

Bees exposed to climate change are more sensitive to pesticides

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Abstract

Bee populations are exposed to multiple stressors, including land-use change, biological invasions, climate change, and pesticide exposure, that may interact synergistically. We analyze the combined effects of climate warming and sublethal insecticide exposure in the solitary bee *Osmia cornuta*. Previous *Osmia* studies show that warm wintering temperatures cause body weight loss, lipid consumption, and fat body depletion. Because the fat body plays a key role in xenobiotic detoxification, we expected that bees exposed to climate warming scenarios would be more sensitive to pesticides. We exposed *O. cornuta* females to three wintering treatments: current scenario (2007–2012 temperatures), near-future (2021–2050 projected temperatures), and distant-future (2051–2080). Upon emergence in spring, bees were orally exposed to three sublethal doses of an insecticide (Closer, a.i. sulfoxaflor; 0, 4.55 and 11.64 ng a.i./bee). We measured the combined effects of wintering and insecticide exposure on phototactic response, syrup consumption, and longevity. Wintering treatment by itself did not affect winter mortality, but body weight loss increased with increasing wintering temperatures. Similarly, wintering treatment by itself hardly influenced phototactic response or syrup consumption. However, bees wintered at the warmest temperatures had shorter longevity, a strong fecundity predictor in *Osmia*. Insecticide exposure, especially at the high dose, impaired the ability of bees to respond to light, and resulted in reduced syrup consumption and longevity. The combination of the warmest winter and the high insecticide dose resulted in a 70% longevity decrease. Smaller bees, resulting from smaller pollen–nectar provisions, had shorter longevity suggesting nutritional stress may further compromise fecundity in *O. cornuta*. Our results show a synergistic interaction between two major drivers of bee declines, and indicate that bees will become more sensitive to pesticides under the current global warming scenario. Our findings have important implications for pesticide regulation and underscore the need to consider multiple stressors to understand bee declines.

KEY WORDS

body size, climate change, global warming, longevity, nutritional stress, *Osmia cornuta*, pesticide exposure, sulfoxaflor, synergistic effects, toxicity

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1 | INTRODUCTION

Bees play a key role in the functioning of terrestrial ecosystems and provide essential pollination services for agricultural crops (Klein et al., 2007; Ollerton et al., 2011). However, bees have experienced significant declines in abundance and diversity over the last century (Goulson et al., 2015; Potts et al., 2010; Sánchez-Bayo & Wyckhuys, 2019). The causes of these declines are at least partially known, and include land-use change, biological invasions, climate change, and the increasing use of pesticides associated with agricultural intensification (Goulson et al., 2015; IPBES, 2021). Importantly, these stressors do not act in isolation and sometimes interact synergistically (Castelli et al., 2020; Goulson et al., 2015; Siviter et al., 2021). Various studies show that the combined exposure of multiple stressors at sublethal levels may cause lethal effects (Doublet et al., 2015; Vanbergen, 2021). For example, disease-induced stress may result in increased sensitivity to pesticides, and, at the same time, sublethal exposure to toxicants may cause immunosuppression and increased vulnerability to pathogenic infections (Aufauvre et al., 2012; Doublet et al., 2015; Grassl et al., 2018; Pettis et al., 2012; Vidau et al., 2011). Insecticide exposure and nutritional stress may also interact synergistically, resulting in reduced thermoregulation capability, food consumption, flight ability, and survival (Castle et al., 2022; Linguadoca et al., 2021; Tong et al., 2019; Tosi et al., 2017). These studies underscore the need to address the combined effects of various stressors to understand the drivers of bee declines.

Like other ectotherms, insects are highly dependent on environmental temperatures for adequate growth, development, and reproduction, which makes them particularly vulnerable to global warming (Deutsch et al., 2008; Portner, 2002). In general, exposure to warm temperatures increases metabolic activity in insects, affecting development rates and overall physiological functioning (González-Tokman et al., 2020; Neven, 2000). These effects are accompanied by an increase in energy expenditure (Brown et al., 2004), resulting in the mobilization and consumption of stored metabolic resources (Storey & Storey, 2004), ultimately affecting body size, longevity, and fecundity (Blanckenhorn & Henseler, 2005; Fischer et al., 2014; Kierat et al., 2017; Vestelund et al., 2014; Zhang et al., 2015). Several studies show that thermal stress enhances the depletion of fat body reserves in different insect groups (Jean et al., 1990; Klepsat et al., 2016; Williams et al., 2012), including bees (Bosch et al., 2010; Fliszkiewicz et al., 2012; Sgolastra et al., 2011). Fat bodies play a crucial role not only in the storage and release of energy in response to metabolic demands (Arrese & Soulages, 2010), but also in the functioning of key physiological processes such as diapause development (Hahn & Denlinger, 2007), hormone regulation, and immune response (Keeley, 1985; Skowronek et al., 2021). Importantly, fat bodies are also the main tissue in which detoxification enzymes, such as cytochrome P450 monooxygenases, are produced and expressed (David et al., 2006; Petersen et al., 2001). Therefore, the alteration of fat bodies caused by heat stress may also impair detoxification

processes in insects (Costa et al., 2020; Linguadoca et al., 2021; Lycett et al., 2006).

In this study we explored the combined effects of increasingly warm wintering temperatures associated with the current scenario of global warming and exposure to sublethal levels of insecticide in the solitary bee *Osmia cornuta*. We expected exposure to warm temperatures to result in increased sensitivity to the insecticide. To the best of our knowledge, the interaction between pesticide exposure and climate change has not been previously addressed in solitary bees. *Osmia* spp. are appropriate organisms for a study of this sort because both their wintering ecophysiology and their sensitivity to insecticides have been studied in some detail. *Osmia* spp. overwinter on a fixed energetic budget (Bosch et al., 2010). Adult eclosion takes place in autumn, but adults remain inside their cocoons within their natal nest, without access to food until next spring. Therefore, wintering adults rely totally on the energy reserves derived from the food provisions ingested by the larval stage in early summer. This is in contrast to bumblebees and honey bees, which overwinter as emerged adults and therefore are able to feed before, and sometimes during, the winter. Previous *Osmia* studies have shown that warm pre-wintering and wintering temperatures enhance fat body depletion, lipid consumption, and body weight loss (Bosch et al., 2000, 2010; Bosch & Kemp, 2003, 2004; Fliszkiewicz et al., 2012; Sgolastra et al., 2011). *Osmia* spp. nest above ground, and therefore are more directly exposed to ambient temperatures than ground nesting bees (Dorian et al., 2022). *O. cornuta* has a strong affinity for fruit tree pollen (Jaumejoan et al., 2023) and, along with other *Osmia* species, is commercially managed for orchard pollination, resulting in frequent exposure to pesticides (Bosch & Kemp, 2002). In 2013, the European Food Safety Authority recommended the use of *O. cornuta* and *O. bicornis* as model species in pesticide risk assessment (EFSA, 2013), and information on the effects of pesticides on these species has notably increased since then (Sgolastra et al., 2019).

The aim of this study is to understand whether climate warming may exacerbate the sensitivity of solitary bees to pesticides. We exposed *O. cornuta* females to three simulated wintering treatments and then assessed their sensitivity to acute oral exposure to the insecticide CloserTM® (a formulation of sulfoxaflor) at two sublethal concentrations. We then measured the combined effects of these two stress factors on the propensity of the bees to respond to a light stimulus (phototactic response), feeding behavior, and longevity.

2 | MATERIALS AND METHODS

2.1 | Life history of *O. cornuta*

O. cornuta, known as the European orchard bee or the horned mason bee, occurs in most of central and southern Europe. Its populations fly in late winter and early spring. Females are active for approximately 20 days (Bosch & Vicens, 2006), during which time they build one or more nests in pre-existing cavities. Each nest consists of a linear series of cells, delimited by mud partitions, each containing a

pollen-nectar provision and an egg. After consuming the provision, the larva spins a cocoon and undergoes a summer diapause in the prepupal stage (Sgolastra et al., 2012). Pupation occurs in mid or late summer, and adult eclosion in late summer or early autumn. Eclosed adults remain inside their cocoons and lower their metabolic rates (Bosch et al., 2010; Sgolastra et al., 2010). Adults require exposure to cold temperatures (wintering) to complete diapause and emerge the following spring as temperatures increase (Bosch & Kemp, 2004; Sgolastra et al., 2010).

2.2 | Wintering and emergence

We used the progeny of an *O. cornuta* population that nested in February–March 2021 in an almond orchard near Lleida (Catalonia, Spain). In mid-September, when bees reached the adult stage, we dissected a subset of nests and collected 825 female cocoons. Cocoon sex can be reliably established based on size and position within the nest (Bosch, 1994). The collected cocoons were individually weighed and randomly assigned to one of three simulated wintering treatments ($n=275$ females per treatment): (a) Current scenario (average hourly temperatures recorded in the area of origin of the population during 2007–2012); (b) near-future scenario (projected temperatures for 2021–2050); and (c) distant-future scenario (projected temperatures for 2051–2080). Future wintering treatments were based on the temperature projections of the 8.5 Representative Concentration Pathways (RCPs) used in the IPCC AR5 assessment report on climate change (Moss et al., 2010). Our projections cover a 30-year period and reflect a mean temperature increase of 0.6 and 2.9°C for the near-future and distant-future scenarios, respectively, compared to the winter temperatures of 2007–2012 (Table 1). Data for the area of origin of the study population were extracted from the Escenarios-PNACC 2017 project (<http://escenarios.adaptecca.es>). We simulated daily temperature curves for each treatment and month (Figure S1; Supporting Information Methods). Cocoons were individually placed in multi-well plates and transferred to temperature-controlled chambers on 1 October until emergence the following year. Actual temperatures within the three chambers were monitored with data loggers throughout the wintering period.

TABLE 1 Mean weight loss and % winter mortality in *Osmia cornuta* females exposed to three wintering treatments representing increasingly warm climate change scenarios.

Wintering treatment	N	Temperatures (°C) ($\bar{X} \pm SE$) (range) ^{1,2}	Wintering duration (days) ¹	Pre-wintering weight (mg) ($\bar{X} \pm SE$) ³	% Winter mortality ($\bar{X} \pm SE$) ³	% Weight loss ($\bar{X} \pm SE$) ³
Current	275	9.4 ± 0.3 (2.6–20.1)	141	224.2 ± 1.6a	2.2 ± 0.8a	3.9 ± 0.04a
Near-future	275	10.0 ± 0.4 (3.2–22.5)	134	224.0 ± 1.6a	1.8 ± 0.6a	5.8 ± 0.05b
Distant-future	275	12.3 ± 0.4 (4.4–25.3)	128	227.0 ± 1.6a	4.0 ± 1.2a	8.4 ± 0.09c

¹From 1 October until 5% female emergence.

²Daily temperature curves provided in Figure S1.

³Values followed by different letters are significantly different (Tukey HSD test, $p > .05$).

Bees of the climate change treatments were expected to emerge before bees of the current treatment (Bosch & Blas, 1994a; Bosch & Kemp, 2003, 2004). Cocoons were checked daily, and when emergence of a given treatment reached 5%, cocoons of that treatment were transferred to an incubation chamber in which they were exposed to 15°C for 24 h and subsequently to 20°C until 100% emergence. Before being transferred to the incubation chamber cocoons were again individually weighed to obtain a measure of weight loss over the winter.

2.3 | Pesticide exposure

Upon emergence, bees were individually kept for 24 h in transparent plastic containers (diameter: 11 cm; height: 7 cm) capped with a pin-perforated lid to allow them to deposit the meconium. Bees were then orally and acutely exposed to one of three insecticide treatments using the “petal method” (Azpiazu et al., 2023). Each bee was offered 20 µL of test solution. Only bees that consumed 100% of the test solution within 3 h ($\geq 90\%$ in all treatments) were included in the analyses. Following this exposure phase, bees were left in the plastic cages and fed ad libitum with a 1-mL calibrated syringe filled with a feeding solution (henceforth syrup; 33% w/w sucrose–water). A petal of *Euryops* spp. (Asteraceae) was attached to the tip of the syringe to enhance prompt location by the bees (Azpiazu et al., 2023). During the experiment, test containers were maintained at $20 \pm 2^\circ\text{C}$ and 50%–70% relative humidity, and received indirect natural light.

We worked with the commercial formulation of sulfoxaflor ClosertM® (Sulfoxaflor 11.43% SC, Corteva Agriscience, Spain S.L.U.). We tested two doses of sulfoxaflor (SUL), 4.55 ng/bee (henceforth low dose) and 11.64 ng/bee (high dose), along with a control (0 ng/bee; 0 dose). The two SUL doses correspond to the LD₁₀ and LD₅₀ at 72 h after exposure of female *O. bicornis* (Azpiazu et al., 2021), adjusted to the greater body weight of *O. cornuta* ($0.149 \text{ g} \pm 0.0142$; Bosch & Vicens, 2002). To obtain the test solutions (20 µL/bee), we prepared a primary stock solution of 1.16 g/L SUL by dissolving Closert in distilled water. This solution was subsequently diluted and finally mixed with syrup at a ratio of 50 µL/mL to achieve the desired doses.

2.4 | Phototaxis test

Two hours after the exposure phase, approximately 25 individuals of each wintering-pesticide treatment were subjected to a phototactic test in which bees in a dark chamber were exposed to a light stimulus. The response of each bee was scored as either positive (the bee walked to the light source within 60 s) or negative (the bee walked but did not reach the light source; see [Supporting Information Methods](#) for details).

2.5 | Syrup consumption and survival

Test cages were inspected daily to monitor syrup consumption (assessed by checking the level of syrup in the calibrated syringe; accuracy: 0.01 mL) and bee mortality. Three additional containers without bees were used as controls to measure and account for changes in syrup levels due to evaporation. The syrup solution was renewed every 3–4 days until all the bees died. Sample sizes for syrup consumption and survival were approximately 60 individuals per wintering treatment and insecticide dose.

2.6 | Data analysis

To test the effect of wintering treatment on winter mortality we used a binomial generalized linear model (GLM). To determine the effect of wintering treatment on percent weight loss, we used a beta regression model, with individual pre-wintering weight as a covariate (betareg package; Cribari-Neto & Zeileis, [2010](#)).

We used GLMs to analyze the effects of wintering treatment, insecticide exposure and their interaction on phototactic response (binomial error distribution and identity link function), daily syrup consumption (zero-inflated Gamma error distribution and log link function), and longevity (Poisson error distribution and log link function). Because body size may affect food consumption (Azpiazu et al., [2019](#); Sgolastra et al., [2018](#)) and pesticide sensitivity (Thompson, [2016](#)), pre-wintering weight was added as a covariate in the syrup consumption and longevity analyses. Pairwise comparisons were done with Tukey's *p*-value adjustment method (emmeans package; Lenth et al., [2019](#)).

We used Kaplan–Meier (K–M) survival curves to illustrate the combined effects of wintering and insecticide treatments on post-exposure survival. Then, we ran a log-rank omnibus test to explore overall differences among treatments (survdiff function of the survival R package with $\rho=0$; Therneau et al., [2020](#)). Pairwise comparisons between survival curves were done with Holm multi-comparison corrections and $\rho=0$ (pairwise_survdiff function of the survminer package; Kassambara et al., [2020](#)).

To explore potential synergistic effects between wintering and insecticide exposure on survival we used the Bliss drugs' independence criterion (Demidenko & Miller, [2019](#)) to compare the observed survival curves of the near- and distant-future populations (at the

different insecticide doses) with the corresponding expected survival probability curves, built assuming no interaction between the two factors. The analyses (details provided in [Supporting Information Methods](#)) were conducted with the Fhtestrcc function of the Fhtest package (Oller & Langohr, [2017](#)).

All analyses were conducted in R (R Core Team, [2020](#)). Primary data and associated R scripts are accessible on the repository Dryad (Albacete et al., [2023](#)).

3 | RESULTS

3.1 | Winter mortality and weight loss

As expected, bees exposed to climate change wintering treatments emerged earlier than bees of the current climate scenario ([Table 1](#)). Winter mortality was very low and was not affected by wintering treatment (GLM, $\chi^2=2.8$; df=2; $p=.2516$). On the other hand, body weight loss increased with wintering temperature (GLM, $\chi^2=2311.8$; df=2; $p<.0001$). Bees of the distant-future scenario lost twice as much body weight as bees of the current scenario ([Table 1](#)). Regardless of the wintering treatment, bees with lower pre-wintering weight lost a greater proportion of body weight (GLM, $\chi^2=16.7$; df=1; $p<.0001$).

3.2 | Phototactic response

Phototactic response was affected by wintering treatment (GLM, $\chi^2=14.7$; df=2; $p=.001$), insecticide dose (GLM, $\chi^2=109.2$; df=2; $p<.0001$), and their interaction (GLM, $\chi^2=16.1$; df=4; $p=.003$). The vast majority of bees not exposed to the insecticide (0 dose) responded positively to light, irrespective of the wintering treatment ([Figure 1](#)). The percentage of bees that responded positively to light decreased with increasing insecticide dose, and this decrease was especially pronounced in bees of the distant-future scenario ([Figure 1](#)). In the current and near-future scenarios, the proportion of positively responding bees was hardly affected by the low insecticide dose, but dropped to ca. 50% when bees were exposed to the high dose. In bees of the distant-future scenario, the proportion of positively responding bees went from 95.8% (0 dose) to 73.1% (low dose) and 11.1% (high dose).

3.3 | Syrup consumption

Daily consumption of the feeding solution was not affected by wintering treatment (GLM, $\chi^2=2.5$; df=2; $p=.2827$) but varied with insecticide exposure (GLM, $\chi^2=65.6$; df=2; $p<.0001$). The interaction between wintering and pesticide exposure was significant (GLM, $\chi^2=17.7$; df=4; $p=.0014$) because differences in syrup consumption across insecticide doses were especially pronounced in bees of the distant-future treatment ([Figure 2A](#)). The effect of

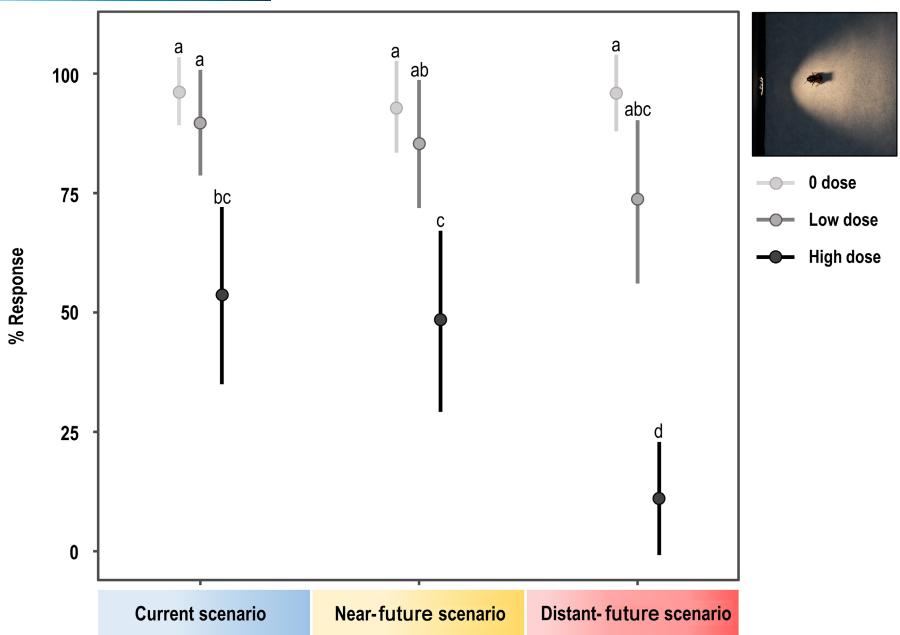


FIGURE 1 Model-estimated means and 95% confidence intervals of percent positive response to a phototaxis test in *Osmia cornuta* females exposed to three wintering treatments representing increasingly warm climate change scenarios, and three orally administered doses of the insecticide sulfoxaflor (0, 4.55 and 11.64 ng/bee). Different letters denote significant differences (Tukey HSD test, $p < .05$). $N = 24\text{--}29$ individuals per wintering scenario and dose.

the high insecticide dose on syrup consumption was evident from day 1 (Figure S2). We expected large bees to consume more syrup than small bees, but the relationship between pre-wintering body weight and daily syrup was not significant (GLM, $\chi^2 = 1.6$; $df = 1$; $p = .1987$).

3.4 | Survival probability and longevity

Survival curves differed significantly among treatments (log-rank test: $\chi^2 = 244.0$; $df = 8$; $p < .0001$; Figure 3). For a given insecticide dose, the current and near-future survival curves were similar ($p > .05$). Survival probability dropped faster in bees of the distant-future scenario than in bees of the current and near-future scenarios at all the insecticide doses tested, including 0 ng/bee. Consequently, longevity differed significantly across different treatments (Figure 2B). Longevity was affected by wintering treatment (GLM, $\chi^2 = 262.1$; $df = 2$; $p < .0001$), insecticide exposure (GLM, $\chi^2 = 613.3$; $df = 2$; $p < .0001$), and their interaction (GLM, $\chi^2 = 39.6$; $df = 4$; $p < .0001$). Pre-wintering body weight had a significant effect on longevity (GLM, $\chi^2 = 27.7$; $df = 1$; $p < .0001$), with large bees living longer than small ones.

To assess potential synergism between wintering treatment and insecticide exposure on survival probability, we compared the observed survival curves of the near and distant-future populations at the two insecticide doses with the expected survival curves based on the Bliss criterion for drugs independence. We found that the combination of the distant-future scenario and exposure to the high insecticide dose resulted in a synergistic decrease in survival

(Figure 4a). We also found a significant antagonistic effect in bees of the near-future scenario exposed to the low insecticide dose (Figure 4b).

4 | DISCUSSION

The aim of this study was to establish whether climate warming could affect the ability of adult bees to cope with pesticide exposure. We used climate change projections from IPCC RCP8.5 and realistic concentrations of a widely used insecticide to assess the combined effects of increasingly warm wintering temperatures and sublethal insecticide exposure on the behavior and longevity of a solitary bee. Our results demonstrate synergistic effects between realistic scenarios of two of the main drivers of bee declines. Importantly, these effects were obtained following acute oral exposure to a single insecticide. In field conditions bees may experience repeated and/or chronic exposure to a variety of chemicals via different exposure routes (Knapp et al., 2023; Sanchez-Bayo & Goka, 2014). At the same time, the temperatures of our most pessimistic climate scenario are already occurring in particularly warm winters (winter temperatures in Europe in 2019–2020 were 3.4°C higher than the mean of 1981–2010; AEMET, 2021; Copernicus, 2020). Therefore, both our pesticide and climate scenarios may be considered conservative. Our results underscore the need to study combinations of stressors to fully understand the effects of global change on bee populations (Goulson et al., 2015). Our findings also have important implications for pesticide regulation. Pesticide risk assessment is based on median lethal and effect doses (LD50 and ED50). Given

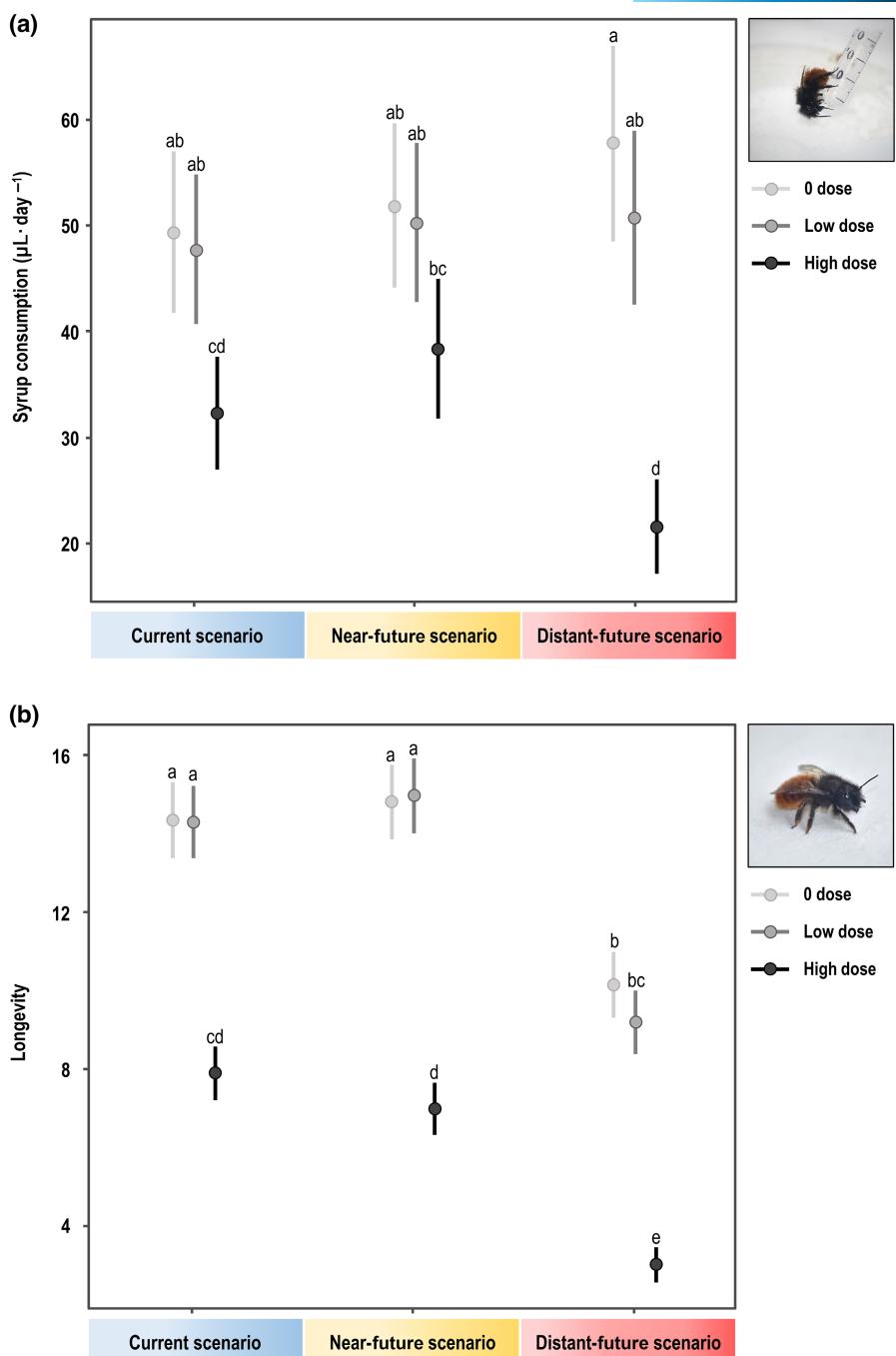


FIGURE 2 Model-estimated means and 95% confidence intervals of daily syrup consumption (a) and longevity (b) in *Osmia cornuta* females exposed to three wintering treatments representing increasingly warm climate change scenarios, and three orally administered doses of the insecticide sulfoxaflor (0, 4.55, and 11.64 ng/bee). Different letters denote significant differences (Tukey HSD test, $p < .05$). $N = 53\text{--}65$ individuals per wintering scenario and dose.

our results, current LD₅₀ and ED₅₀ values may not represent sufficiently protective thresholds as bee populations are confronted with increasingly warm temperatures.

Wintering treatment did not have a significant effect on winter mortality, which was very low and similar to mortality values found in studies in which *Osmia* populations were wintered under natural conditions (Bosch & Blas, 1994b; Bosch & Kemp, 2000; CaraDonna et al., 2018; Sgolastra et al., 2012). Similarly, wintering

treatment by itself did not impair the ability of females to respond to light. On the other hand, wintering treatment had an important impact on weight loss, which, in agreement with previous studies, increased with wintering temperatures. Because body weight loss during wintering is accompanied by the depletion of energy reserves in *Osmia* (Fliszkiewicz et al., 2012; Sgolastra et al., 2011), we expected that bees exposed to climate warming would consume more syrup to rebuild their metabolic reserves (Nestel et al., 2016).

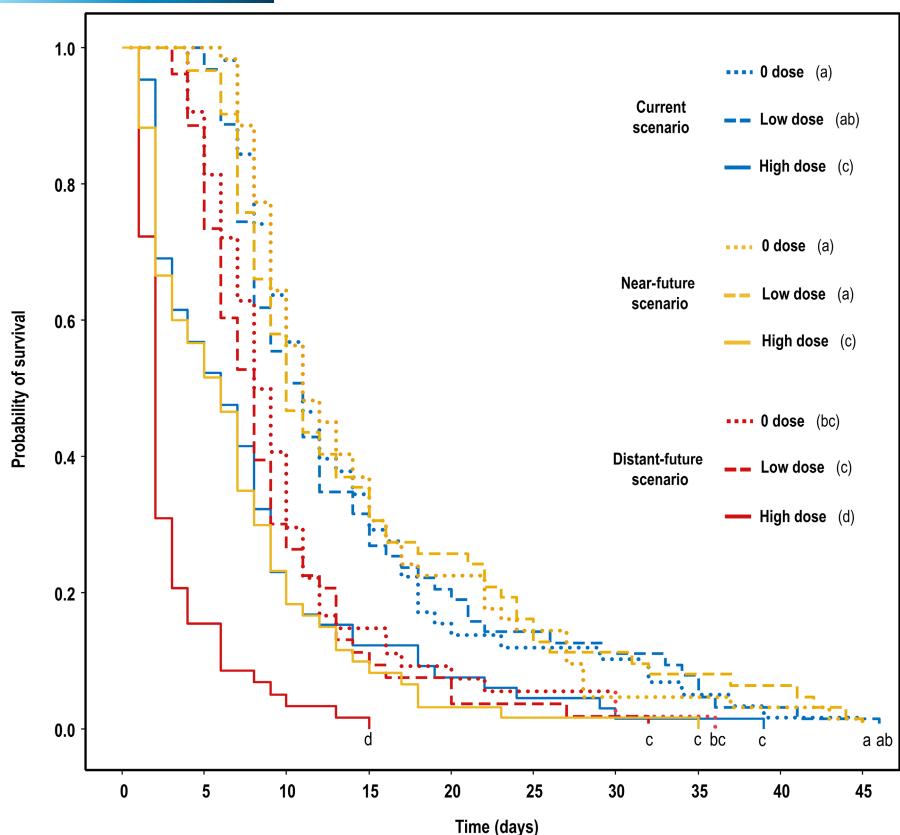


FIGURE 3 Cumulative survival probability of *Osmia cornuta* females exposed to three wintering treatments representing increasingly warm climate change scenarios, and three orally administered doses of the insecticide sulfoxaflor (0, 4.55, and 11.64 ng/bee). Curves with different letters are significantly different (pairwise comparisons, log-rank test, $p < .05$).

Contrary to this expectation, wintering treatment did not affect daily syrup consumption. So far, these findings suggest that the climate change scenarios tested would not compromise winter survival, feeding success and post-emergence performance in *O. cornuta*. However, even with similar feeding rates, bees wintered at the warmest temperature regime had significantly reduced mean longevity (10 days compared to 14–15 days in bees of the other two wintering scenarios), a strong predictor of realized fecundity in *Osmia* (Bosch & Vicens, 2006; Sgolastra et al., 2016). Longevity was also significantly affected by body size, with small individuals having shorter life spans. Adult body size in *Osmia* is directly dependent on the amount of food provision allocated to the larva by the nesting female (Bosch & Vicens, 2002). Therefore, historical declines in bee body size attributed to scarcity of floral resources in simplified landscapes may be further compromising bee longevity and realized fecundity (Chole et al., 2019; Grab et al., 2019; Herrera et al., 2023; Oliveira et al., 2016).

Like most solitary bees, *Osmia* spp. overwinter on a fixed budget, and experience a considerable depletion of lipid reserves during wintering (Fliszkiewicz et al., 2012; Sgolastra et al., 2011). Upon emergence, adults fly to nearby flowers and take a first, long, nectar meal that presumably allows them to rebuild their energetic resources (Bosch & Kemp, 2001; Nestel et al., 2016). In agricultural environments, however, the nectar ingested in this first meal may

contain sublethal levels of pesticides (David et al., 2016; Dively & Kamel, 2012; Heller et al., 2020; Hladik et al., 2016). To mimic this scenario, we exposed newly emerged bees to two sublethal doses of Closer, a widely used insecticide. The doses used correspond to concentrations of 0.58 and 0.23 ppm of active ingredient, which fall within the range of sulfoxaflor residues found in the nectar of various crop flowers 2–7 days after application (USEPA, 2019). Our results show that these realistic levels of exposure, especially the high dose, impaired the ability of bees to respond to light resulting in a drastic reduction of phototactic response in bees of the distant-future climate scenario (Figure 1). The inability to respond to light is indicative of an alteration of the sensitivity or the functioning of the visual system (Klein et al., 2017). Exposure to sublethal doses of imidacloprid, a neonicotinoid insecticide with a mode of action similar to sulfoxaflor (Sparks et al., 2013), increases the expression of genes related to biogenic amine receptors, such as serotonin, tyramine, and octopamine, associated with a lack of phototactic response in *Drosophila* (Martelli et al., 2020). High levels of octopamine have also been linked to reduced response to light in honey bees (Bloch & Meshi, 2007; Scheiner et al., 2014).

The interaction between wintering and pesticide exposure was also evident in the rate of daily syrup consumption. Exposure to the insecticide depressed feeding rates in bees of the three wintering treatments, but this decrease was especially pronounced in

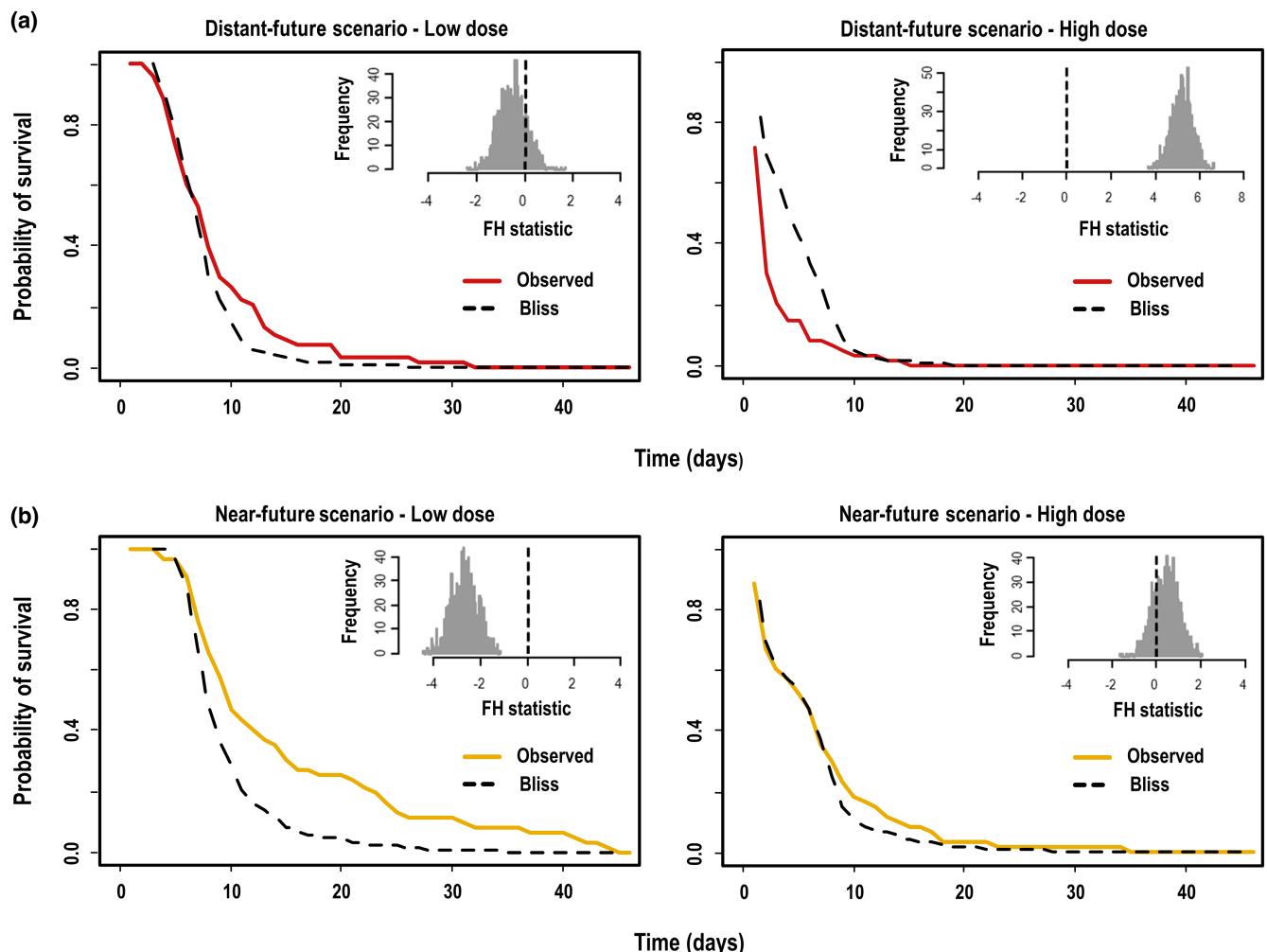


FIGURE 4 Observed (red/yellow lines) and expected (black dashed lines) survival probability curves of *Osmia cornuta* females exposed to distant- (a) and near-future (b) climate change scenarios and to two orally administered doses of the insecticide sulfoxaflor (4.55 and 11.64 ng/bee). Interaction significance is based on the Bliss criterion of drugs independence (FH statistic distribution >0 indicates synergism between the two stressors; FH statistic distribution <0 indicates antagonism).

bees exposed to the warmest winter (Figure 2A). The inhibitory effect of sulfoxaflor on syrup consumption has been documented in both solitary and social bees (Azpiazu et al., 2022; Li et al., 2021; Siviter et al., 2020). Longevity was reduced by ca. 50% in bees of the current and near-future scenarios exposed to the high insecticide dose. In bees of the distant-future scenario, exposure to the low dose led to an estimated 11% reduction in longevity and exposure to the high dose resulted in a synergistic 70% reduction (Figure 3). As mentioned, the cognitive abilities of the bees of the latter treatment were significantly impaired, further reducing the effective time frame available for reproduction (Bosch & Vicens, 2006; Sgolastra et al., 2016). We also found that bees exposed to the near-future scenario and the low insecticide dose lived longer than expected. However, this antagonistic effect did not result in an increase in longevity compared to bees of the near-future scenario exposed to the 0 insecticide dose. Antagonistic interactions are not uncommon in studies addressing interactions between stressors (Bird et al., 2021; Bruckner et al., 2023; Siviter et al., 2021; Zaragoza-Trello et al., 2021).

The increased sensitivity to Closter in bees exposed to climate warming scenarios may be mediated by the effects of warm winter temperatures on the consumption of energy reserves and fat body depletion in *Osmia* (Bosch et al., 2000, 2010; Bosch & Kemp, 2003, 2004; Fliszkiewicz et al., 2012; Sgolastra et al., 2011). The fat body is a dynamic, "liver-like", tissue that acts as an organ of energy storage and other metabolic functions in insects (Arrese & Soulages, 2010). Studies on butterflies and mosquitoes have found that exposure to xenobiotics increases the expression of cytochrome P450 monooxygenases genes, involved in detoxification, in the fat body (David et al., 2006; Petersen et al., 2001). In addition, studies on bumblebees have found that the expression of these genes in the fat body is enhanced by a sucrose-rich diet (Costa et al., 2020), and that queens, which have significantly higher fat body reserves than males and workers, are more resilient to pesticides (Linguadoca et al., 2022). In honey bees, attack by the mite *Varroa destructor*, that feeds on the fat body of adults (Ramsey et al., 2019) disrupts detoxification ability and increases sensitivity

to pesticides (Blanken et al., 2015; Schwartz et al., 2021; Zhu et al., 2022). Based on this line of evidence, we suggest that the ability to produce detoxification enzymes to confront sublethal levels of insecticide is depressed in solitary bees emerging with depleted fat bodies as a result of warm winter temperatures.

Our findings indicate that ongoing global warming may exacerbate the impact of pesticides on bee health and compromise bee reproductive success, with potentially important consequences on population dynamics. The magnitude of these impacts will depend on our ability to reduce the dependence of agriculture on pesticides (Siviter et al., 2023; Sponsler et al., 2019) and on the extent to which bee populations are able to adjust to the new climate scenario through adaptation and/or phenotypic plasticity. The distribution of *O. cornuta* ranges from northern Africa to southern Sweden (Müller, 2022), suggesting that the species has the capacity to adapt to local climates. Temperature increases such as those simulated in our study are likely to have a stronger impact in populations from already warm environments, living closer to the thermal safety limits of the species, than in northern populations (CaraDonna et al., 2018). Bees may also mitigate the effects of climate warming by actively selecting cooler nesting sites, as shown in *O. bicornis* (Ostap-Chec et al., 2021), or through latitudinal or altitudinal migration to cooler areas (Kerr et al., 2015). At any rate, the fact that temperature increases similar to those of our most pessimistic scenario have been recorded in recent years (AEMET, 2021; Copernicus, 2020) suggests that the combined effects of climate warming and pesticide exposure are already affecting bee population dynamics.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support findings of this study are available on Dryad at <https://doi.org/10.5061/dryad.dz08kps3f>.

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