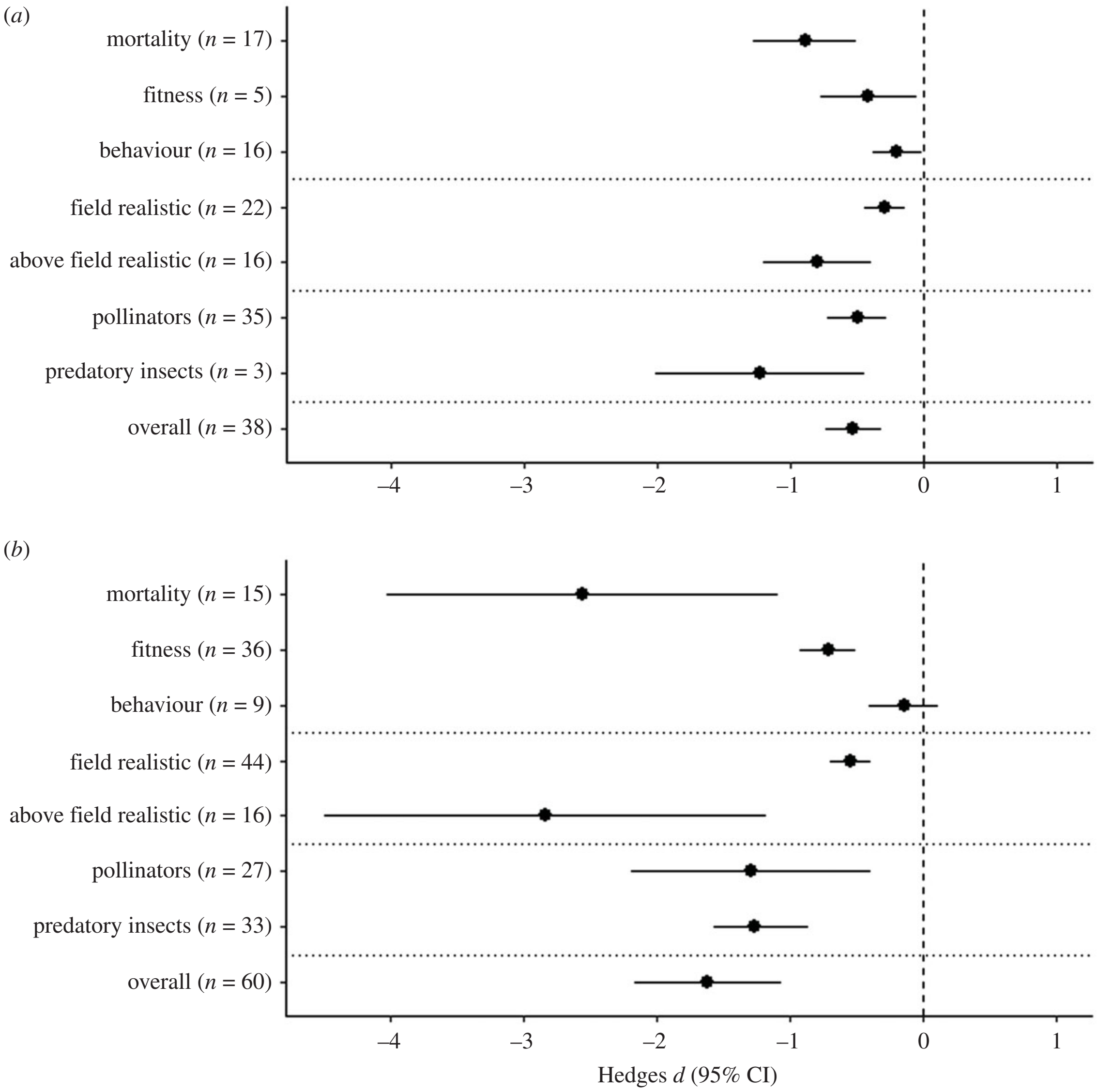

Figure 1. Hedges *d* ± 95% confidence intervals for the impacts of flupyradifurone (*a*) and sulfoxaflor (*b*) on beneficial insects. Negative Hedges *d* values that do not overlap the zero line indicate a significant negative effect of the insecticide on beneficial insects. *n* = the number of effect sizes in each sub-group.

produced during the experimental period). Other sub-lethal effects, such as those on bee behaviour, will only be consequential if they in turn affect individual or colony fitness. Furthermore, measuring fecundity offers an endpoint that can be modelled on a population scale [20,88] from which acceptable levels of risk can be calculated.

One of the difficulties in assessing the potential impact of novel insecticides on bumblebees is that reproduction occurs at the colony level, which both takes a significant period of time (most bumblebee species have an annual lifecycle) and requires large numbers of individuals to be used (each colony can have hundreds of workers). One method, previously suggested in a European Food Safety Authority (EFSA) report [29], that can be used to assess bumblebee fecundity, is the use of 'microcolonies' [29,65,66,89,90]. Bumblebee workers have reproductive plasticity, and when removed from the queen, will develop their ovaries and start laying eggs [91,92]. This means that bumblebee workers can be used to assess the sub-lethal impact of insecticides on colony egg laying, larval production and adult mortality, making microcolony-based experiments a useful tool for assessing the sub-lethal impacts of chronic insecticide exposure on bumblebee fecundity. Less research has been conducted on solitary bees, despite them being both the majority of bee species and more vulnerable to agrochemical exposure than social bees [93–96]. Experiments that assess the impact of sub-lethal insecticide exposure on solitary bee adults [97–99] and larvae [100] have been developed and could be implemented within the regulatory process. Methods that measure the fecundity of commercially available solitary bees (e.g. *Osmia bicornis*) after exposure to novel insecticides are an obvious candidate for the regulatory process owing to their availability, and importance in agriculture [97,98]. These suggested changes to the regulatory process are not necessarily novel (e.g. see [29]), but importantly, we suggest that these sub-lethal assessments on wild bees should be mandatory in the first tier of risk-assessment, before an insecticide is licenced for use.

(b) Assessments of novel insecticides on non-bee beneficial insects

As highlighted in this review, there is a lack of research on the potential impact of flupyradifurone and sulfoxaflor exposure on insects aside from bees, despite their important role in ecosystems and agriculture [101,102]. Furthermore, as with native bees [3,62,103], insects more broadly are in decline globally [4–6], with knock-on consequences for wildlife in general [5,104]. Insect declines are occurring for multiple reasons [9,105] and our meta-analysis shows that novel insecticides could contribute to the decline of beneficial insects. It is therefore critical that the insecticide regulatory process considers the wider impact of agrochemical use on beneficial insects, and develops and implements methodologies (as described in §3d) that assess the sub-lethal impacts of novel insecticides on beneficial insects, particularly those that can aid with pest control.

(c) Assessment of interactions between agrochemicals and other anthropogenic stressors

Beneficial insects face many different anthropogenic stressors such as habitat loss (causing loss of key nutritional resources and nesting sites), agrochemicals, pathogens and climate change [9,105]. As highlighted in §3a, interactions between multiple stressors can exacerbate negative effects on insects [49,55,106,107]. For example, when used in combination, certain agrochemicals can lower the LD_{50} of an insecticide, increasing mortality [49,55,106]. Insecticide exposure can also make bees more vulnerable to pathogens and disease by impairing their immune response [107,108]. Understanding how and to what extent anthropogenic stressors interact is therefore of utmost importance.

Testing the potential interactions between agrochemicals and every other anthropogenic stressor that insects may experience is unfeasible. However, likely stressors, such as nutritional stress, could easily be introduced to current and proposed methodologies (see §4a) used within the regulatory process [54]. Likewise, testing the interactions between insecticides and other agrochemicals such as fungicides and herbicides, especially those that are used in the same commercial formula, can be easily conducted with other commonly used methodologies [49,55,97]. Testing the potential interactions between agrochemicals and pathogens is also important, but the sheer number of insect pathogens similarly makes it unfeasible to test all possible interactions. Therefore, understanding how insecticides interact with the most commonly occurring pathogens, such as *Varroa destructor* in honeybees, or *Critihdia bombi* in bumblebees, should be prioritized. More importantly, post-monitoring licencing, that is currently non-existent, is essential for understanding the interactions between insecticides and other anthropogenic stressors in beneficial insects [33]. Only with such continued monitoring will we gain a thorough understanding of how novel insecticides will influence beneficial insects under field conditions [9,105].

5. Conclusion

Intensive agriculture is heavily reliant on insecticides for controlling insect pests [12]. Our analysis demonstrated that flupyradifurone and sulfoxaflor can have significant negative sub-lethal impacts on beneficial insects, confirming that (i) in its current form, the regulatory process is failing to detect the sub-lethal but significant negative impacts of novel insecticides on beneficial insects, and (ii) bans on commonly used insecticides will only protect beneficial insects if replacement insecticides do not have similar sub-lethal impacts. Whether an insecticide will ever exist that controls pest species while having no impact on beneficial insects is unknown. However, a failure to modify the regulatory process and consider the sub-lethal impacts of novel insecticides will result in the continuing cycle of insecticides being licenced for use without a full understanding of their potential impact on beneficial insects. Moving forward, programmes that incentivize agrochemical reduction and promote an integrated pest management approach will better safeguard beneficial insects and the ecosystem services we rely on for global food production.

Data accessibility. All data are available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.x3ffbg7gv [109].

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