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2 **Title:** Do pesticide and pathogen interactions drive wild bee declines?

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11 **Abstract**

12 There is clear evidence for wild insect declines globally. Habitat loss, climate change, pests, pathogens
13 and environmental pollution have all been shown to cause detrimental effects on insects. However,
14 interactive effects between these stressors may be the key to understanding reported declines. Here,
15 we review the literature on pesticide and pathogen interactions for wild bees, identify knowledge
16 gaps, and suggest avenues for future research fostering mitigation of the observed declines. The
17 limited studies available suggest that effects of pesticides most likely override effects of pathogens.
18 Bees feeding on flowers and building sheltered nests, are likely less adapted to toxins compared to
19 other insects, which potential susceptibility is enhanced by the reduced number of genes encoding
20 detoxifying enzymes compared with other insect species. However, to date all 10 studies using a fully-
21 crossed design have been conducted in the laboratory on social bees using *Crithidia* spp. or *Nosema*
22 spp., identifying an urgent need to test solitary bees and other pathogens. Similarly, since laboratory
23 studies do not necessarily reflect field conditions, semi-field and field studies are essential if we are to

24 understand these interactions and their potential effects in the real-world. In conclusion, there is a
25 clear need for empirical (semi-)field studies on a range of pesticides, pathogens, and insect species to
26 better understand the pathways and mechanisms underlying their potential interactions, in particular
27 their relevance for insect fitness and population dynamics. Such data are indispensable to drive
28 forward robust modelling of interactive effects in different environmental settings and foster
29 predictive science. This will enable pesticide and pathogen interactions to be put into the context of
30 other stressors more broadly, evaluating their relative importance in driving the observed declines of
31 wild bees and other insects. Ultimately, this will enable the development of more effective mitigation
32 measures to protect bees and the ecosystem services they supply.

33 **Key words:** fitness, interactions, pesticides, pathogens, wild bees

34

35 **1. Introduction**

36 Global declines of the entomofauna are occurring at an alarming rate (Cardoso et al., 2020; Eisenhauer
37 et al., 2019; Hallmann et al., 2017). This is of considerable concern as insects play an indispensable
38 role in terrestrial as well as aquatic environments by providing key ecosystem services (Costanza et
39 al., 1997). A wide array of stressors likely govern the observed insect declines and losses, including
40 habitat destruction (Marshall et al., 2017), pest and pathogens (Neumann and Carreck, 2010; Ravoet
41 et al., 2014), climate change (Soroye et al., 2020), intensified agriculture (Díaz et al., 2019; Winfree,
42 2010) and environmental pollution (Straub et al., 2020). These stressors, however, most certainly do
43 not act in isolation. Rather they simultaneously interact with one another thereby generating complex
44 effects that may amplify the direct consequences of a single given stressor (Jackson et al., 2016). Insect
45 pollinators are no exemption to such concurrent exposure scenarios (Goulson et al., 2015a; Siviter et
46 al., 2021a; Vanbergen et al., 2013), which are argued to be a core explanation for increasing reports
47 of wild bee declines (Biesmeijer et al., 2006; Potts et al., 2010). However, there are wide gaps of
48 knowledge surrounding these complex interactions and how they may affect wild bee health and
49 populations (Dicks et al., 2021).

50 Bees are key pollinators of various native plant and crop species, thereby providing immense
51 ecosystem services and sustaining human food security (Diaz et al., 2019; Garibaldi et al., 2016; Potts
52 et al., 2010). With roughly 20'400 described species (Engel et al., 2020; Michener, 2000), bees are a
53 highly diverse group of pollinators, encompassing a range of morphological differences, nesting
54 behaviours, life-histories (e.g., solitary vs. eusocial), phenologies, and foraging habits (e.g., specialists
55 vs. generalists) (Michener, 2000). However, various bee species are currently considered to be
56 critically endangered (Nieto et al., 2014; Zattara and Aizen, 2021), including solitary as well as social
57 bee species (Biesmeijer et al., 2006; Cameron et al., 2011; Powney et al., 2019). Recent research
58 efforts focused on understanding the relationship between environmental stressors and reported wild
59 bee declines have implicated intensive agricultural management practices as being a major driver
60 (Baude et al., 2016; Hayes and Hansen, 2017; Potts et al., 2016; Sánchez-Bayo and Wyckhuys, 2019)).

61 Indeed, large-scale intensified agriculture has reshaped our natural landscapes (Kremen et al., 2002;
62 Tilman et al., 2002), which has led to the reduction of foraging and nesting sites, as well as increased
63 agrochemical exposure for bees and other wild animals (Mancini et al., 2019; Neumann et al., 2015;
64 Woodcock et al., 2016b). A further factor argued to influence population dynamics of wild bees are
65 parasites and pathogens (Cameron et al., 2011; Meeus et al., 2011; Tsvetkov et al., 2021). Undeniably,
66 a plethora of laboratory studies have revealed negative impacts of pesticides and pathogens
67 individually on bee survival, behaviour, physiology, and reproduction (e.g., Blacquière et al., 2012;
68 Schmid-Hempel, 1998). Yet, while the single effects of common bee pathogens (e.g., viruses or
69 *Nosema* spp. parasites) as well as of frequently used pesticides (e.g., neonicotinoid insecticides) have
70 been comparatively well studied (e.g., Grupe and Alisha Quandt, 2020; Pisa et al., 2014; Siviter et al.,
71 2021b, 2021a; Tehel et al., 2016), their interactive effects are poorly understood (Collison et al., 2016).
72 Furthermore, it remains unclear whether a direct link between the exposure to these two groups of
73 stressors and recent observed field declines is even present. Indeed, while some field data are
74 available suggesting the impact of agrochemicals on wild bees in the field (Powney et al., 2019;
75 Rundlöf et al., 2015), there is a lack in knowledge on the actual role of any pathogen on wild bee
76 populations. One exception seems to be the impact of the ectoparasitic mite *Varroa destructor* and
77 associated viruses (Neumann et al., 2012) on wild and feral honey bees in Europe and North America
78 (Kraus and Page, 1995). The latter is an important point as honey bees (*Apis* spp.) consist of at least
79 11 species (Otis, 2019) and only two species are managed (*Apis mellifera* and *Apis cerana*). Even for
80 these two managed honey bees species, the vast majority of colonies in Africa and Asia are still wild
81 rather than managed (Hepburn and Radloff, 1998; Michener, 2000; Otis, 2019). Here, we review the
82 literature on the impact of pesticide and pathogen interactions on wild bees. Based on the current
83 evidence we put this specific interaction scenario into context with other stressors and evaluate their
84 relative importance for recent global wild bee declines. Furthermore, we identify current knowledge
85 gaps and suggest avenues for the future research required if we aim to effectively mitigate the role of
86 pesticide and pathogen interactions in the ongoing decline of wild bees.

87 **2. Methods**

88 All bee species were considered for the literature review. However, studies using managed honey bees
89 (*Apis mellifera*) were excluded as numerous previous reviews have focused on this species to the
90 exclusion of other bees (e.g., Bird et al., 2021; Collison et al., 2016; Siviter et al., 2021b). We used Web
91 of Science as our search engine, using the databases 'Web of Science Core Collection' (1990 to present)
92 and 'BIOSIS Citation Index' (2006 to present). The search terms used were based on three groups: (1)
93 Family or study organism (e.g., Andrenidae or solitary bee); (2) environmental stressors (i.e.,
94 parasite/pathogen or pesticide); and (3) response variable (e.g., survival or sperm). The full search
95 terms used can be found in the supplementary information.

96 The literature search was conducted on 18 November 2021 and yielded 6'458 papers. Articles
97 that did not include data (e.g., reviews, comments, opinions, or editorials), as well as irrelevant studies
98 (e.g., 'rheumatology'), were excluded. Thereafter, 5'069 publications remained. We screened the titles
99 of all papers and excluded papers that did not mention one of the potential environmental stressors
100 as well as papers that used managed honey bees as the only model organism. In total, 3'576 titles
101 were excluded, leaving 1'493 papers. The abstracts were then screened to determine whether (1) the
102 study included combined stressor exposure (i.e., pesticide and parasites or pathogens), and (2)
103 measured a response variable relating to bee health (e.g., survival, physiology, fitness). A further 1'460
104 were excluded at this stage, leaving a total of 33 papers. The remaining papers were carefully read by
105 one researcher (L.S., V.S., or O.Y.) to determine if the study followed the inclusion criteria. For a study
106 to be included, it had to satisfy the following inclusion criteria: (1) the publication had to address the
107 effect of a combination of parasite/pathogen/pest and agrochemical (i.e., herbicides, fungicides,
108 insecticides, acaricides, miticides, biocides, etc.) on wild bee health; and (2) the experimental design
109 had to be fully crossed (i.e., control, treatment stressor 1, treatment stressor 2, and treatment
110 stressor 1 & 2). All studies of individual bees, bees grouped in cages, or colonies at any life stage were
111 included and all measured response variables were considered. Studies were included even if the
112 interaction between stressors was not explicitly tested or stated. This ultimately led to a total of 10

113 publications, which were considered within this review. We cross-checked our search with Google
114 Scholar by using the same terms as described above. However, no additional studies were revealed,
115 thus confirming our search in Web of Science was sufficient.

117 Table 1: Overview of the literature meeting our criteria assessing individual and combined pesticide and pathogen exposure on wild bees.

Authors	Model organism	Pesticide(s)	Chemical(s)	Pathogen(s)	Life-stage(s) exposed	Experiment settings	Assessed parameters	Interaction type(s)	Key findings
Fauser-Mivlun et al. 2014	Bumble bee	Insecticide	Clothianidin, thiamethoxam	<i>Ochriloba bombi</i>	Colony	Laboratory	Survival of mother queens	N.A.	Chronic dietary exposure lead to negative effects on worker production, reduced worker longevity and decreased overall colony reproductive success. Further, the authors revealed a significant interaction between neonicotinoid exposure and parasite infection on mother queen survival. Under combined presence of parasite infection and neonicotinoid exposure, mother queen survival was lowest.
Baron et al. 2014	Bumble bee	Insecticide	Imidacloprid	<i>Ochriloba bombi</i>	Colony and individual workers	Laboratory	Mortality, colony development, reproductive output and body size	None	No significant impact on the susceptibility of workers to <i>C. bombi</i> or intensity of parasitic infection; no impact on survival in workers and males.
Baron et al. 2017	Bumble bee	Insecticide	Thiamethoxam	<i>Ochriloba bombi</i>	Colony and individual queens	Laboratory	Mortality, colony founding, body mass	None	Exposure to thiamethoxam caused a 20% reduction in the proportion of queens that laid eggs, and advanced the timing of colony initiation, yet no effects were observed on the ability of queens to produce adult offspring. No interactive effects were observed between parasite and pesticide.
Fauser et al. 2017	Bumble bee	Insecticide	Thiamethoxam and clothianidin	<i>Ochriloba bombi</i>	Queens	Laboratory	Hibernation survival and hibernation weight change of queens	None	Both reduced hibernation success individually, but no additive or synergistic effects were found.
Bollas et al. 2020	Bumble bee	Insecticide and fungicide	Thiamethoxam, cypermethrin and tebuconazole	<i>Neosoma crassus</i>	Colony	Laboratory exposure; evaluation effects in the field (colonies)	Prevalence of <i>N. crassus</i> , expression levels of immunity and detoxification related genes, food collection, weight gain, worker and male numbers, and production of worker brood and reproductive	Synergistic and antagonistic	Exposure to pesticide mixtures reduced food collection by bumble bees. All immune related genes were up-regulated in the bumble bees inoculated with <i>N. crassus</i> when they had not been exposed to pesticide mixtures, and bumble bees exposed to the fungicide and the pyrethroid were less likely to have <i>N. crassus</i> . Combined exposure to the three-pesticide mixture and <i>N. crassus</i> reduced bumble bee colony growth, and all treatments had detrimental effects on brood production. The groups exposed to the neonicotinoid insecticide produced 40%-70% fewer queens than control colonies.
Gumardes-Castaro et al. 2022	Stingless bees	Herbicide	Glyphosate	Six different strains (DWV, ABPV, BCCV, KBV, IAPV, and CBPV) and <i>Microsporida</i> (<i>Microsporida</i> sp. sp. and <i>N. crassus</i>)	Individual bees	Bee collection in the field, molecular analysis in the laboratory	Six different viruses (DWV, ABPV, BCCV, KBV, IAPV, and CBPV), microsporida (Sp. sp. and <i>N. crassus</i>) and pesticide residues	N.A.	40.55% of samples had <i>N. crassus</i> but not in the mitiqut. 23.4% of samples were positive for viruses. ABPV was the most prevalent, followed by DWV and BCCV. All samples of the <i>T. strongii</i> showed c. 0.25 mg/kg glyphosate and no artemisinylalcohols and (AMPA) metabolites that is the microsporida levels, whereas for the other pesticides analysed were not detected. Due to this low pesticide occurrence, the authors could not evaluate the interaction between pesticide exposure and pathogens in the stingless bees.
Macías-Macias et al. 2020	Stingless bee	Insecticide	Thiamethoxam	<i>Neosoma crassus</i>	Newly emerged bees	Laboratory	Survivability and cellular immunity (hemocyte concentrations)	Synergistic	<i>Neosoma crassus</i> did not affect survivability. Thiamethoxam at a sublethal concentration reduced the survival. Lowest survivability was for the bees treated with both stressors, which suggests a detrimental synergistic effect due to the interaction of <i>N. crassus</i> and thiamethoxam on the lifespan of <i>M. ciliatus</i> . Bees treated with <i>N. crassus</i> only had significantly lower concentrations of hemocytes in the hemolymph than bees of the rest of the treatments. <i>N. crassus</i> may infect and replicate in stingless bees in the Americas and it may inhibit cellular immunity. Thiamethoxam seems to restrain the replication of <i>N. crassus</i> but may be toxic to <i>M. ciliatus</i> bees at sublethal concentrations, particularly in combination with <i>N. crassus</i> infections, which could have negative implications on their populations and pollination services.
Sviter et al. 2020	Bumble bee	Insecticide	Sulfathiazol	<i>Neosoma bombi</i>	Larvae	Laboratory	Mortality, larval growth	Additive and antagonistic	We found no significant impact of sulfathiazol (5 ppm) or <i>N. bombi</i> exposure (20 000 spores) on larval mortality when tested on isolation but found an additive, negative effect when larvae received both stressors in combination. Individually, sulfathiazol and <i>N. bombi</i> exposure each impaired larval growth, although the impact of combined exposure fell significantly short of the predicted sum of the individual effects (i.e. they interacted antagonistically).
Calhoun et al. 2021	Bumble bee	Fungicide	Chlorothalonal	<i>Neosoma bombi</i>	Worker-produced microcolonies	Laboratory	Microcolony development and production. Individual males were assessed for body size, protein amounts, total infection intensity, extracellular spore loads, and survival	None	Development, size, survival and protein amounts of males from microcolonies were not significantly negatively affected by <i>Neosoma</i> exposure or infection, chlorothalonal exposure, nor their interaction. Additionally, the prevalence and infection intensities of 3 bees post-eclosion did not differ. Bees from microcolonies exposed to chlorothalonal exhibited increased spore loads, with spores representing a greater proportion of the total infection intensity. This indicates that in bumblebees, chlorothalonal exposure can interact with <i>N. bombi</i> infection to influence a parameter important for transmission dynamics that could affect colony, population or community health.
Straw and Brown 2021	Bumble bee	Herbicide	Glyphosate	<i>Ochriloba bombi</i>	Microcolonies	Laboratory	Mortality, <i>C. bombi</i> concentration, and worker reproduction	None	Authors found no effects of acute or chronic exposure to glyphosate, over a range of treatment post-exposure, on mortality or a range of sublethal metrics. Further, they found no interaction between glyphosate and <i>Ochriloba bombi</i> in any metric, although there was conflicting evidence of increased parasite intensity after an acute exposure to glyphosate.

120 4. Discussion

121 Here, we show that only a limited number of publications have so far addressed the interactive effects
122 of pesticides and pathogens on wild bees. All studies were performed under laboratory conditions
123 using social species (i.e., bumble bees and stingless bees) and exclusively focussed on interactions
124 between insecticides (mainly neonicotinoids) and either *Crithidia* or *Nosema* spp. Whilst often no
125 significant interaction was observed, some studies found evidence for interactions ranging from
126 antagonism to synergism depending on the measured variable. The limited data so far suggest that
127 effects of pesticides most likely override effects of pathogens, probably because bees, feeding on
128 flowers and building sheltered nests, are less adapted to toxins compared to other insects (but see
129 e.g., Tiedeken et al., 2016). There is an evident need to (i) test pesticide and pathogen interactions
130 across a wider range of bee species, (ii) consider other pathogens, (iii) conduct semi-field and field
131 studies, and (iv) focus on measuring impacts on fitness or fitness-relevant traits when assessing these
132 concurrent exposure scenarios. An improved understanding of the mechanistic pathways and
133 consequences of pesticide and pathogen interactions is essential for adequate conservation to
134 mitigate the ongoing global decline of wild bee species.

135 In contrast to wild bees, studies on interactions between agrochemicals and
136 pathogens/parasites using managed Western honey bees, *A. mellifera*, are far more common (see
137 reviews by (Bird et al., 2021; Collison et al., 2016; O'Neal et al., 2018; Sánchez-Bayo et al., 2016; Siviter
138 et al., 2021a). This is likely due to their economic relevance for pollinating agricultural crops as well as
139 wild plants (Calderone, 2012; Hung et al., 2018; Potts et al., 2010), their use, until recently, as the
140 single model bee species for risk assessments of pesticides, but also because their biology is well
141 known and they are easily maintained under both laboratory (Carreck et al., 2020; Williams et al.,
142 2013) and field conditions (Crane, 2009). In brief, findings of both agrochemical exposure and
143 pathogen infection on managed honey bee health vary among studies, making it difficult to draw
144 general robust conclusions on interactive effects of these two stressors (Collison et al., 2016), although
145 a recent meta-analysis concluded that effects are likely additive overall across bees (Siviter et al.,

146 2021a). The variation in findings may be explained by varying exposure and infection regimes,
147 differences in the developmental stages of the insects (e.g., larvae vs adults), inherent variability (e.g.,
148 genetics or seasonal variability in pathogen loads) and/or variation amongst studies in methodological
149 approaches. The last issue calling for standardized approaches to investigate managed honey bee
150 health using similar methods (Carreck et al., 2020). In a recent meta-analysis from 26 studies testing
151 combined effects of parasites and pesticides on managed honey bee health, the authors concluded
152 that the combined pesticide-pathogen treatments often revealed antagonistic effects, rather than
153 predicted additive or multiplicative effects (Bird et al., 2021; but see Siviter et al., 2021a). The
154 physiological and genetic mechanisms underlying these antagonistic interactions remain unclear and
155 additional research is needed. Furthermore, the majority of managed honey bee studies focus on
156 *Nosema* spp., *Varroa destructor*, and various bee viruses (e.g., Annoscia et al., 2020; Aufauvre et al.,
157 2012; Coulon et al., 2020; Di Prisco et al., 2013; Harwood and Dolezal, 2020; Odemer et al., 2018;
158 Retschnig et al., 2015; Straub et al., 2019). While the role of *Nosema* spp. for colony health remains
159 controversial, i.e. colonies surviving winter have higher *Nosema* spp. loads (Dainat et al., 2012), there
160 is general consensus that the ectoparasitic mite *V. destructor* and associated viruses currently
161 represent the greatest threat to managed honey bee health (Neumann and Carreck, 2010; Rosenkranz
162 et al., 2010). Of particular concern are the negative impacts of these parasites on host immune
163 competence in honey bees (Di Prisco et al., 2016, 2013). Such negative impacts on immune barriers
164 can then be further exacerbated by concurrent pesticide exposure. For instance, pesticide exposure
165 in honey bees has been shown to interfere with individual immune response by impairing the NF- κ B
166 immune signalling pathways, as well as reducing antimicrobial capacity, delaying wound healing and
167 lowering the number of circulating haemocytes (Brandt et al., 2017; Di Prisco et al., 2013; James and
168 Xu, 2012), thus favouring the spread of pathogens and parasites (Annoscia et al., 2020; Di Prisco et al.,
169 2013).

170 Yet, despite significant advances in identifying interactions at the individual level of managed
171 honey bees, few data exist as to why many of the interactions observed fail to translate into

172 quantifiable effects at the colony level (O’Neal et al., 2018; Osterman et al., 2019). This most likely is
173 due to the ability of honey bees and other social insect species to buffer negative impacts at the colony
174 level (i.e., “superorganism resilience” (Straub et al., 2015)). Moreover, laboratory findings do not
175 necessarily translate into quantifiable effects in the field(Retschnig et al., 2015). Indeed, pesticide
176 exposure and pathogen infection have not yet been found to interact and affect managed honey bee
177 worker survival under field-realistic scenarios (Collison et al., 2016). Whilst consequences of pesticide
178 effects on *Nosema* spp. infection levels, viral titres, or individual immunity have been observed under
179 controlled laboratory conditions (Doublet et al., 2014; Gregorc et al., 2016; Grupe and Quandt, 2020;
180 Harwood and Dolezal, 2020; Pettis et al., 2012), similar colony-level effects remain unclear (Collison
181 et al., 2016). Lastly, it is well known that management of honey bee colonies by beekeepers can not
182 only limit natural selection, but may also impose stress itself by exacerbating parasite populations and
183 disease transmission (Neumann and Blacquière, 2016), adding to the complexity of understanding
184 combined pathogen-parasite interactions at the honey bee colony level (O’Neal et al., 2018).
185 Ultimately, while there are significantly more studies investigating the interactions between pesticides
186 and pathogens on managed honey bee health, we still face various uncertainties as to what role these
187 two stressors and their interactive effects play in understanding increased colony losses and wild
188 honey bee health. Furthermore, findings from managed honey bee studies are most likely not ideal
189 for predicting potential effects on wild bees (Wood et al., 2020), in particular solitary bee species, as
190 we discuss below in more depth.

191 Focusing on interaction studies in wild bees, and in particular those of interactions between
192 agrochemicals and parasites and pathogens, these are also limited in breadth. As our results and
193 previous studies show (e.g., Siviter et al., 2021a), most of these experiments have used viruses and
194 *Nosema* spp. in honey bees (e.g., Doublet et al., 2014; Harwood and Dolezal, 2020; Paris et al., 2020,
195 2018; Retschnig et al., 2015; Vidau et al., 2011), and *Crithidia bombi* in bumble bees (Baron et al.,
196 2017, 2014; Fauser-Misslin et al., 2014; Fauser et al., 2017; Straw and Brown, 2021a). While important
197 parasites, these are only a tiny subset of the parasites and pathogens known to infect these two groups

198 of social bees (Schmid-Hempel, 1998). In addition, while these parasites can have significant impacts
199 on bee health, their use in interaction experiments has also likely been driven by the presence of
200 standard protocols for their use and the proportion of the research community who already work on
201 them. Again, there is a general lack of knowledge of the parasite community for most of the ~20,400
202 species of wild bees and their actual impact in the field. In an ideal world, interactive stressor studies
203 would use parasites and pathogens that are known to have significant impacts on wild bees in the
204 laboratory. In the wild, parasite impacts are driven by a combination of virulence and prevalence –
205 highly prevalent parasites with low virulence could still overall have a higher population impact than
206 rarely present parasites with high virulence. For example, from prevalence studies we know that
207 *Crithidia bombi* is highly prevalent in wild bumble bees (e.g., Shykoff and Schmid-Hempel, 1991), and
208 laboratory experiments have shown that it can have significant impacts on bumble bee health under
209 stressful conditions (Brown et al., 2003, 2000; Yourth et al., 2008), but whether it actually impacts the
210 population health of bumble bees in the wild remains unknown. While concerns have been raised that
211 viral spillover from managed honey bees into wild bees might drive wild bee decline (e.g., Fürst et al.,
212 2014), leading to the use of these viruses in wild bee studies (Meeus et al., 2014; Morfin et al., 2019;
213 Tehel et al., 2020), we currently have no understanding of whether so-called honey bee viruses have
214 any impact on wild bees in the field, and some studies even suggest that viruses which have previously
215 been categorized as honey bee viruses are actually endemic in wild bee species (Manley et al., 2020;
216 McMahon et al., 2015; Wang et al., 2018). Moving forward, a key need is first to identify the parasite
217 and pathogen community of wild bees (outside of bumble bees, where it is well-known (Schmid-
218 Hempel, 1998)). This must go beyond just detection and should include parasite and pathogen
219 proliferation, development of disease aka clinical symptoms, and ultimately the impact of these
220 organisms on the fitness of a given host, host colony and possibly entire populations. This will enable
221 us to determine which of these parasites and pathogens actually have meaningful impacts on wild bee
222 population health. Only then can we make sensible choices of which parasites to use in interactive
223 experiments with agrochemicals.

224 Most studies of interactions between stressors in bees have involved insecticides (Siviter et
225 al., 2021a). This focus has arguably been driven by the production, marketing, agricultural application,
226 and scientific investigation of neonicotinoids, a group of systemic insecticides. Initial high profile
227 studies of the impact of neonicotinoids on bee health (e.g., Gill et al., 2012; Henry et al., 2012;
228 Whitehorn et al., 2012) led to both an explosion of research and huge public engagement, which fed
229 on each other to produce a scientific industry of examining all aspects of these insecticides on bee
230 health. While this resulted in the banning of three neonicotinoids for outside use in the EU, these
231 insecticides are still widely used around the world, and research into their impact continues. At the
232 same time, new insecticides have been introduced and examined for their possible impacts (Brown et
233 al., 2016; Siviter et al., 2018; Siviter and Muth, 2020). With the recognition that interactions between
234 stressors might play a key role in reducing bee health (e.g., Vanbergen et al., 2013), it is perhaps no
235 surprise that most interaction studies have included insecticides as one of the stressors.

236 However, insecticides are not the only agrochemical group that could impact bee health.
237 Herbicides and fungicides are heavily used around the globe, and have been shown to have negative
238 effects on bee health (e.g., Belsky & Joshi, 2020), as have other ingredients within agrochemical
239 applications (e.g., Straw & Brown, 2021a). Given this, studies of interactions between stressors need
240 to incorporate a more balanced approach, which recognizes the potential importance of other
241 agrochemicals (Straw et al., 2022). This, in turn, requires a knowledge of the extent to which wild bees
242 are exposed to these other agrochemical stressors, as without this, experiments cannot assess real-
243 world hazard or risk (Mesnage et al., 2021; Straw et al., 2022). Of the ~20,400 species of wild bees,
244 actual exposure to any agrochemical has only been investigated for a handful of species (mainly from
245 the genera *Bombus*, *Osmia*, *Megachile*, or *Melipona*), and this is a major lacuna that urgently needs
246 to be filled.

247 Indeed, our review revealed a striking lack of empirical data from designed experiments to
248 examine interactive effects of pesticides and pathogens in solitary wild bees. All studies on wild bees
249 found in our systematic literature search have been conducted on social bees, focusing on only two

250 pathogen taxa (*Crithidia* and *Nosema* spp.). However, the vast majority of the more than 20,000
251 species of wild bees worldwide (approximately 70% in temperate biogeographic regions) are solitary
252 (Engel et al., 2020; Michener, 2000). A solitary life form implies that a female bee constructs her nest
253 and provisions offspring alone, without cooperation with conspecifics. As a consequence, adverse
254 effects of pesticides, pathogens and their interactions should have more pronounced impacts on
255 solitary bee populations compared to social bees, because negative effects e.g. on mortality or
256 performance of nesting females will directly impair fitness, while social bees should be able to buffer
257 negative impacts to some extent at the colony level (Sgolastra et al., 2019; Straub et al., 2015). Thus,
258 there is an urgent need to extend studies on the impact of pesticides, pathogens and their interactions
259 on a range of solitary bee species, but also wild honey bees and other social bee species (e.g., stingless
260 bees).

261 This plea is underpinned by increasing evidence that the levels and pathways of exposure to
262 individual and combined stressors, as well as a bee's sensitivity to them, strongly depends on specific
263 life-history traits (Arena and Sgolastra, 2014; Brittain and Potts, 2011; Grozinger and Flenniken, 2019;
264 Kopit et al., 2021; Kopit and Pitts-Singer, 2018; Proesmans et al., 2021; Truitt et al., 2016; Uhl et al.,
265 2016). For example, solitary and social bee species differ in activity and nesting period, nesting
266 duration, voltinism, body size, foraging range, habitat preference, food plant preference and level of
267 diet specialization, the level of pollen and nectar consumption as adults and larvae, as well as their
268 mode of nesting (i.e., ground-nesting in the soil or above-ground nesting using different nesting
269 structures) and use of nesting materials (e.g., mud, leaves, plant pubescence), which likely results in
270 different routes and levels of exposure to different pesticide contamination and pathogen infection
271 routes (Proesmans et al., 2021; Sgolastra et al., 2019; Uhl and Brühl, 2019). A large knowledge gap
272 concerns the potential exposure of ground-nesting solitary bees to pesticides accumulating in soils,
273 e.g. as adult female bees excavating soil material to construct nests, or as developing larvae through
274 contact with soil that forms nest cells, although a water-resistant coating applied to nest cells may
275 reduce this exposure risk in many ground-nesting species (Chan et al., 2019). Furthermore, a bee

276 species' sensitivity towards different pesticides can vary strongly between social and solitary bee
277 species (Sgolastra et al., 2020; Wood et al., 2020). Body size can be an important trait affecting such
278 sensitivity (Arena and Sgolastra, 2014; Uhl et al., 2016). Social and solitary bee species also vary in
279 different aspects of physiology, e.g., the detoxification abilities and pathways of different taxa
280 (Hayward et al., 2019).

281 Similarly, species-specific traits likely play an important role in governing inter- and
282 intraspecific transmission of pathogens and a wild bee species' infection risk (Graystock et al., 2016;
283 Manley et al., 2015; Proesmans et al., 2021). For instance, foraging traits of bees, such as diet breadth
284 and preference, along with plant and pathogen traits are likely drivers of horizontal transmission of
285 pathogens between different bee species sharing flowers in plant-bee-pathogen interaction networks
286 (e.g., Figueroa et al., 2020; Graystock et al., 2020, 2016; McArt et al., 2014; Proesmans et al., 2021).
287 Sociality is a further key trait affecting pathogen exposure, transmission, and resistance (Cremer et
288 al., 2007). For example, cooperative brood care, along with overlapping generations in densely
289 populated colonies facilitate disease spread in colonies of social bees (Cremer et al., 2007; Graystock
290 et al., 2015; Manley et al., 2015). Further, the typically generalised floral diets and long colony cycles
291 of most social wild bees contribute to increased direct and indirect (e.g., via shared flowers) contact
292 with other bees and thus pathogen infection risk (Proesmans et al., 2021). However, social bee species
293 have also developed mitigation strategies to reduce risks of high pathogen loads through social
294 immunity (i.e., behavioural, physiological and organisational adaptations of the colony level to prevent
295 pathogen entrance, establishment, and spread (e.g., Cremer et al., 2007; Meunier, 2015; Wilson-Rich
296 et al., 2009a). While social immunity in bees has received relatively high attention, we have little
297 understanding of the biological mechanisms behind it, which may be impaired by pesticide exposure,
298 and even less is known about how pesticides may reduce individual immunocompetence (e.g.,
299 reduced induction of antimicrobial peptides or haemocyte production (Brandt et al., 2020; Collison et
300 al., 2016)) and increase pathogen infestation and pathogen loads in solitary bees, and to what extent
301 such mechanisms may vary among species of different phylogenies and traits (Brandt et al., 2020).

302 Moreover, pathogen research is heavily biased towards social bees, and our knowledge on
303 pathogen and parasite communities in solitary wild bees is scarce (Tehel et al., 2016). Although there
304 is increasing evidence for single-stranded RNA viruses or *Crithidia* ssp. crossing phylogenetic
305 boundaries, and therefore possibly being present in a range of different solitary bee taxa (Mcmahon
306 et al., 2015; Ravoet et al., 2014), there is less evidence that these pathogens are also able to replicate
307 in such solitary bee hosts (e.g., Radzevičiūtė et al., 2017; V. Strobl et al., 2019; Tapia-González et al.,
308 2019), and whether they frequently adversely affect fitness and populations dynamics of solitary bees
309 remains unclear (Dolezal et al., 2016; Tehel et al., 2020, 2016). It also remains unknown, whether
310 potential negative effects of pathogens may be additively or synergistically reinforced by pesticides
311 under field conditions (Brandt et al., 2020; Collison et al., 2016).

312 All identified studies that have addressed interactive effects of pesticides and pathogens on
313 wild bees using a crossed design have been conducted under laboratory conditions. Laboratory studies
314 have clear advantages such as (i) the ability to control for a variety of confounding factors potentially
315 affecting measured response variables in addition to applied treatments, (ii) the availability of well-
316 established and repeatable protocols, (iii) no logistical constraints to achieve – depending on the
317 tested factors and study system – sufficient replication and low risk of type II statistical errors (i.e., a
318 real effect of a tested explanatory variable is not detected due to insufficient experimental
319 replication). Laboratory studies are therefore highly suitable to precisely estimate effect sizes of single
320 and combined treatment factors under study, to provide proof of concepts and test hypotheses on
321 interactive effects, and to draw conclusions about mechanistic relationships of interactive effects of
322 specific pesticides and pathogens (Medrzycki et al., 2013). Hence, such laboratory assessments using
323 standard protocols have traditionally been the cornerstone of regulatory risk assessments processes
324 (e.g., EFSA, 2014; OECD, 1998). However, the advantages of reducing complexity and excluding various
325 influencing factors characterizing real-world systems come at a high price. Ignoring them may lead to
326 unrealistic estimates of effect sizes and potentially wrong conclusions about the existence and

327 magnitude of impacts of pesticide-pathogen interactions on wild bees (Sgolastra et al., 2020; Topping
328 et al., 2021; Van Oystaeyen et al., 2020).

329 Among the many pitfalls of laboratory experiments in addressing pesticide-pathogen
330 interactions are importantly unrealistic or irrelevant concentrations of pesticides used (Carreck and
331 Ratnieks, 2014). To avoid this pitfall, knowledge of the extent to which wild bees are exposed to the
332 studied pesticide(s) is essential (Mesnage et al., 2021; Sanchez-bayo and Goka, 2014). However, such
333 data are currently largely lacking for many pesticides and exposure scenarios for different wild bee
334 species (Kopit and Pitts-Singer, 2018; Main et al., 2020). But experiments cannot assess real-world
335 risks of pesticides and their interactive effects with pathogens on wild bees without such data (EFSA,
336 2014b; Mesnage et al., 2021; Sgolastra et al., 2020, 2019). Similarly, laboratory studies testing effects
337 and underlying mechanisms of interactions between pesticides and pathogens should ensure realistic
338 infection scenarios and pathogen loads for different wild bee species. Yet, our understanding of
339 infection pathways and pathogen loads is very limited for most pathogens and wild bee taxa, which is
340 particularly true for solitary bees (IPBES, 2016; Tehel et al., 2016). Here, field studies are of critical
341 importance to identify which pathogens are actually relevant for which wild bee taxa to address this
342 fundamental knowledge gap (Dicks et al., 2021). Furthermore, ignoring important co-drivers of bee
343 health such as interactions with further key stressors such as nutritional stress (Stuligross and
344 Williams, 2020) may lead to under- or overestimating impacts of pesticides, pathogens, and their
345 interactions on wild bee health (Carreck and Ratnieks, 2014; Goulson et al., 2015b; Siviter et al., 2021a;
346 Topping et al., 2021; Vanbergen et al., 2013).

347 Furthermore, certain key response variables can only be reliably studied under (semi-)field
348 conditions. For example, measuring effects of pesticides, pathogens and their interactions on
349 reproductive success and fitness is crucial to understanding their impacts on populations of wild bees
350 and their long-term trends (IPBES, 2016; Straub et al., 2020). This requires experimental settings in
351 which wild bees can nest, forage and provision their offspring ideally during their entire life cycle,
352 which typically need to be (semi-)field settings (Sgolastra et al., 2020; Van Oystaeyen et al., 2020). To

353 move forward, we therefore urgently need more studies of pesticide-pathogen interactions under
354 field-realistic conditions. However, field studies addressing pesticide-pathogen interactions are
355 challenging in many respects. The less controlled and more complex and variable systems are, and the
356 smaller effect sizes of treatments to be detected, the greater the need for high replication to detect
357 such effects reliably (Cresswell, 2011; EFSA, 2013; Woodcock et al., 2016a). In addition, (semi-)field
358 studies are typically conducted at much larger spatial and temporal scales to adequately embrace
359 natural behaviours and life cycles of wild bees, and they are therefore labour, time, and cost-intensive.
360 It can also be challenging to reproduce field studies across different environmental systems varying in
361 a range of influencing factors such as climatic conditions, land use types etc. (e.g., Woodcock et al.,
362 2017). A key challenge of field experiments studying interactive effects of pesticides and pathogens
363 on wild bees is therefore to balance the level of control and complexity (Suryanarayanan, 2015). More
364 “control-orientated” study designs risk failing to adequately account for important indirect and
365 multifactorial processes affecting bee health, while more “complexity-orientated” studies have a
366 higher risk to fail to detect significant effects and mechanistic relationships for factors of interest
367 (type II statistical error, see above (Woodcock et al., 2016a)).

368 In addition, the deliberate use and potential spread of pathogens for research purposes in
369 field experiments poses significant ethical concerns. Field studies therefore generally rely on
370 quantifying existing pathogen prevalence and loads in wild bees (e.g., Wintermantel et al., 2018).
371 However, researchers can perform *a priori* pathogen screenings and use this information to design
372 experiments testing for single and combined impacts of pathogens and pesticides to increase control
373 over these factors in field experiments and integrate mechanistic models as guidance to design
374 experiments for relevant pesticide-pathogen interactions (Campbell et al., 2016). A promising first
375 step moving forward towards more field-realistic studies on pesticides and their interactions with
376 pathogens or further stressors of wild bees are semi-field experiments (Bramke et al., 2019; Stuligross
377 and Williams, 2020). Such experiments ideally combine advantages such as field-realistic exposure
378 routes and levels, long-term assessments and include measures of fitness and population growth with

379 those of a high level of control of influencing factors e.g. by using caged wild bee populations or
380 colonies (e.g., Strobl et al., 2021a; Strobl et al., 2021b; Tamburini et al., 2021). Last but not least, risks
381 of pathogen spread, at least for some pathogen groups, can be minimized in semi-field experiments
382 conducted with caged wild bees (e.g., Bramke et al., 2019).

383 If we aim to understand pesticide-pathogen interactions, and so effectively mitigate their role
384 in the ongoing loss of wild bee species, we must first strive to improve our understanding of how these
385 stressors individually act on bees. To do so, it appears essential to take evolutionary biology into
386 account and we, therefore, propose future studies should have a stronger focus on fitness, the
387 essential factor governing all wild populations (Straub et al., 2020). For instance, studies using PCR
388 and qPCR methods to detect the prevalence of certain pathogens (e.g., viruses) in bees in the field do
389 not provide proof of an infection (Brown, 2017). As pathogens are likely to be encountered on shared,
390 contaminated food resources (i.e., flowers), the detected pathogen may not even be in the bee, but
391 rather only on the surface of the body. In addition, the bee may only act as a transient host without
392 causing infection or any pathogenic effects to the host (Durrer and Schmid-Hempel, 1995). To exclude
393 these possibilities and adequately address the role of pathogens on wild bee populations, studies must
394 first provide robust evidence that an infection is indeed occurring and that there are clear fitness
395 constraints (e.g., fewer offspring produced) or at least on fitness-relevant traits (e.g., male sperm
396 capacities). The same holds true for understanding the role of pesticide exposure on wild bee declines.
397 While a plethora of studies have demonstrated negative impacts of various pesticides on bees and
398 other pollinators (Blacquièrè et al., 2012; Lu et al., 2020), clear knowledge gaps remain as to how
399 pesticides affect wild bee populations under field conditions. Despite previous large-scale field studies
400 showing causal data suggesting reduced wild bee density and population growth due to pesticide
401 exposure (Rundlöf et al., 2015), the underlying mechanisms are yet to be identified. As it is close to
402 impossible to test each and every pesticide and pathogen interaction in each of the ~20,400 bee
403 species, we must strive to improve our understanding of the underlying mechanistic pathways and
404 how frequent they are across different phylogenetic groups of bees. Only then can we use this

405 knowledge to design more relevant experiments in terms of involved pesticides, pathogens, and bee
406 species, and also move towards a more predictive science and modelling of interactive effects in
407 different environmental contexts (e.g., Topping et al., 2021). Thus, there is an urgent need for
408 additional long-term data on the likelihood of pesticide and pathogen exposure of wild bee
409 communities in the field, as well as data revealing direct causality between such exposure and the loss
410 of wild bee abundance and richness (Brühl et al., 2021; Rundlöf et al., 2015).

411

412 **5. Conclusions**

413 In conclusion, there is a clear need for empirical field studies on a range of pesticides, pathogens, and
414 wild bee species to better understand the nature of interactions, underlying mechanisms, and in
415 particular their relevance for bee fitness. Based on our review it is currently not possible to draw
416 general conclusions on the role of pesticide-pathogen interactions in the ongoing decline of wild bees.
417 However, it appears clear that the interaction of these stressors must be considered within context.
418 Indeed, Bird et al. (2020) revealed that at least for managed honey bees, pesticide-pathogen
419 interactions often yielded antagonism and that the common assumption of additive or synergistic
420 effects may be overrated. For wild bees, habitat destruction and degradation, and the subsequent
421 side effects (e.g., loss of adequate floral food resources, nesting sites or increased fragmentation of
422 food and nesting habitats and thus longer foraging distances (Ganser et al., 2021)) in combination with
423 the ongoing threat of climate change are likely to be far more profound factors (Brown and Paxton,
424 2009; Dicks et al., 2021; IPBES, 2016). A holistic approach is therefore required to first identify the
425 most common and most severe stressor interactions (i.e., synergism) in the natural habitats of various
426 bee species. Later, standardized laboratory studies can help improve our understanding of the
427 physiological and genetic mechanisms underlying such interactions and how they negatively affect
428 fitness. In a final step, these findings must be investigated under field conditions to provide reliable
429 data for models to predict the interactive effects of stressors and so protect bees and other insect

430 species from future risks. Furthermore, it appears long overdue that regulatory authorities
431 incorporate the evaluation of combined stressor interactions into current environmental risk
432 assessments (Topping et al., 2020), including estimates of fitness as the key factor governing any wild
433 population (Straub et al., 2020). This would not only improve our understanding of how stressors
434 interact but also reflect a more field-realistic scenario and enable policy-makers to implement
435 adequate and sustainable measures to safeguard biodiversity.

436

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