Incorporating selection pressures into risk predictions of chemical resistance evolution in pest organisms

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ABSTRACT

The evolution of chemical resistance in pests is a global threat to food security and human health, yet resistance issues are mostly dealt with after they occur. Predictive models of resistance risk provide an opportunity for field practitioners to implement proactive strategies to manage pest species more effectively. These models require identification of variables that are associated with resistance risk. Phagy and voltinism, for example, have been previously shown as useful predictors of resistance evolution. Yet despite the importance of chemical selection pressure in resistance evolution, this predictor has been difficult to incorporate into predictive models due to incomplete and (or) poor datasets on chemical usage patterns. Here we test whether chemical registrations of pesticide products can act as a proxy for selection pressures in predictive models. We obtained pesticide product registrations from publicly available chemical databases for 427 agricultural arthropod pest species in the USA and 209 Australian species. We constructed Bayesian logistic regressions of resistance status as a function of the number of pesticide product registrations for 42 chemical Mode of Action (MoA) groups, as well as phagy and voltinism. These models were well supported by our data and cross-validation analyses and could discriminate between observations of resistance and susceptibility in both USA and Australian species sets. Moreover, we found strong support for a positive correlation between pesticide product registrations and resistance status. We propose a "registration–selection–resistance" hypothesis to explain this positive association, involving a positive feedback loop between marketing and social factors of pesticide use with the evolutionary processes of selection and adaptation. Pesticide product registrations provide a predictive variable that is specific to both pest species and chemical MoA groups. Our work aids the development of predictive models for proactive resistance management, combining ecological and operational factors, with broad applicability across a suite of agricultural pests, including weeds and fungi.

INTRODUCTION

Decades of research into the evolution of pesticide resistance and its molecular basis have contributed to a rich understanding of the dynamics of resistance development, which has benefited management strategies in agricultural and human health contexts (Crow, 1957; Georghiou & Taylor, 1986; Hawkins, Bass, Dixon, & Neve, 2019; McKenzie & Batterham, 1994). One of the major mitigation strategies of pesticide resistance is reducing chemical selection pressures on pest populations, a strategy deeply rooted in adaptive evolutionary theory (Downes

et al., 2010; Forrester, 1990; Georghiou, 1994; Helps, Paveley, White, & van den Bosch, 2020). However, despite our understanding of pesticide resistance evolution, resistance remains a prevalent global issue for pest management and food security (Gould, Brown, & Kuzma, 2018; Liu, 2015; Pimentel et al., 1992; Pu, Wang, & Chung, 2020; Sparks & Nauen, 2015). Indeed, notwithstanding the best efforts of scientists, field practitioners and multi-national chemical companies, entire chemical mode of action (MoA) groups have become ineffective against certain pest groups due to the evolution of resistance (Bass, Denholm, Williamson, & Nauen, 2015; Horowitz, Ghanim, Roditakis, Nauen, & Ishaaya, 2020; Nauen, 2007).

Challenges in managing pesticide resistance are partially attributable to the ongoing importance of chemical control, which places populations under repeated selective pressure to evolve resistance. Pest management strategies are often *reactive* in nature, only being implemented once resistance has evolved and resistant genotypes have reached a detectable frequency in field populations (Sparks & Nauen, 2015; Tabashnik, Mota-Sanchez, Whalon, Hollingworth, & Carrière, 2014; Umina, McDonald, Maino, Edwards, & Hoffmann, 2019). More *proactive* strategies would implement protocols to routinely assess resistance risks prior to control failures developing. To this end, predictions about where and when a species might exhibit high risks of resistance evolution could be used to flag such species for targeted research and monitoring efforts. To achieve this, a comprehensive understanding of factors that increase the risk of resistance evolution is required.

Numerous operational factors directly under human control influence resistance evolution through their effect on pest populations (Georghiou, 1994; Georghiou & Taylor, 1977). One of the most important operational factors is chemical selection pressure (Crow, 1957; Georghiou, 1994; Georghiou & Taylor, 1977; McKenzie & Batterham, 1994). Populations experiencing greater pesticide exposure will be under stronger selection because resistance phenotypes will almost always exist in a region of trait space beyond that available to standing genetic variation, requiring *de novo* mutations to introduce resistance-conferring variants (Georghiou & Taylor, 1977; McKenzie & Batterham, 1994; Roush & McKenzie, 1987). Therefore, repeated exposure of pesticides over multiple generations provide longer temporal windows for resistance mutations to appear and be favored by selection (Georghiou, 1994; Georghiou & Taylor, 1986; Hawkins et al., 2019). In some cases, populations might already contain genetic variants to produce resistant phenotypes, but these variants are at low frequency or (in the case of polygenic resistance) dispersed among individuals, requiring ongoing selection to bring resistant alleles to higher frequency and generate fit genotypic combinations (Bass et al., 2014; Hawkins et al., 2019; Walsh et al., 2018).

Factors influencing resistance evolution include characteristics of a species and how these interact with the environment (Georghiou, 1994; Georghiou & Taylor, 1986). These ecological factors can influence the underlying genetic properties of a species and modulate the action of selection (Georghiou & Taylor, 1977, 1986; Rosenheim & Tabashnik, 1991). Two ecological traits important to resistance evolution in herbivorous arthropod pests are phagy (host breadth) and voltinism (number of generations per year). Increasing phagy and voltinism are expected to favor more rapid resistance evolution due to biochemical preadaptation (Wannes Dermauw et al., 2012; Georghiou, 1994; Rane et al., 2019) and population genetic or population growth effects (Baer, Miyamoto, & Denver, 2007; Georghiou & Taylor, 1986; Li, Tanimura, & Sharp, 1987; Robertson, 1960; Weber, 1990), respectively. Prior work has identified putatively curvilinear effects of these ecological traits, where resistance risk is minimized at intermediate levels of phagy, and maximized at intermediate levels of voltinism (Crossley, Snyder, & Hardy, 2020; Hardy, Peterson, Ross, & Rosenheim, 2018; Rosenheim & Tabashnik, 1991). In contrast to these factors, it has been difficult to incorporate selection pressures into predictive models because data on pesticide applications are generally lacking for pests or else held in commercial databases that cannot be readily accessed.

Here, we constructed predictive models of pesticide resistance status that include an indirect measure of selection pressure. We model the probability of pesticide resistance as a function of two ecological factors, phagy and voltinism, and an operational factor representing a proxy for selection pressure, the number of registrations of pesticide products for individual pest and chemical MoA combinations. We find that all three predictors explain variation in resistance status and contribute toward resistance risk predictions in two independent species sets from the United States of America (USA) and Australia. Our finding that pesticide product registrations help predict resistance status points to a novel way of estimating selection pressures imposed on agricultural pests in the absence of pesticide usage data. We suggest that the association between pesticide product registrations and resistance emerges from a positive feedback loop between pest severity, pesticide popularity, consumer use, selection, and evolving tolerances in the field.

METHODS

DATASET COMPILATION

Data on pesticide products, phagy and voltinism were collected for agricultural arthropod pests from the USA (n = 427 species) and Australia (n = 209 species). Our working dataset was

compiled from publicly available databases and published studies. All data filtering was performed in R v4.1.2 (R Core Team, 2021).

Pesticide products — In the absence of detailed information on chemical usage patterns against agricultural pests in most parts of the world, our study takes a novel approach of using pesticide product registration data as a potential proxy for selection pressure. Our rationale is that highly problematic arthropod pests will have many pesticide products registered against them and will be exposed to greater pesticide load in the field.

For USA pesticide products, we downloaded pesticide product registration data from the Environmental Protection Agency (EPA; https://www.epa.gov/; accessed February 11th, 2021). Likewise, registrations of Australian pesticide products were obtained from the Australian Pesticides and Veterinary Medicines Authority (APVMA; https://apvma.gov.au/; accessed February 9th, 2021). Each of these databases contain tens of thousands of product registrations across time that include agricultural and non-agricultural uses (EPA, n = 165,661; APVMA, n = 22,090). Keyword searches were used to isolate those registrations related to pesticide products for agricultural pests. For the EPA database, we filtered the "Site" variable for keywords like "FOLIAR TREATMENT" or "SEEDLING" (List S1). For the APVMA database, we filtered the "Category" variable for "AGRICULTURAL" products and then filtered the "Product_type" variable for the keywords: "INSECTICIDE", "MITICIDE", and "MOLLUSCICIDE".

Pesticide product registrations in both the EPA and APVMA databases are listed against pest common names. These common names were assigned to species scientific names, and multiple common names per species were merged. For logistical reasons, we reduced the number of pest common names queried to the top 50% of pesticide product registrations. For the EPA data, the number of unique pesticide registrations per common name ranged from 1–2,376, and for the APVMA data, the range was 1–5,062 unique pesticide registrations. Initially, taxonomy assignment was automated with the R package TAXIZE (Chamberlain & Szöcs, 2013; Chamberlain et al., 2020). Those pest common names that could not be assigned through automation were manually assigned.

Because automation and human error could potentially assign species to common names that might not be present in that country, we validated species presence manually. An initial screen was performed whereby USA species were compared against a published inventory of USA pests (Hardy et al., 2018) and Australian species were compared against occurrence records obtained from the Atlas of Living Australia (https://www.ala.org.au/; accessed July 7th, 2021). We then manually inspected the list of species to remove those species that are not pests of agricultural

crops. Such non-agricultural pests that had escaped our initial automated filters included cockroaches, invasive ant species, and pests that were exclusive to ornamentals, conifers, and turf. We were left with 427 USA species (750 pest common names) and 209 Australian species (247 pest common names).

Chemical MoA groups were assigned to each product registration based on their listed active ingredients from the Insecticide Resistance Action Committee (IRAC) classifications (Table S1). Next, we summed the number of unique chemical registrations per species for each chemical MoA across relevant pest common names. In both the EPA and APVMA databases, some chemical registrations are listed at taxonomic classifications higher than the species level (*i.e.,* genus or higher), for example: "aphids", "thrips", or "moths". We considered two alternate ways to deal with these ambiguous assignments. Firstly, all entries that cannot be assigned to species level could be removed. However, this would substantially decrease the number of entries in certain pests where many registrations are not at the species level (e.g., cereal aphids). Secondly, entries could be assigned to all species within that taxonomic rank. However, this would inflate the total number of entries for pests that are not targeted by a pesticide product but occur in the same taxonomic rank as a targeted species. This is expected to increase the similarity between targeted and non-targeted species with respect to the number of products registered against them, and hence reduce signals of selection pressure. To retain as much data as possible, we opted to allocate pesticide product registrations up to the family level, ignoring registrations at the order level or higher.

Phagy and voltinism — We collected data on two ecological traits that have been associated with increased rates of pesticide resistance evolution: phagy (number of host plant families) and voltinism (number of generations per year). For both traits, we leveraged the data published in Hardy et al. (2018), which expanded on work presented in Rosenheim et al. (1996). For each candidate species, we extracted available values of phagy and voltinism. For those species not included in Hardy et al. (2018), we performed a literature search to acquire this information.

We performed our literature search for missing trait values using Google Scholar. Different describing terminology was used in combination with the species names to find relevant references for phagy (List S2) and voltinism (List S3). Prospective references were manually screened based on the following criteria: (1) the pest was identified by its scientific name, not its common name; and (2) the values of phagy and voltinism could be clearly linked to the focal pest. The average value was taken in instances where multiple values were reported among different references.

In several cases, we were unable to collect trait data from published studies. We therefore imputed missing values using a hierarchical stepwise procedure with respect to taxonomic rank. For a species with a missing phagy or voltinism value, we obtained an estimate by taking the genus average. When no congeners were available, we took the family average, and when no family members were available, we took the order average. This approach is conservative as it reduces the variance among species with shared taxonomy, although we demonstrate it has little effect on our general conclusions (see Results).

Resistance status — For each species, for each chemical MoA group, we assigned resistance status (present or absent), as reported in the Arthropod Pesticide Resistance Database (APRD; Mota-Sanchez & Wise, 2021) and from the literature. For Australian species, we combined APRD records with a literature search. For USA species, we combined APRD records with pesticide resistance statuses documented in Crossley et al. (2020).

STATISTICAL ANALYSES

Our final USA species set included 427 species, 81 families, and 10 orders, and for the Australian species set, there were 209 species, 65 families, and 12 orders. Of the USA species, 30.9% (n = 132) had at least one ecological trait imputed, whereas for Australian species, 56.0% (n = 117) of species had at least one ecological trait imputed. The USA species set contained 42 chemical MoAs, and the Australian species set contained 39 chemical MoAs. Our working datasets were structured with respect to species–MoA observations, where the number of pesticide products for each unique chemical MoA was assigned to each pest species. There were 17,934 species–chemical MoA observations in the USA species set and 8,151 for the Australian species set.

Predictive models of resistance — We used Bayesian logistic regression to model the resistance status of each species against different chemical MoA groups. Our basic model involved the additive effects of our operational factor (pesticide products) and our two ecological factors (phagy and voltinism):

$$\textsc{Resistance} \sim \textit{Bernouilli}(p)$$

$$\textit{logit}(p) = \textsc{Products} + \textsc{Phagy} + \textsc{Voltinism} + \textsc{Taxonomy} + \textsc{Chem}$$

In this 'additive' model, RESISTANCE was a Bernoulli response for resistance status, 0 for susceptible and 1 for resistant, for each species–chemical MoA combination. PRODUCTS (number of product registrations), PHAGY (number of host plant families), and VOLTINISM (number of generations per year), are continuous fixed effects. Each of these fixed effect predictors were log-scaled: where $\vec{x}$

was the vector of predictor values, we applied the transformation $\log_{10}(\vec{x} + 1)$ and then scaled to a mean of 0 and variance of 1. TAXONOMY is a random effect to account for taxonomic structure, fitting a random intercept for each genus, nested in family, nested in order, and has been used elsewhere (Crossley et al., 2020; Hardy et al., 2018). CHEM is a random effect, fitting a random intercept for each chemical MoA group.

Because prior work has inferred potential curvilinear relationships between rate of resistance evolution with phagy and voltinism (Crossley et al., 2020; Hardy et al., 2018; Rosenheim et al., 1996), we additionally fitted a more complex model that included second order polynomials of our ecological factors:

$$logit(p) = \text{PRODUCTS} + \text{PHAGY} + \text{PHAGY}^2 + \text{VOLTINISM} + \text{VOLTINISM}^2 + \text{TAXONOMY} + \text{CHEM}$$

Terms for this 'polynomial' model were as per the additive model, except we used the *poly* function in R to obtain orthogonal polynomials for phagy and voltinism.

To fit our models in a Bayesian framework, we used the *brms* R package (Bürkner, 2017). To compare relative performance of our predictors of resistance, we also constructed a series of subset models. A 'null' model simply fitted the global mean and the random effects of taxonomy and chemical MoA group. A 'products' model fitted the effect of product registrations only. An 'ecology' model fitted the additive effects of phagy and voltinism only, while an 'ecology^2' model fitted the first and second order polynomials of phagy and voltinism only. All models were fitted using 10 chains, each with 8,000 iterations, for a total of 80,000 iterations. The first 50% of iterations were used as burn-in, leaving 40,000 iterations for estimating model coefficients. An adaptive delta value of 0.999 was used to set a high average target acceptance rate and prevent divergent transitions after the burn-in phase. Models were compared using the *bayestestR* R package (Makowski, Ben-Shachar, & Lüdecke, 2019) to obtain Bayes factors of all models relative to the null model. A Bayes factor >3, or a log-Bayes factor >1.1, would indicate substantial support for a focal model relative to the null model (Wetzels et al., 2011).

Model generality — We used *K*-fold cross-validation to evaluate the generality and predictive power of our models. Training subsets of our full imputed datasets were used to parameterize models that were then used to predict resistance in testing subsets. We analyzed 100 training–testing partitions. For each partition, 85% of the resistant and susceptible species were randomly selected for the training subset, and the remaining 15% of resistant and susceptible species were allocated to the testing subset. Thus, proportion of resistant to susceptible species was retained in both the training and testing subsets. The additive and polynomial models were fitted to each

training subset using the *brms* function with 10 chains, 1,000 iterations per chain, and a burn-in of 5,000 chains, with 5,000 iterations for coefficient estimation, and an adaptive delta of 0.999. Predictions on the testing subsets were made using the POSTERIOR_PREDICT function from the *brms* package without inclusion of random effects. Random effects were excluded because random subsampling of species led to non-overlapping combinations of order, family, and genus between the training and testing subsets. Because predictions were made without consideration of random intercepts for taxonomy and chemical MoA group, our cross-validation analyses provided a more conservative assessment of the generality of our predictive models. For direct comparison, additive and polynomial models were also fitted to the same training–testing species subsets.

To quantify predictive power, we calculated AUC (area under the receiver–operator characteristic curve) scores for each testing subset. AUC scores describe the relative rate of true to false positives for increasing predicted risk scores. AUC scores range from 0–1: as values approach 1, there is increasing likelihood that resistant species will be assigned higher predicted risk scores than susceptible species. For each testing subset, observed (0 or 1) and predicted (probability from 0 to 1) values were passed to the AUC function from R's *Metrics* package to obtain an AUC score.

Marginal effects in polynomial models — The effect of modelling multiple predictors with higher degree polynomials can be challenging to interpret. We therefore examined the marginal effects of each focal predictor in our polynomial models. Each focal predictor, x_1 (one of PRODUCTS, PHAGY or VOLTINISM), was allowed to vary from 1 to its 98% value (q_{98}) in the observed dataset. The 98% value was chosen as the maximum value in these marginal effects analyses to reduce the influence of extreme outliers. The two non-focal predictors, x_2 and x_3, respectively, were held constant at four value combinations with respect to the observed data: (1) their minimum values; (2) their median values; (3) the 98% value of x_2 and minimum value of x_3; and (4) the minimum value of x_2 and the 98% value of x_3.

Because models were fitted using the log-scaled observed values of the predictors, we used the same scaling parameters when testing marginal effects. For the focal predictor x_1, with $\vec{x}_1$ as the vector of values on the untransformed scale (from 1–q_{98}), the new log-scaled values, $\vec{x}_{1(\text{stan})}$, were obtained as:

$$\vec{x}_{1(\text{stan})} = \frac{\log_{10}(\vec{x}_1 + 1) - \bar{x}_{1(\text{obs})}}{\sigma_{1(\text{obs})}}$$

where $\bar{x}_{1(obs)}$ is the mean log-scaled value of the focal predictor in the observed data, and $\sigma_{1(obs)}$ is its standard deviation. Predicted risks were then estimated using values $\vec{x}_1$ with each of the four combinations of x_2 and x_3, using fixed effect coefficient estimates generated from the models.

RESULTS

PREDICTIVE MODELS OF RESISTANCE

Because predicted risk scores obtained from imputed and non-imputed datasets exhibited very high correlations ($r > 0.97$), irrespective of model (Figure S1), all our interpretations will be for models fitted to the imputed datasets.

As hypothesized, the number of pesticide products, host plant families, and generations per year was generally greater for resistant versus susceptible pest species (Figure 1). These positive trends were reflected in the coefficient estimates in our additive models. For the USA species set, coefficients were: products, $\beta = 0.78$; phagy, $\beta = 0.93$; and voltinism, $\beta = 0.56$. For the Australian species sets, coefficients were: products, $\beta = 1.02$; phagy, $\beta = 3.23$; and voltinism, $\beta = 0.97$. In the polynomial models, the fixed effect of products was $\beta = 0.77$ for the USA species set, and $\beta = 1.09$ for the Australian species set. The second order effect of phagy was convex, suggesting that an intermediate number of host plant families minimizes resistance risk. For the USA species set, phagy coefficients were: phagy^1, $\beta = 116.38$; and phagy^2, $\beta = 79.82$. For the Australian species set, phagy coefficients were: phagy^1, $\beta = 220.21$; and phagy^2, $\beta = 200.44$. The second order effect of voltinism was concave, suggesting that an intermediate number of generations per year maximizes resistance risk. For the USA species set, voltinism coefficients were: voltinism^1, $\beta = 56.26$; and voltinism^2, $\beta = -107.05$. For the Australian species set, voltinism coefficients were: voltinism^1, $\beta = 103.53$; and voltinism^2, $\beta = -180.97$. Diagnostic statistics indicate that we reliably sampled the posterior distributions for these fixed effect coefficients (Table S2); the $\hat{R}$ statistics were equal to 1.00, indicating convergence, and ESS values were >1,000, indicating many uncorrelated draws were obtained (see Muth, Oravecz, & Gabry, 2018).

Our models incorporating operational and ecological risk factors were substantially more likely to explain resistance status relative to a null model excluding these factors. For the USA species set, the polynomial and additive models had estimated log-Bayes factors of 145.91 and 108.39, respectively. For the Australian species, the polynomial and additive models had estimated Bayes factors of 83.28 and 51.23, respectively. These large log-Bayes factors (>>1.1) indicate variation in

resistance status is more likely in either the polynomial or additive models, relative to the null model. In addition, the much larger log-Bayes factors for the polynomial models suggest the resistance data has a higher probability of being observed under these models relative to the additive model.

Examination of log-Bayes factors for sub models indicated that all predictors explained variation in resistance status, but the probability of observing the resistance data was highest when operational and ecological factors were combined in the same model. For the USA species set, the rank of models based on log-Bayes factors was polynomial (145.91) > additive (108.39) > operational (88.65) > ecological^2 (69.96) > ecological (28.31), and model ranks for the Australian species set were polynomial (83.28) > additive (51.23) > ecological^2 (50.28) > operational (30.54) > ecological (21.47). Predicted risk scores were highly correlated between the polynomial and additive models ($r > 0.98$; Figure 2a). The Bayesian coefficient of variation, R^2_{Bayes}, indicated that for the USA species set, the polynomial and additive model explained 39.6% and 38.3% of the variation in resistance status, and for the Australian species set, they explained 44.7% and 41.0% of the variation, respectively (Table S3). The USA and Australian null models explained 31.4% and 29.0% of the variation, respectively, which is attributable to the random effects, reflecting structuring of resistance status by taxonomy and chemical MoA group. Fixed effects therefore explained an additional 6.9–15.7% of the variation in resistance status when included with the random effects of taxonomy in polynomial and additive models.

MODEL GENERALITY

K-fold cross-validation demonstrated that both the polynomial and additive models were equally generalizable and had substantial power to correctly discriminate between resistance and susceptible observations. For the USA species set, the mean AUC scores were 0.82 (±0.004 SEM) for the polynomial model and 0.82 (±0.003 SEM) for the additive model. For the Australian species set, the mean AUC scores were 0.82 (±0.007 SEM) for the polynomial model and 0.82 (±0.008 SEM) for the additive model. Both models therefore had a high probability of assigning higher risk scores to resistant species relative to susceptible species. Mean AUC scores for each country were similar, but there was greater variation in predictive power in the Australian species set (Figure 2b). Note, AUC scores were obtained using only the estimated fixed effect coefficients and not the estimated random intercepts for taxonomy or chemical MoA group. Hence, these *K*-fold cross-validation analyses show that whilst taxanomy and chemical MoA class explain a lot of the variation in resistance status, the fixed effects alone can be used to discriminate among resistant

and susceptible observations, because resistant species on average have greater product registrations and tend to have greater phagy and voltinism.

MARGINAL EFFECTS IN POLYNOMIAL MODELS

Examination of marginal effects allowed us to assess how different combinations of predictor values affected the predicted risk of resistance. While varying products (Figure 3a & 3d), risk was lowest at minimum values of phagy and voltinism ("Minimum"). Increasing the value of phagy elevated the resistance risk more so than increasing the value of voltinism ("98% phagy" versus "Median" versus "98% voltinism" versus "Minimum"). However, higher phagy and voltinism values resulted in the highest resistance risk ("98% both").

While varying phagy (Figures 3b & 3e), predicted risk was lowest at minimum values of products and voltinism ("Minimum"). Increasing the value of products increased risk more than increasing the value of voltinism ("98% products" versus "Median" versus "98% voltinism" versus "Minimum"). Indeed, the effect of high values of both products and voltinism did little to increase risk above that obtained when increasing products alone ("98% both" versus "98% products").

While varying voltinism (Figures 3c & 3f), predicted risk was low and comparable with minimum and median values of products and phagy ("Minimum" versus "Median"). Increasing the value of phagy alone did little to increase the risk ("98% phagy"). However, the effect of increasing products, or increasing both products and phagy, led to an elevated resistance risk ("98% products" versus "98% both").

These marginal effect predictions recapitulate expectations from the polynomial model coefficients. Based on the simple linear effect of products, increasing products will increase resistance risk on average. The expected convex relationship between phagy and resistance led to increasing resistance risk when phagy was fixed at a high value, relative to when it was fixed at its median value. Moreover, the expected concave relationship between voltinism and resistance led to decreasing resistance risk when voltinism was fixed at a high value, relative to when it was fixed at its median value.

DISCUSSION

Identifying key variables that explain variance in resistance status and pinpointing high-risk species unlocks new possibilities for making proactive, data-driven risk management decisions for important pest organisms. Some of the best examples of pesticide resistance risk prediction

frameworks incorporating relevant eco-evolutionary predictors come from agro-ecosystems in the USA, as reported in Rosenheim et al., (1996), Hardy et al. (2018), and Crossley et al. (2020). Yet we are unaware of attempts to incorporate a general multi-species measure of chemical selection pressure, which should be an important predictor of resistance evolution. We successfully used pesticide product registrations as a key predictor of resistance in agricultural arthropod pests in both the USA and Australia. This suggests pesticide product registrations can be a useful proxy for selection pressures in agricultural settings.

We propose a "registration–selection–resistance" hypothesis to explain the positive relationship between pesticide product registrations and resistance status. Our rationale is as follows. Pesticide product registrations reflect the availability and popularity of a pesticide product to farmers and land managers for pest control. For a given pest, readily available and popular pesticide products are more frequently used, increasing selection pressure. Additionally, intensive pesticide use will reduce the abundances of natural enemies (Bommarco, Miranda, Bylund, & Björkman, 2011; Prischmann, James, Wright, Teneyck, & Snyder, 2005). Consequently, as pest populations start to accumulate pesticide tolerances and experience reduced suppression by natural enemies, the frequency, rates, and demand for pesticide products will increase and feed back into further selection for resistance. Use of pesticide product registrations in our model is in some ways analogous to the "pest severity" predictor used in other studies (Crossley et al., 2020; Hardy et al., 2018; Rosenheim & Tabashnik, 1991), where a severity index was defined as the number of published studies per pest, with the expectation that more commonly studied pests are more severe and experience greater selection pressure. However, we believe pesticide product registrations better reflect, and are a more generalizable, proxy for selection pressure that can be readily compiled for a specific region. Nevertheless, it remains important to examine how pesticide product registrations covary with the amount of pesticide use. We are presently exploring this question through a concurrent study.

Importantly, the predictive models developed in our study enable the assignment of risk scores to specific combinations of species and chemical MoA groups. This provides a practical framework that can guide monitoring strategies and help develop preemptive management programs to minimize resistance evolution in the field. We illustrate such predicted risks for the top ten resistant pests (those with the most resistances) in the USA (Figure 4a) and Australian (Figure 4b) species sets. From a future management perspective, we are most interested in species–chemical MoA combinations that are currently susceptible but have a high relative risk score. Here, we detail some examples within an Australian context of the most high-risk (but currently susceptible) species–chemical MoA combinations.

1. ***Tetranychus urticae*, the two-spotted mite, to avermectins (MoA 6, $\hat{y}$ = 0.70).** *Tetranychus urticae* has resistance to 12 different chemical MoA groups in Australia, and there are only six MoA groups for which *T. urticae* is susceptible. Within Australia, avermectins are widely used to control *T. urticae* in grain, vegetable, cotton, and fruit crops (APVMA, 2021; Dodds & Fearnley, 2021; Grundy et al., 2021). Avermectins are the third most registered chemical MoA for *T. urticae* (following organophosphates and pyrethroids), so resistance to this chemical MoA would constitute a non-trivial loss of chemical control options. Field resistance of *T. urticae* to avermectins has already been reported in other parts of the world, involving metabolic mechanisms (Stumpf & Nauen, 2002), and reported laboratory-evolved resistance has been underpinned by target-site mutations (W Dermauw et al., 2012; Kwon, Yoon, Clark, & Lee, 2010). Our results indicate Australian *T. urticae* populations have a moderate risk of evolving resistance to avermectins, highlighting the value of screening field populations in order to assess the status of local tolerances to this chemical group.
2. ***Epiphyas postvittana*, light brown apple moth, to pyrethroids (MoA 3A, $\hat{y}$ = 0.48).** Reported resistances in this pest are to older chemical groups (*i.e.,* carbamates, organophosphates and organochlorines) from the 1960s through to the 1980s (Kerr, 1964; APRD, Mota-Sanchez & Wise, 2020). There are many chemical options for *E. postvittana* control, but pyrethroids are the third most registered chemical MoA for *E. postvittana* (following organophosphates and carbamates) and are used for control of this pest in fruit, vegetable, and ornamental crops (APVMA, 2021). Although non-chemical management options are available to control *E. postvittana* (e.g. Suckling & Brockerhoff, 2010), the moderately high predicted risk to pyrethroids suggests judicious chemical rotations are needed to avoid the unintended development of resistance to this chemical group.
3. ***Helicoverpa armigera*, corn earworm, to amitraz (MoA 19, $\hat{y}$ = 0.47).** Amitraz is primarily used in the Australian cotton industry to manage *H. armigera*, with up to four applications often recommended per growing season (Grundy et al., 2021). Amitraz is the only chemical MoA group currently registered against *H. armigera* for which no current resistance data is available in Australia (Grundy et al., 2021), although it was presumably still susceptible in the early 2000s (Gunning, 2002). *Helicoverpa armigera* are already resistant to eight chemical MoA groups in Australia, many of which are widely distributed throughout the country (Thia et al., 2021). Although there are no reports of resistance to amitraz globally in *H. armigera* (Mota-Sanchez & Wise, 2020), our results suggest Australian populations have a moderately high risk of evolving resistance. Baseline data on current amitraz susceptibilities in Australia would be valuable to develop a more complete picture

of chemical tolerances and evaluate the need for preemptive strategies to maintain amitraz susceptibilities in the field.

The curvilinear effects of phagy and voltinism that we observed have been noted elsewhere with respect to the number of resistances a pest has evolved (Hardy et al., 2018) and the rate of resistance evolution following the release of a new chemical (Crossley et al., 2020). The convex relationship between phagy and resistance has been interpreted as a product of two processes that may elevate the rate of resistance evolution: (1) for more specialized pests with low phagy, a greater proportion of the population is constrained to treated crops, and therefore, more of the population is exposed to selection (Georghiou & Taylor, 1986); and (2) for more generalist pests with high phagy, a greater arsenal of biochemical machinery used in metabolism of plant phytochemicals are available to detoxify pesticides (Wannes Dermauw, Pym, Bass, & Leeuwen, 2018; Rane et al., 2019). The concave relationship between voltinism and resistance has a less clear interpretation. In some cases, voltinism has been described as a nuisance parameter (Crossley et al., 2020). However, the number of generations per year might be an important life history trait that modulates the effect of other operational, ecological, and population genetic factors on resistance evolution (Georghiou & Taylor, 1977; Rosenheim & Tabashnik, 1990). Although we observed greater support for the polynomial model relative to the additive model using Bayesian inference, these models were virtually identical in their ability to discriminate susceptible and resistant observations in cross-validation analyses. Hence, whilst the polynomial model might explain greater variation in resistance status, both models have comparable predictive capacity.

The predictive framework developed here has some caveats, including (1) legacy effects captured in the pesticide registration and resistance status data; (2) ephemeral resistances; and (3) the coarse scale of our predictions. Legacy effects in our work pertain to the analysis of temporally accumulated data. For pesticide registrations, we summed the cumulative number of products across years, and for resistance status, we scored pests as resistant to a chemical MoA if there was at least one record, irrespective of when it was reported. Some MoA groups are no longer used due to their negative health and ecotoxicology effects, such as organochlorines and DDTs, or are no longer registered because pesticide resistance is commonplace, such as pyrethroids for the control of *Frankliniella occidentalis* (western flower thrips) in Australia (Herron & Gullick, 2001). The transience of certain resistances contributes toward these legacy effects. Some species have periodically exhibited high levels of resistance, presumably in response to intense short-term selection pressure, which has later disappeared. In Australia, two such examples include *Therioaphis trifolii* (spotted alfalfa aphid) resistance to carbamates and organophosphates

(Holtkamp, Edge, Dominiak, & Walters, 1992), and *Helicoverpa punctigera* (native budworm) resistance to pyrethroids (Gunning, Moores, & Devonshire, 1997). This spatially and temporally patchy evolution of resistance creates dynamics that somewhat misalign with our models, which consider all observations as contemporaneous. Our predictive model therefore has a coarse temporal and spatial scale. The risk scores produced by our model reflect the likelihood of resistance given certain combinations of a species' ecology and market indicators of pesticide usage. Whilst these risk predictions are useful for identifying candidate species for proactive management at a region-wide level, the models lack fine-scale resolution that would be necessary to guide action at a local level. Whilst localized models can be successfully developed, they are almost always constrained to single species (Feng, Gould, Huang, Jiang, & Wu, 2010; Ives et al., 2017; Ma et al., 2021; Maino, Umina, & Hoffmann, 2018). We recommend future research and data management infrastructures capture fine-scale chemical usages patterns and the spatio-temporal variation in pesticide tolerance phenotypes across key pest species (see Thia et al., 2021). Such data is necessary to generate multi-species predictive models at scales relevant for localized management that can be readily refined through time.

CONCLUSIONS

Pest management strategies would benefit from the identification and monitoring of pesticide resistance in high-risk species prior to resistance evolution in the field. This occurs for a discrete number of economically important arthropod species including agricultural pests (Anstead, Mallet, & Denholm, 2007; Anstead, Williamson, & Denholm, 2008; Baker, 2018; Bird, 2015; de Little & Umina, 2017; Durigan et al., 2017; Endersby et al., 2011) and disease vectors where resistance has become a major health issue (Matiya, Philbert, Kidima, & Matowo, 2019; Matowo et al., 2019; Nauen, 2007). Developing analytical methods that delimit high-risk versus low-risk species can guide future resistance monitoring efforts and facilitate decisions on resource allocation. In this study, we detail the novel use of pesticide product registrations as a predictor of resistance in agricultural arthropod pests from the USA and Australia. Our "registration–selection–resistance" hypothesis posits that knowledge of available pesticide product registrations for each species could be beneficial in pinpointing when the intensity and duration of chemical selection in the field warrants careful attention. Our work should aid the development of proactive pest management programs and has broad applicability across a suite of agricultural pests beyond arthropods, including to weeds and fungi.

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FIGURES

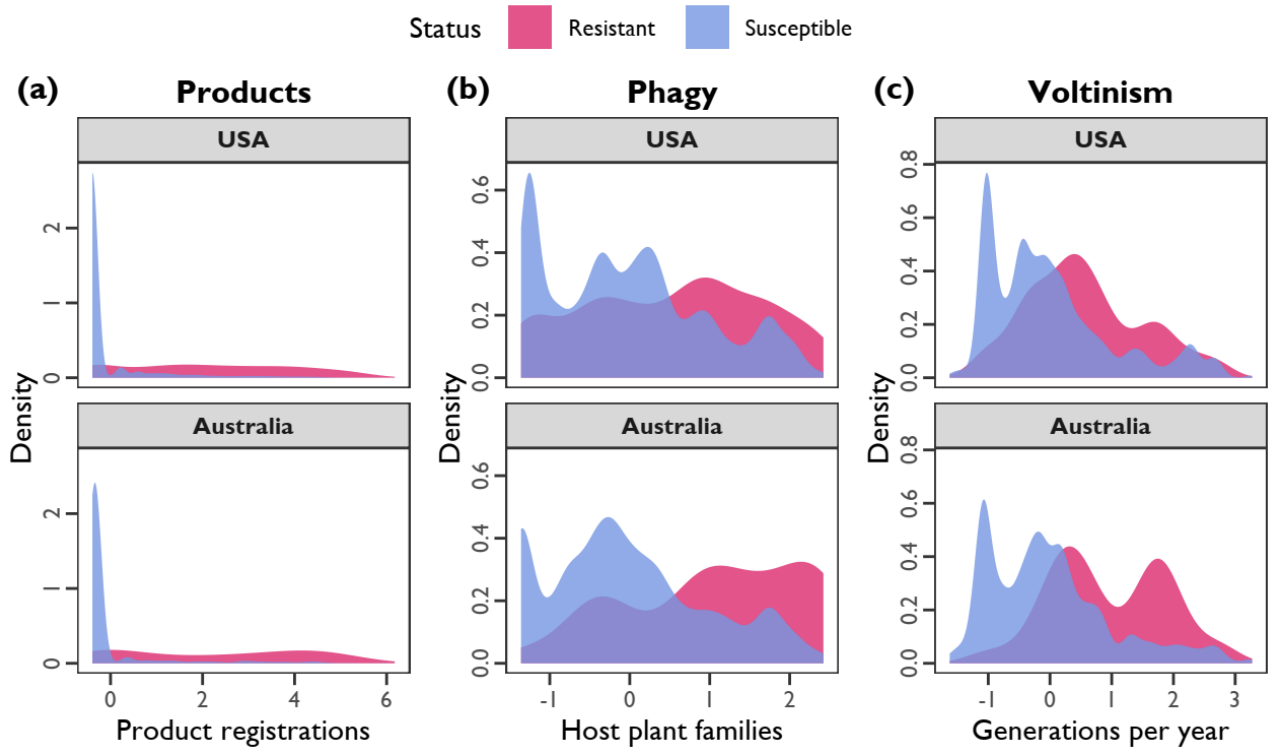

Figure 1. Resistance predictor distributions. Curves depict the kernel density estimate, with area under the curve equal to 1.00. Resistant species–chemical MoA observations are depicted by pink curves, and blue curves depict susceptible species–chemical MoA observations. Panels contain observations from the USA and the Australian species sets separately. (a) Products, the log-scaled number of product registrations. (b) Phagy, the log-scaled number of host plant families. (c) Voltinism, the log-scaled number of generations per year.

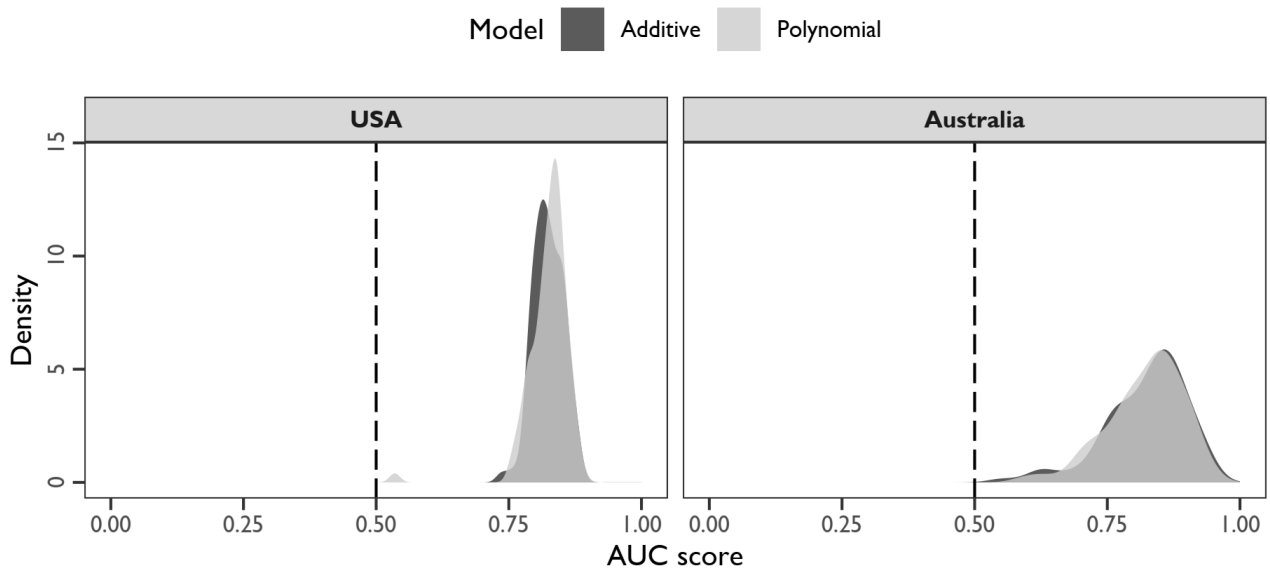

Figure 2. Comparisons of predictive power between models using AUC score using 100 training–testing partitions. Curves depict the kernel density estimate, with area under the curve equal to 1.00. Densities were estimated from 100. Dark grey curves depict the distribution of AUC scores obtained from the additive model and light grey curves depicts scores obtained from the polynomial model. The dashed lines depict an AUC score of 0.50, that is, an equal probability that the model assigns a higher score to resistant or susceptible species–chemical MoA observation. AUC scores approaching 1.00 indicate an increasing probability that resistance species–chemical MoA observations will be assigned higher scores than susceptible observations. Panels contain results from the USA and the Australian species sets separately.

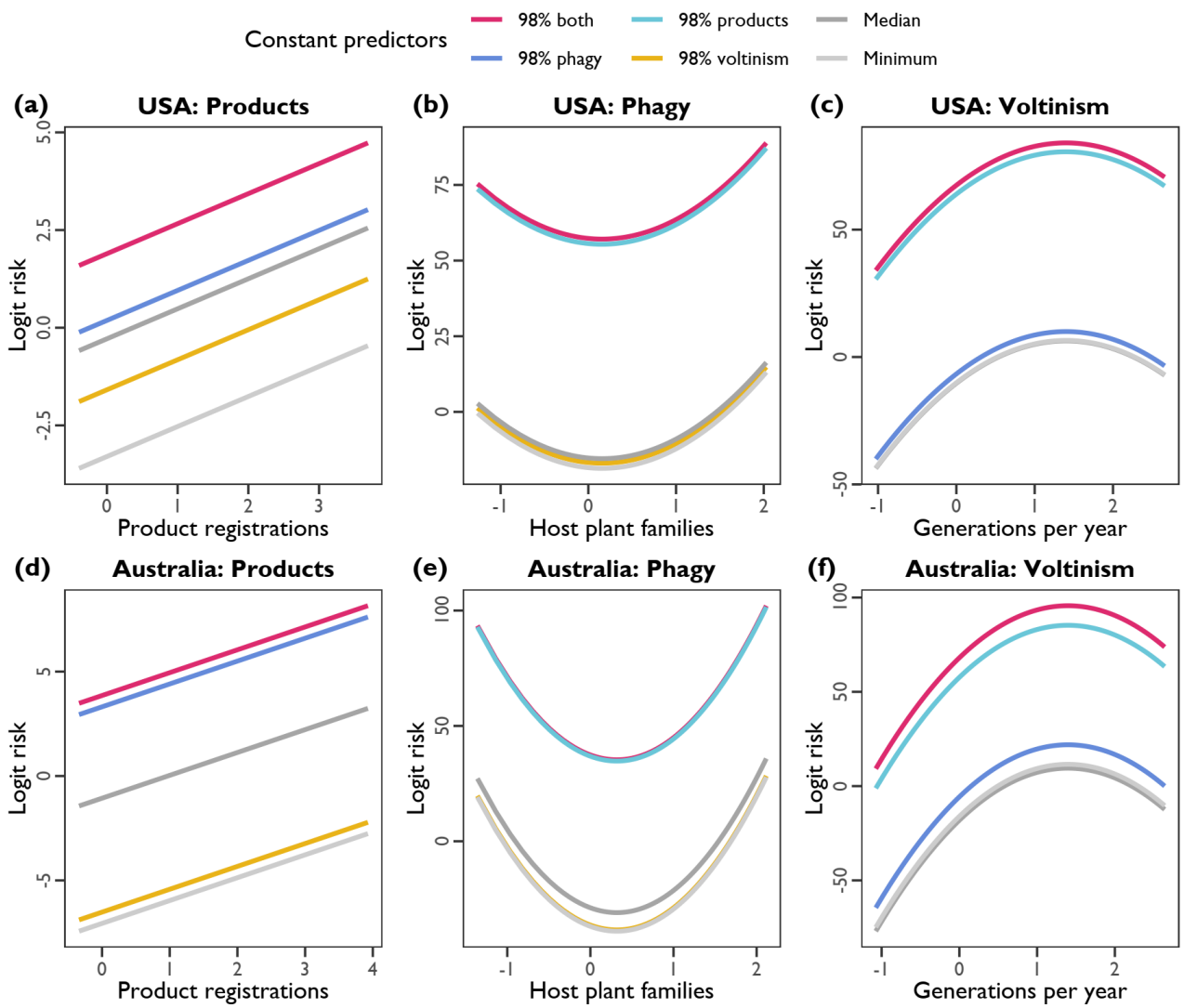

Figure 3. Marginal effects for polynomial models of resistance risk. Coloured lines depict the predicted resistance risks on the logit scale whilst varying a focal predictor at different combinations of non-focal predictors (see legend). Predictors are log-scaled. (a–c) Predictions from the USA species set. (d–f) Predictions from Australian species set. (a, d) Varying products, whilst holding phagy and voltinism constant. (b, e) Varying phagy, whilst holding products and voltinism constant. (c, f) Varying voltinism, whilst holding products and phagy constant.

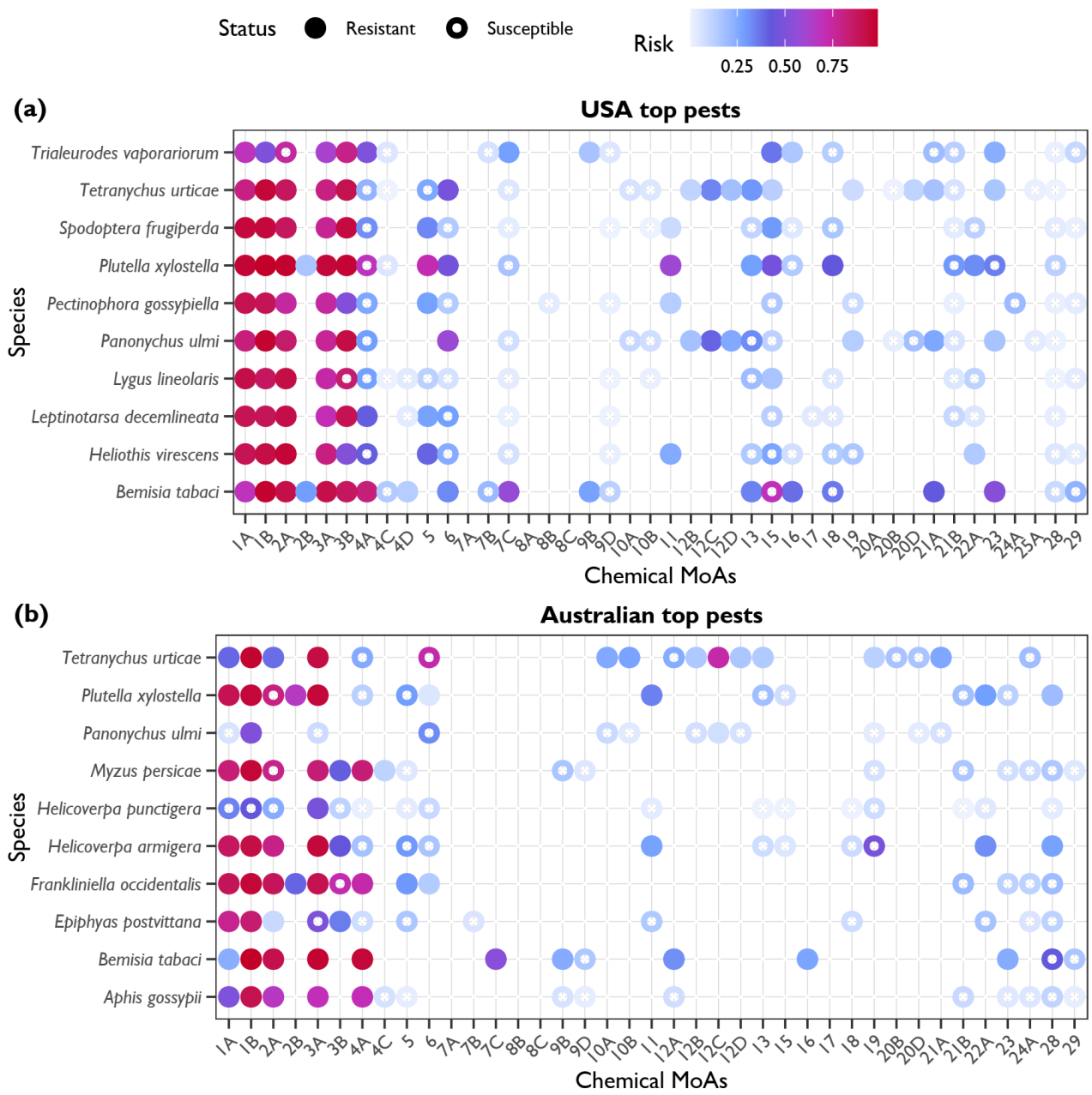

Figure 4. Predicted risks for the ten most resistant agricultural pest species in the USA and Australia. Closed circles represent species–MoA combinations that exhibit resistance, whereas open circles represent species–MoA combinations that are susceptible. Circles are coloured by the magnitude of predicted risk, with low risk in pale blue (0.00) to high risk in red (1.00). Only risks for chemical MoAs registered for each pest species are shown. (a) The USA top ten pest species with most cases of resistance. (b) The Australian top ten pest species with most cases of resistance.

SUPPLEMENTARY INFORMATION

List S1. Key words used to filter EPA database of chemical registration in America.

- BAIT APPLICATION
- BARK TREATMENT
- DIP TREATMENT
- DORMANT APPLICATION
- FOLIAR TREATMENT
- FORAGE
- GRAIN
- GREENHOUSE
- NURSERY
- PASTURE
- POSTHARVEST
- ROOT
- SEED
- SEEDLING
- SEED CROP
- SEED TREATMENT
- SOIL FUMIGATION
- SOIL TREATMENT
- WATER TREATMENT

List S2. Key words used to search for phagy values in Google Scholar.

- food plant
- host
- hosts
- host plant
- host plants
- phagy

List S3. Key words used to search for voltinism values in Google Scholar.

- biology
- ecology
- generation per year
- generations per year
- life cycle

- life history
- multivoltine
- phenology
- reproductive rate
- univoltine
- voltinism

Table S1. Chemical MoA groups and active ingredients included in this study.

MoA	Chemical class	Target	Active ingredients	USA	Australia
1A	Carbamates	Acetylcholinesterase inhibitors	Aldicarb, Bendiocarb, Carbaryl, Carbofuran, Methomyl, Promecarb, Propoxur, Thiodicarb, Methiocarb, Pirimicarb, Carbosulfan, Oxamyl	✓	✓
1B	Organophosphates	Acetylcholinesterase inhibitors	Fenitrothion, Malathion, Acephate, Azinphos-ethyl, Azinphos-methyl, Chlorpyrifos-methyl, Chlorpyrifos, Diazinon, Dichlorvos, Dimethoate, Disulfoton, Fenamiphos, Fenthion, Methamidophos, Methidathion, Naled, Omethoate, Parathion-methyl, Parathion, Phorate, Phosmet, Prothiofos, Sulprofos, Thiometon, Trichlorfon, Vamidothion, Ethion, Isofenphos, Monocrotophos, Cadusafos, Mevinphos, Profenofos, Ddvp, Ronnel, Oxydemeton-methyl, Phosphamidon, Carbophenothion, Dicrotophos, Phosalone, Terbufos, Dioxathion, Tetrachlorvinphos, Fonofos, Tetraethyl pyrophosphate, Pirimiphos-methyl, Chlorethoxyfos, Isazofos, Fosthiazate	✓	✓
2A	Cyclodiene organochlorines	GABA-gated chloride channel blocks	Chlordane, Dieldrin, Lindane, Endosulfan, Endrin, Dienochlor	✓	✓
2B	Phenypyrazoles	GABA-gated chloride channel blocks	Fipronil	✓	✓
3A	Pyrethroids	Sodium channel modulators	Deltamethrin, Bioallethrin, Bioresmethrin, Pyrethrins, Alpha-cypermethrin, Cyfluthrin, Cypermethrin, Tau-fluvalinate, Bifenthrin, Esfenvalerate, Zeta-cypermethrin, Lambda-cyhalothrin, Permethrin, Gamma-cyhalothrin, Imiprothrin, Resmethrin, Beta-cyfluthrin, Tetramethrin, Fenvalerate, Fluvalinate, Flucythrinate, Fenpropathrin, Phenothrin, Prallethrin, Etofenprox, Allethrin, Tralomethrin, Tefluthrin	✓	✓
3B	DDT	Sodium channel modulators	DDT, Methoxychlor	✓	✓

4A	Neonicotinoids	Nicotinic acetylcholine receptor competitive modulators	Imidacloprid, Thiamethoxam, Thiacloprid, Acetamiprid, Clothianidin, Dinotefuran	✓	✓
4C	Sulfoximines	Nicotinic acetylcholine receptor competitive modulators	Sulfoxaflor	✓	✓
4D	Butenolides	Nicotinic acetylcholine receptor competitive modulators	Flupyradifurone	✓	
5	Spinosyns	Nicotinic acetylcholine receptor allosteric modulators	Spinosad, Spinetoram	✓	✓
6	Avermectins and milbemycins	Glutamate-gated chloride channel allosteric modulators	Abamectin, Milbemectin, Emamectin benzoate	✓	✓
7A	Juvenile hormone analogues	Juvenile hormone mimics	Methoprene	✓	✓
7B	Fenoxycarb	Juvenile hormone mimics	Fenoxycarb	✓	✓
7C	Pyriproxyfen	Juvenile hormone mimics	Pyriproxyfen	✓	✓
8A	Alkyl halides	Miscellaneous non-specific inhibitors	Ethylene dibromide	✓	
8B	Chloropicrin	Miscellaneous non-specific inhibitors	Chloropicrin	✓	✓
8C	Fluorides	Miscellaneous non-specific inhibitors	Sulfuryl fluoride	✓	✓
9B	Pyridine azomethine derivatives	Chordontonal organ TRPV channel modulators	Pymetrozine	✓	✓

9D	Pyropenes	Chordontonal organ TRPV channel modulators	Afidopyropen	✓	✓
10A	Clofentezine, Diflovidazin, Hexythiazox	Mite growth inhibitors affecting chs1	Clofentezine, Hexythiazox	✓	✓
10B	Etoxazole	Mite growth inhibitors affecting chs1	Etoxazole	✓	✓
11	Bacillus products	Microbial disruptors of insect midgut membranes	Bacillus thuringiensis subsp. kurstaki, Bacillus thuringiensis subsp. israelensis	✓	✓
12A	Diafenthiuron	Inhibitors of mitochondrial ATP synthase	Diafenthiuron		✓
12B	Organotin miticides	Inhibitors of mitochondrial ATP synthase	Azocyclotin, Cyhexatin, Fenbutatin oxide	✓	✓
12C	Propargite	Inhibitors of mitochondrial ATP synthase	Propargite	✓	✓
12D	Tetradifon	Inhibitors of mitochondrial ATP synthase	Tetradifon	✓	✓
13	Pyrroles, dinitrophenols, sulfuramid	Oxidative phosphorylation uncouplers via proton gradient disruption	Chlorfenapyr, Dinocap	✓	✓
15	Benzoylureas	Inhibitors of chitin biosynthesis affecting chs1	Triflumuron, Diflubenzuron, Novaluron	✓	✓

16	Buprofezin	Inhibitors of chitin biosynthesis	Buprofezin	✓	✓
17	Cyromazine	Moulting disruptor, dipterans	Cyromazine	✓	✓
18	Diacylhydrazines	Ecdysone receptor agonists	Tebufenozide, Methoxyfenozide	✓	✓
19	Amitraz	Octopamine receptor agonists	Amitraz, Chlordimeform	✓	✓
20A	Hydramethylnon	Mitochondrial complex III electron transport inhibitors	Hydramethylnon	✓	
20B	Acequinocyl	Mitochondrial complex III electron transport inhibitors	Acequinocyl	✓	✓
20D	Bifenazate	Mitochondrial complex III electron transport inhibitors	Bifenazate	✓	✓
21A	METI acaricides and insecticides	Mitochondrial complex I electron transport inhibitors	Pyridaben, Tebufenpyrad, Fenpyroximate, Fenazaquin	✓	✓
21B	METI acaricides and insecticides	Mitochondrial complex I electron transport inhibitors	Rotenone	✓	✓
22A	Oxadiazines	Voltage-dependent sodium channel blocks	Indoxacarb	✓	✓
23	Tetronic and tetramic acid derivatives	Acetyl CoA carboxylase inhibitors	Spirotetramat (iso), Spirotetramat, Spiromesifen, Spirodiclofen	✓	✓
24A	Phosphides	Mitochondrial complex IV electron transport inhibitors	Phosphine	✓	✓

25A	Beta-ketonitrile derivatives	Mitochondrial complex II electron transport inhibitors	Cyflumetofen	✓	
28	Diamides	Ryanodine receptor modulators	Chlorantraniliprole, Flubendiamide, Cyantraniliprole, Cyclaniliprole	✓	✓
29	Flonicamid	Chordontonal organ modulators, undefine target site	Flonicamid	✓	✓

Note: The "Active ingredients" column contains the names of all chemical compounds associated with each chemical MoA observed in this study. Ticks in the "USA" and "Australia" column indicate that the associated chemical MoA was modelled in our analyses, but it does not indicate that all associated active ingredients listed in this table were present in that country.

Table S2. Posterior estimates of model coefficients and Bayesian diagnostic statistics.

Country	Model	Term	β	$CI_{2.5\%}$	$CI_{97.5\%}$	$\hat{R}$	Bulk ESS	Tail ESS
USA	Polynomial	Intercept	−8.51	−10.04	−7.10	1.00	16908	21561
		Products	0.77	0.64	0.90	1.00	37376	30564
		Phagy^1	116.38	68.29	167.40	1.00	25587	28060
		Phagy^2	79.82	42.40	119.14	1.00	29331	29720
		Voltinism^1	56.26	−9.13	121.68	1.00	21806	27053
		Voltinism^2	−107.05	−150.68	−65.17	1.00	32438	30757
	Additive	Intercept	−8.35	−9.68	−7.17	1.00	15945	20663
		Products	0.78	0.66	0.91	1.00	38451	30430
		Phagy	0.93	0.58	1.30	1.00	21294	27313
		Voltinism	0.56	0.11	0.99	1.00	23807	28255
Australia	Polynomial	Intercept	−14.37	−20.18	−10.14	1.00	15302	20506
		Products	1.09	0.83	1.38	1.00	37746	31110
		Phagy^1	220.21	95.50	378.80	1.00	20327	23738
		Phagy^2	200.44	96.73	329.04	1.00	21962	26238
		Voltinism^1	103.53	−68.10	296.84	1.00	24422	23949
		Voltinism^2	−180.97	−385.69	−25.97	1.00	19355	19987
	Additive	Intercept	−12.69	−17.88	−9.12	1.00	11259	15789
		Products	1.02	0.77	1.28	1.00	27197	30248
		Phagy	3.23	1.74	5.33	1.00	10134	16008
		Voltinism	0.97	−0.42	2.40	1.00	18268	23958

Table S3. Bayesian coefficients of variation, R^2_{Bayes}, for models using imputed ecological trait data.

Country	Model	R^2_{Bayes}	$CI_{2.5\%}$	$CI_{97.5\%}$
USA	Polynomial	0.396	0.362	0.427
	Additive	0.383	0.349	0.415
	Ecological	0.336	0.299	0.371
	Ecological^2	0.352	0.315	0.387
	Operational	0.370	0.336	0.402
	Null	0.314	0.277	0.349
Australia	Polynomial	0.447	0.378	0.506
	Additive	0.410	0.336	0.472
	Ecological	0.348	0.270	0.417
	Ecological^2	0.384	0.307	0.451
	Operational	0.342	0.272	0.404
	Null	0.290	0.217	0.358

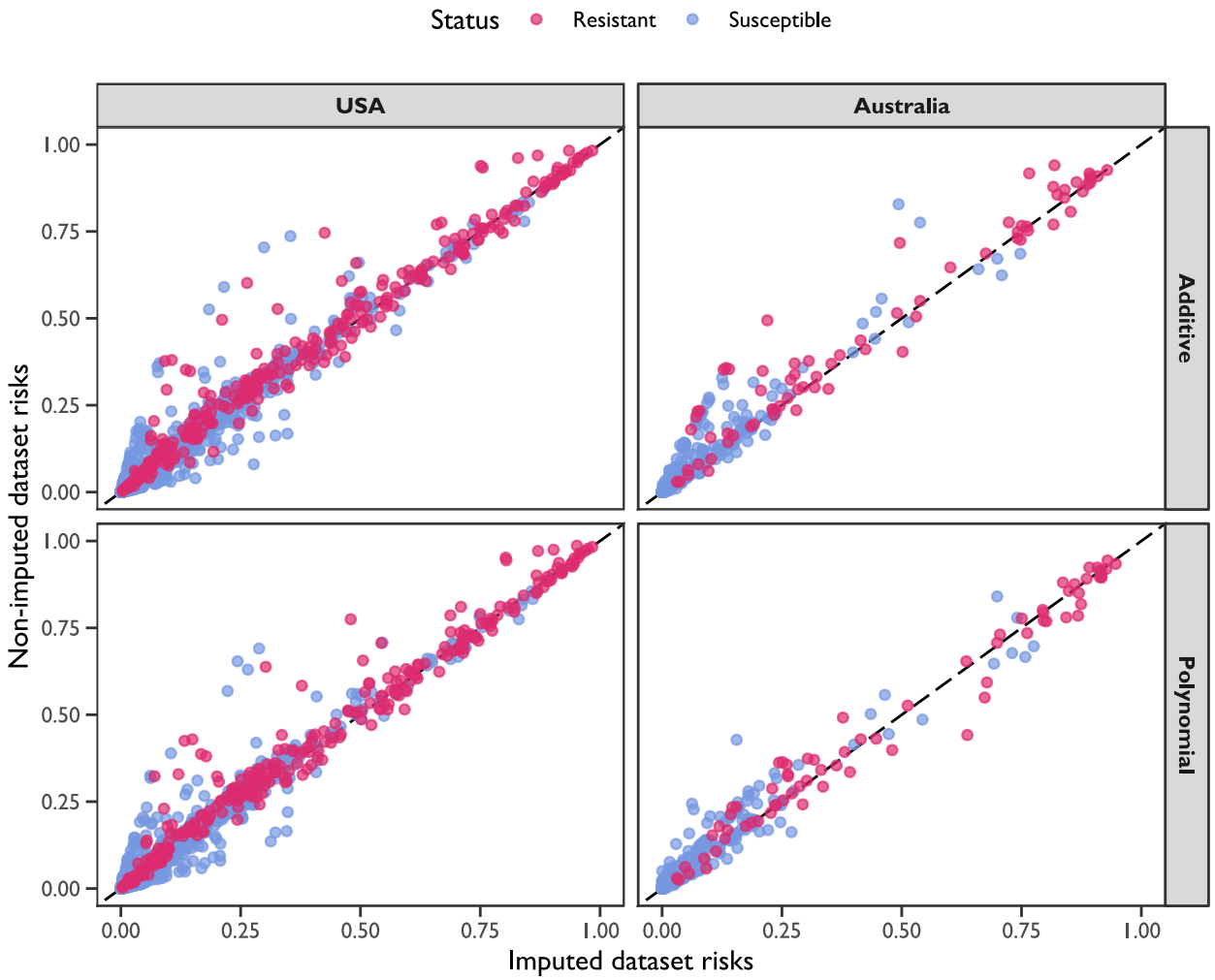

Figure S1. Comparisons of predicted resistance risks from datasets with imputed and non-imputed ecological traits. Points represent predicted risks for species–chemical MoA combinations, coloured by resistance status: pink for resistant, and blue for susceptible. The dashed line demarcates the 1:1 association. Panels contain combinations of models (additive and polynomial, in the rows) executed on species sets from each country (USA and Australia, in the columns).