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ORIGINAL PAPER

Phosphine resistance among stored product insect pests: A global meta-analysis-based perspective

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Abstract
Phosphine is the most common fumigant used for stored product protection, and its use intensified with the global phasing out of methyl bromide due to its ozone depletion characteristics. These use patterns led to phosphine resistance, which was subjected to a globe-wide survey in the 1970's, but without a subsequent (global) update. Thus, the present work aimed to undertake a comprehensive review of the phosphine resistance literature published since the initial survey in 1975 until 2021. Next, meta-analyses were used to synthesize and quantify the resistance observed within the main insect pest species of stored products. Forty-six papers were recognized surveying 13 species of stored product insect species, encompassing 980 populations around the world; 72.96% of these populations exhibited phosphine resistance, and 10 out of the 13 species evaluated exhibited resistance in more than 60% of the populations tested. The most widespread problems were observed with the lesser grain borer (*Rhyzopertha dominica*), the rice weevil (*Sitophilus oryzae*), and the red flour beetle (*Tribolium castaneum*). The frequency of resistant individuals ranged from 12 to 48% for the populations. The levels of phosphine resistance were higher for the lesser grain borer (73-fold on average), followed by the red flour beetle (32-fold), and the maize weevil (28-fold). Furthermore, a considerable variability was observed within species and among localities. Therefore, phosphine resistance remains an ongoing problem and worldwide concern, with increasing levels and prevalence among key pest species of stored products, although reports and monitoring are largely circumscribed to four countries–Australia, Brazil, Greece, and the US.

Keywords Hydrogen phosphide · Fumigation · Stored grains · Grain weevils · Flour beetles · Grain borers

Key message

- Phosphine is the fumigant used against stored product insects with concerns of phosphine resistance
- Global surveys of phosphine resistance are lacking since the 1970's, reason for the present study
- Ten out of the 13 species surveyed exhibited phosphine resistance in more than 60% of the populations
- The lesser grain borer, the rice weevil, and the red flour beetle exhibited the most widespread problems
- The surveys available are largely circumscribed to four countries–Australia, Brazil, Greece, and the US

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Introduction

Food storage by pre-historic human societies was accompanied by the intrinsic risk of its destruction and spoilage by biological agents, and insects feature in the forefront among these agents, as they not only consume stored foodstuffs, but also produce diverse contaminants and by-products (e.g., frass, exuviae fragments) that render the stored goods unfit for consumption (Rees 2004). The results are food losses, eventual health concerns and massive monetary deficits imparted by beetles, moths and booklice (Hagstrum and Subramanyam 2009a; Hagstrum et al. 2013; Nayak et al. 2014), the most frequent groups of stored product pests that cause losses in the range of 5–10% and 20–30% in temperate and tropical regions, respectively (Hodges et al. 2014;

Tadesse 2020). A variety of pest control methods are used for stored product protection to mitigate these losses (Phillips and Throne 2010; Hagstrum and Phillips 2017), but fumigation remains the dominant practice, and phosphine is the prevalent fumigant (Nayak et al. 2020).

A fumigant is a chemical that exists as a lethal gas at normal environmental conditions of temperature and pressure. The gas can diffuse through air, penetrating and/or permeating a diversity of materials and products, ultimately interfering with biological processes of exposed organisms, and leading to their death. Methyl bromide and phosphine are the two historically dominant fumigants, but the former has been phased out since the mid-1990s, excepted from some rather restricted uses, due to its ozone-depleting properties (United Nations Environmental Programme [UNEP] 1994). In contrast, the 100-year-long history of phosphine started with its description by Philippe Gengembre, in 1783. Its easy application, effectiveness against major pest species, low cost, and acceptance by markets and regulatory agencies as a residue-free treatment led to its dominant use for the last three decades (Chaudhry 2000; Thoms and Busacca 2016; Nayak et al. 2020). A consequence of the overreliance on phosphine for stored product protection, besides standing poisoning concerns (Gurjar et al. 2011; Bumbrah et al. 2012), is the occurrence of insect pest resistance, which seems to increase in frequency, level, and distribution (Champ and Dyte 1976; Nayak et al. 2020).

Repeated and suboptimal phosphine use in storage facilities increases the selection for phosphine resistance, while numerous reports of control failure with this fumigant around the globe drew the attention of the Food and Agriculture Organization (FAO) of the United Nations (Champ and Dyte 1976; Chaudhry 2000). This fact led to the FAO sponsoring the development of a diagnostic concentration bioassay to recognize phosphine resistance (Food and Agriculture Organization [FAO] 1975). This bioassay uses the lowest phosphine concentration able to kill the susceptible adult insects allowing the recording of the percent (or frequency) of resistant individuals in the population. The development of this diagnostic bioassay subsequently led to the FAO worldwide survey of phosphine resistance in the early 1970s, which provided a comprehensive picture of the problem and emphasized its scope and relevance (Champ and Dyte 1976) Since then, reports of phosphine resistance became more frequent, but scattered among different research groups and focused on different species, although suggesting that the phenomenon is likely increasing and further aggravated by the lack of suitable alternative fumigants (Afful et al. 2018; Agrafioti et al. 2019; Nayak et al. 2020).

No global survey on phosphine resistance was carried out after 1975, despite the increase and dispersion of the studies across different stored product insect species and countries. Such fact makes it difficult to obtain a global perspective of the problem of phosphine resistance, with its eventual bias and knowledge gaps. This shortcoming invited the present systematic review of the literature on phosphine resistance among insect pests, which aimed at covering the period from the last global survey, 1975, until 2021. The effort had two primary objectives. First, it aimed to carry out a systematic literature survey to recognize the temporal patterns of the studies, the insect species surveyed, and the mapping of their occurrence.

The second goal was to summarize and quantify the frequency of incidence and level of phosphine resistance within the main groups of stored product insects across the globe, using meta-analyses. An increased number of species studied was expected, with reports from different parts of the world and increasing levels of incidence of phosphine resistance, due to the overreliance on this fumigant frequently used under unsuitable airtightness conditions. The results will allow the recognition of the current patterns of phosphine resistance and research needs important to provide directions for improved management practices and further studies.

Materials and methods

The procedures for the systematic literature survey and subsequent meta-analyses followed the general PRISMA guidelines (i.e., *Preferred Reporting Items for Systematic Reviews and Meta-Analysis*) (Moher et al. 2009), which are described below.

Data collection, screening, and literature review

The general procedure for the data collection and screening is described in Fig. 1. First, a literature search was carried out on the topic of phosphine resistance among insects. Keyword combinations were used in the *Web of Science* and *Scopus* databases, encompassing the literature published between January 1975 and March 2021. The search was carried out with general keywords to identify a broad initial dataset, and included the following terms: “phosphine,” and “resistance” in mandatory combination with either “insect” or “arthropod.” Duplicate papers were removed from the dataset after individually checking them, and the remaining were further screened for inclusion in the qualitative analysis, by adding to the dataset only studies that met the following criteria: (i) publication in English in a peer-reviewed journal; (ii) inclusion of a stored product insect pest species as target organism; (iii) inclusion of a clear measure of resistance (i.e., frequency of resistant individuals and/or level of resistance; which were analyzed independently). We excluded any narrative review, case report, protocol, editorial, book, book chapter, thesis, dissertation and proceedings

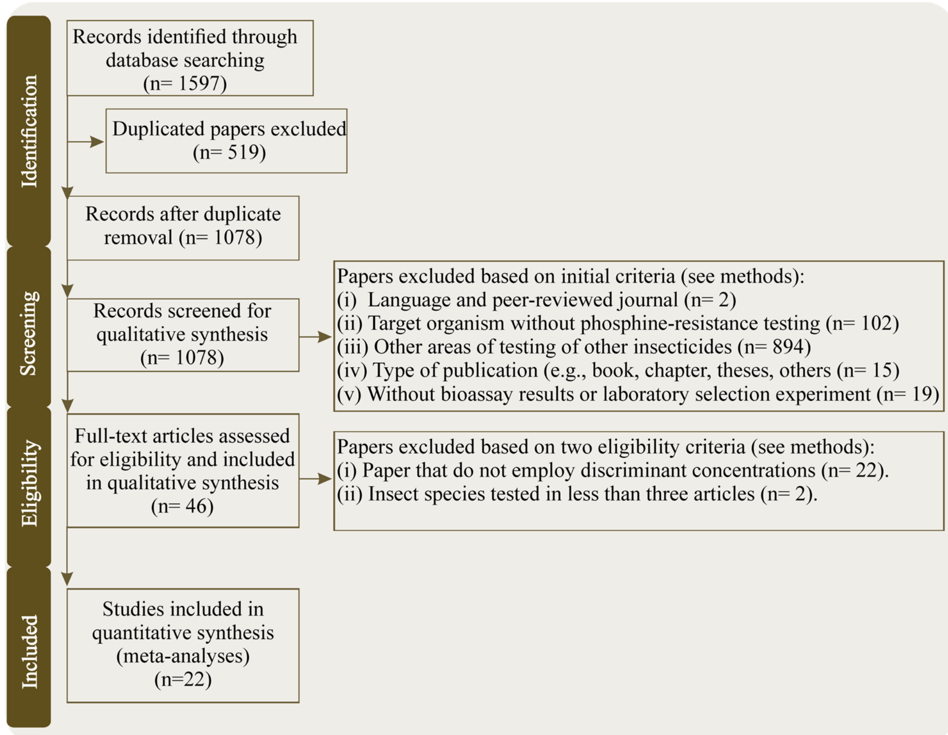

Fig. 1 Flowchart describing, step-by-step, how scientific articles were included/excluded in the literature dataset at the four stages of the systematic review process ('Identification', 'Screening', 'Eligibility' and 'Included'). Refer to the Materials and Methods for details on screening and eligibility criteria

of meetings or conferences, besides publication on other subjects or insecticides.

Qualitative analyses

The selected papers constituting the initial dataset were used to recognize overall temporal trends of research publications of phosphine resistance and to identify the main insect species targeted, the geographic distribution of the studies and samples (i.e., populations by country), and the resistance status of the insect populations tested. This information was compiled and summarized (Supplementary file S1).

Quantitative analyses

In order to establish the dataset for the quantitative analyses, the research papers were selected for inclusion based on two eligibility criteria: (i) record of the frequency of resistant individuals based on the FAO method or similar method, but using discriminating concentration; and (ii) the insect species should be tested in at least three research papers to allow proper testing. This dataset was subjected to meta-analyses with proportion outcomes to determine the frequency of incidence of phosphine resistance within each species. The insect species and geographic distribution (i.e., populations by country) were used as moderators (i.e., a variable that conditions the relationship between two others). The frequency of resistance and 95% confidence intervals were used to determine the overall effect measured. The random-effect model was used because the individual studies differ, and their effects are usually assumed to be heterogeneous. The quantification and heterogeneity-tests (i.e., Q, H, and I^2) were carried out, and the inverse variance and DerSimonian–Laird methods were used to estimate the between-study variance (τ^2). The former summarizes effect sizes from multiple independent studies, while the latter is a variation of the former that incorporates the assumption that the different studies are estimating different, yet related, effects to estimate the between-studies variance. A similar meta-analysis was carried out for the level of resistance to phosphine (i.e., resistance ratio or resistance factor, whenever the study and dataset provides that), but only insect species were included as moderators; the same eligibility criteria of the frequency of resistant individuals was used. The resistance level is obtained as the ratio between the LC_{50} or LD_{50} of the assessed population and that of a standard susceptible population, while the frequency of resistant individuals (or resistant genotype) is the percent of individuals surviving a discrimination concentration able to the kill the susceptible insects. All analyses were performed using the R-software version 4.1.0 (R Development Core, Vienna, Austria), with the packages "*meta*", "*metafor*" and "*stats*" (R Development Core; https://www.r-project.org/) (Schwarzer et al. 2015). The graphical illustrations were produced with Wacom creative table (Intuos S, Tokyo, Japan) using Corel Painter (Essential 7, Ottawa, ON, Canada).

Results

Summary of literature

The summary flowchart depicted in Fig. 1 exhibits the results of the article selection procedure, which started with an initial literature survey recording 1597 papers from the *Web of Sciences* and *Scopus* databases from January 1975 through March 2021. A subsequent duplicate removal reduced the total number of papers to 1078, which were screened based on titles and abstracts to verify their consistency with the criteria of inclusion in the dataset (see Materials and Methods for details). This resulted in 46 papers that were used in the qualitative analysis to describe the temporal trends, insect species, geographic distribution, and resistance status. In order to conduct the meta-analyses, two additional eligibility criteria were applied to the 46 papers—records of frequency of resistant individuals and records of at least three studies (see Materials and methods for details), which totaled 22 papers.

Qualitative trends: distribution by species, incidence, and countries

The 46-year publishing pattern recorded in the literature survey indicated a steady growth trend of papers published within a span of about two decades, particularly

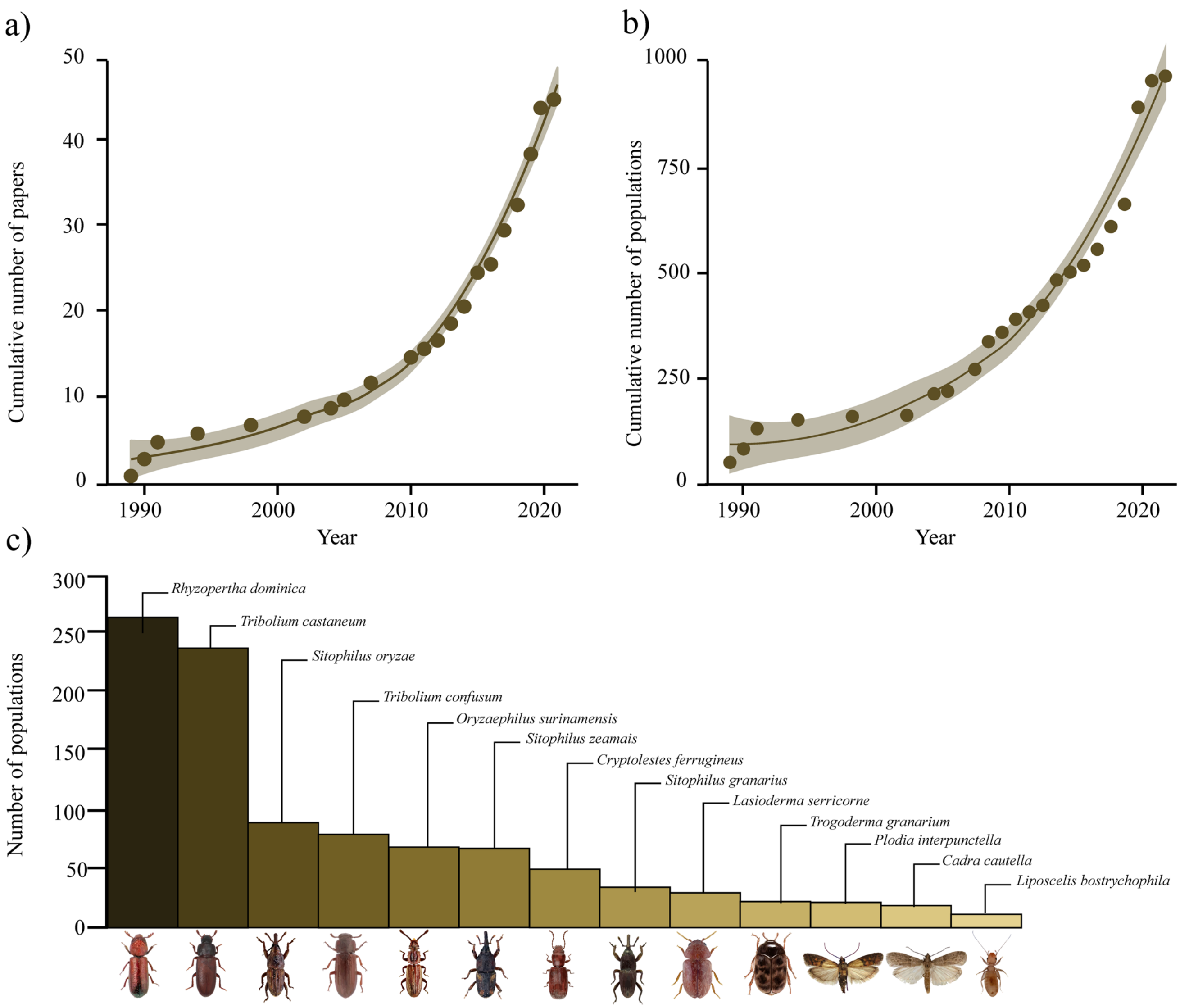

Fig. 2 Scatterplot exhibiting (**a**) the cumulative number of papers with phosphine resistance in insects, published between 1975 and 2021; (**b**) the number of populations tested with phosphine between 1975 and 2021; (**c**) the number of populations used in phosphine resistance tests for each insect species

between 1989 and 2010 (< 15 papers, Fig. 2a). This trend was followed by a fast-growing number of published studies (Fig. 2a), which totaled 46 papers by the end of 2021. Although the number of papers on phosphine resistance is relatively small, each paper reports results of different populations with an overall average of 21.30 ± 3.49 populations tested per research paper (Fig. 2b), thus totalling 980 populations tested until March of 2021 and providing a global picture of phosphine resistance in storage product insect pests.

A total of 13 species of stored product insect pests were assessed in these 46 articles (Fig. 2c). The populations most frequently studied from these articles belonged to the lesser grain borer *Rhyzopertha dominica* (Fab.) (26%), red flour beetle *Tribolium castaneum* (Herbst) (24%), rice weevil *Sitophilus oryzae* (L.) (9%), confused flour beetle *Tribolium confusum* Du Val (8%), sawtoothed grain beetle *Oryzaephilus surinamensis* (L.) (7%), maize weevil *Sitophilus zeamais* (Motsch.) (7%), rusty grain beetle *Cryptolestes ferrugineus* (Stephens) (5%) and granary weevil *Sitophilus granarius* (L.) (3%). Five other species, including the cigarette beetle *Lasioderma serricorne* (Fab.), khapra beetle *Trogoderma granarium* Everts, Indian meal moth *Plodia interpunctella* (Hübner), almond moth *Cadra cautella* (Walker) and the psocid *Liposcelis bostrychophila* Badonnel, encompassed only 11% of all the populations tested in this survey (Fig. 2c).

Phosphine resistance was detected in 72.96% populations from a total of 980 cumulative populations across the 13 species. The 13 main insect species studied were grouped into three categories—most studied internal grain feeders and external feeders, and other miscellaneous species less frequently studied—to better understand their geographic distribution and resistance status. The former encompasses the lesser grain borer and *Sitophilus* weevils, while the main external feeders studied encompassed *Tribolium* flour beetles, saw-toothed and rusty grain beetles. The five remaining species were clustered into the category "other insect pest species".

Phosphine resistance was recorded in 80% of the populations of internal feeders, regardless of the species ($n = 443$ populations tested). In this category, we found that lesser grain borer (94% of the populations [$n = 260$ populations tested]; Fig. 3a) and rice weevil (84% of the populations [$n = 88$ populations tested]; Fig. 3b) presented the greatest number of populations with phosphine resistance, whereas maize weevil (64% of the populations [$n = 66$ populations tested]; Fig. 3c) and granary weevil (28% of the populations [$n = 29$ populations tested]; Fig. 3d) exhibited a moderate proportion of resistant populations. Furthermore, the lesser grain borer and the rice weevil presented the broadest distribution of sampled populations, unlike the maize weevil, for which tested populations were restricted to North and South America (particularly in Brazil), and the granary weevil, whose studies were restricted to Europe (mainly Greece and the Czech Republic) and Australia (Fig. 3).

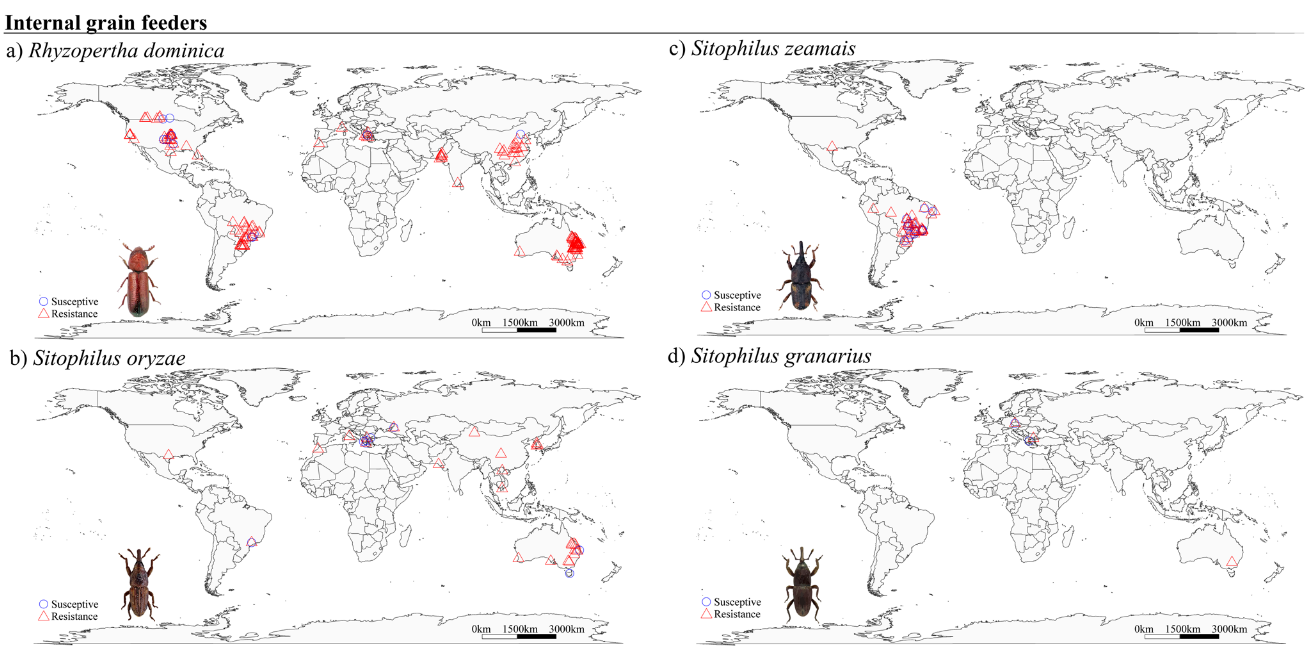

Fig. 3 Location of the sampling sites of the beetle populations tested of internal grain feeders: (**a**) *Rhyzopertha dominica*; (**b**) *Sitophilus oryzae*; (**c**) *Sitophilus zeamais*; and (**d**) *Sitophilus granarius,* indicating the populations susceptible and resistant to phosphine. (Blue circles refer to susceptible populations, while the red triangles refer to resistant populations)

Phosphine resistance was recorded in 77% of the main external feeder populations, regardless of the species ($n=430$ populations tested). The rusty grain beetle was the species with the greatest proportion of resistant populations (90% of the population [$n=49$ populations tested]; Fig. 4d), followed by the red flour beetle (65% of the populations [$n=235$ populations tested]; Fig. 4a), confused flour beetle (63% of the populations [$n=78$ populations tested]; Fig. 4b), and saw-toothed grain beetle (62% of the populations [$n=68$ populations tested]; Fig. 4c). Phosphine resistance among red flour beetles has been confirmed in North America, Europe, North Africa, Asia, and Australia receiving the broadest worldwide attention when contrasted with the remaining species (Fig. 4).

The last group of (miscellaneous) species registered phosphine resistance in 56% of the populations, regardless of the species ($n=107$ populations tested). The khapra beetle (90% of the populations [$n=21$ populations tested]; Fig. 5b), and the psocid *L. bostrychophila* (82% of the populations [$n=11$ populations tested]; Fig. 5e) exhibited the greatest proportion of resistant populations, whereas the cigarette beetle (65% of the population [$n=34$ populations tested]; Fig. 5a), Indian meal moth (32% of the population [$n=22$ populations tested]; Fig. 5c), and almond moth (16% of the population [$n=19$ populations tested]; Fig. 5d) exhibited a range of moderate to low proportion of resistant populations. Furthermore, high association was observed between the geographic distribution of the study and the species studied; for example, the cigarette beetle studies prevailed in the USA and Japan (Fig. 5a), the khapra beetle studies are mainly from Pakistan and India (Fig. 5b), the studies on Indian meal moth and almond moth are mainly produced in the USA and Greece (Fig. 5c, d), and the psocid studies, in the Philippines (Fig. 5e), which suggests greater local concern with phosphine resistance in these species, rather than their global importance as pest species. Nonetheless, a few studies of phosphine resistance from Australia and the US were published, but not adhering to the criteria of inclusion in our study. These studies often lacked a clear measure of the level or the frequency of phosphine resistance, eventually favoring an alternative estimate or with another research objective (e.g., Nayak and Collins 2008), or were published after the survey period covered (e.g., Danso et al. 2022).

In summary, a total of 46 papers were selected for qualitative analysis. In these papers, we identified a total of 13 species of storage pests distributed among 980 populations around the world. According to our findings, 72.96% of these insect populations were resistant to phosphine, and 10 out of 13 species exhibited resistance in more that 60% of their tested populations. Furthermore, among the species surveyed, the lesser grain borer, rice weevil and red flour beetle showed the most widespread distribution.

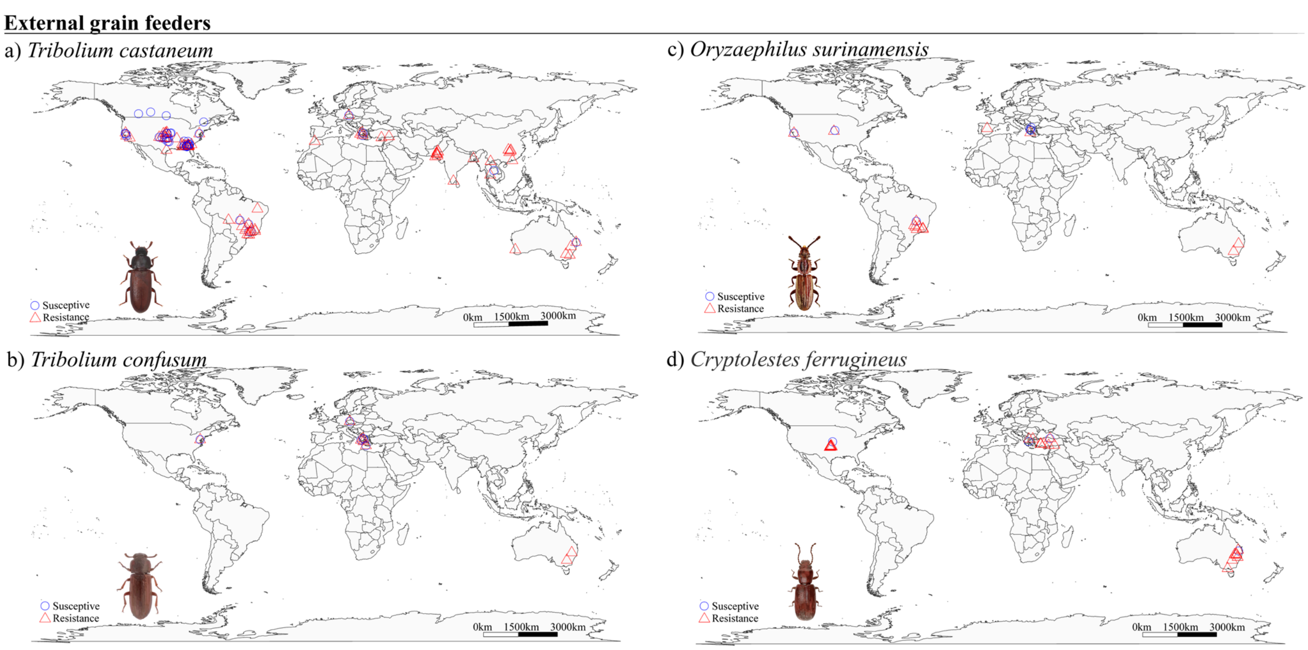

Fig. 4 Location of the sampling sites of the beetle populations tested of external grain feeders: (**a**) *Tribolium castaneum*; (**b**) *Tribolium confusum*; (**c**) *Oryzaephilus surinamensis*; and (**d**) *Cryptolestes ferrugineus,* indicating the populations susceptible and resistant to phosphine. (Blue circles refer to susceptible populations, while the red triangles refer to resistant populations)

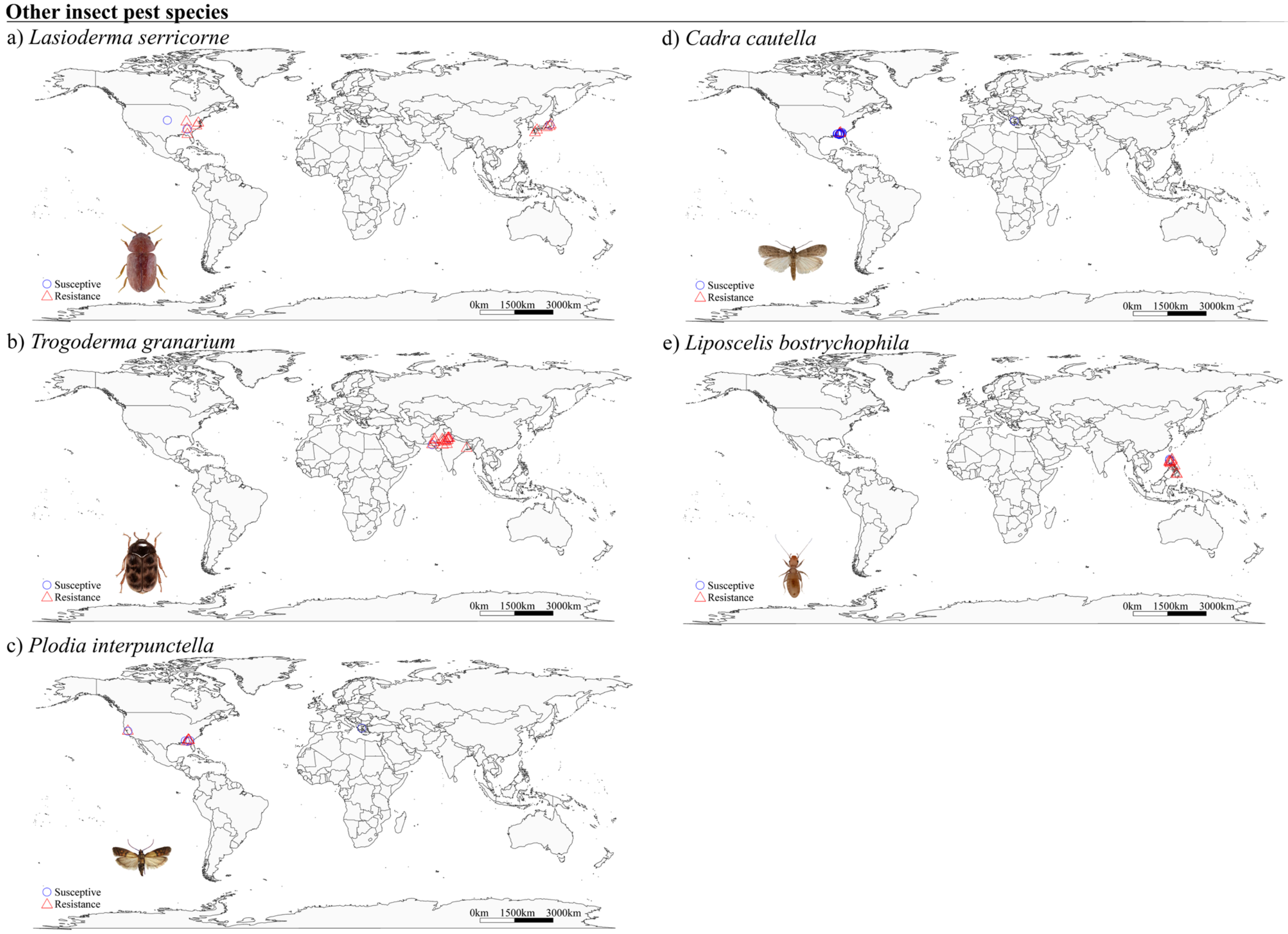

Fig. 5 Location of the sampling sites of the populations of the other insect pest species (regardless if internal or external feeders), which were less studied for phosphine resistance: (**a**) *Lasioderma serricorne*; (**b**) *Trogoderma granarium*; (**c**) *Plodia interpunctella;* (**d**) *Cadra cautella;* and (**e**) *Liposcelis bostrychophila,* indicating the populations susceptible and resistant to phosphine. (Blue circles refer to susceptible populations, while the red triangles refer to resistant populations)

Meta-analyses: frequency of resistant individuals by populations

Out of the 46 research papers surveyed, 22 met the two eligibility criteria for meta-analyses, namely–determination of frequency of resistant individuals through a standardized procedure (the diagnostic FAO-based or similar; see Material and Methods section for details), and exhibited at least three independent studies to allow proper statistical estimates. These papers include three insect species of grain internal feeders and three beetle species of (main) external feeders. The species from the group of other miscellaneous insects did not meet the qualifying requirements, and were therefore excluded. The remaining papers were subjected to meta-analyses to synthesize and quantify the incidence and frequency of resistant individuals within populations of the insect pest species of the main stored products across the globe.

Among the internal feeder species, the overall effect estimated by the meta-analysis model indicated that the average proportion of phosphine resistant individuals across populations ranged from 12 to 41% in the populations tested worldwide using discriminating dose or concentration bioassays (Fig. 6). Furthermore, it is noteworthy that the dataset showed considerable variability within species ($I^2 = 95–100\%$, $P < 0.01$; Fig. 6), which invites additional scrutiny. For the lesser grain borer *R. dominica*, for instance, the overall effect indicated an average incidence of 41% of resistant individuals per population tested (proportion = 0.41; $k = 13$; $P < 0.001$; Fig. 6a), and Brazil, Greece and the US showed the highest proportion of resistant populations (i.e., 0.55–0.83; Fig. 6a), when compared to other countries (Fig. 6a). Similarly, the overall effect estimated for the rice weevil *S. oryzae* indicated that this species populations exhibited an average of 38% of resistant insects (proportion = 0.38; $k = 8$; $P < 0.001$;

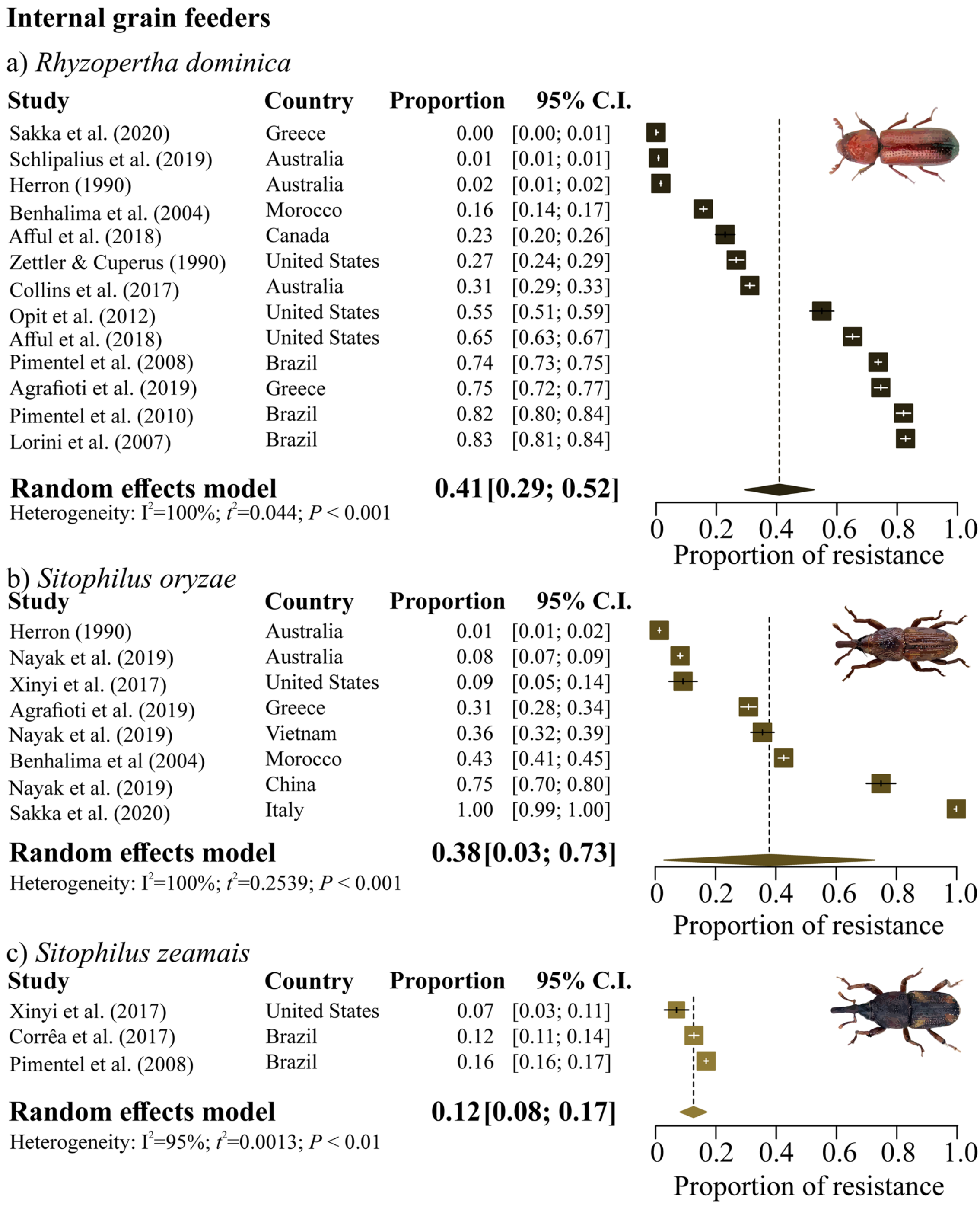

Fig. 6 Forest plot, a typical meta-analysis display, summarizing the results of the frequency of resistant insects in populations of beetle species of internal grain feeders, considering the insect species and country. The proportion (95% CIs) is denoted by coloured boxes (horizontal lines). The combined frequency of resistance estimate for overall trends is represented by a coloured diamond, whose width corresponds to 95% CI bounds. The vertical dashed line shows the overall estimated effect resulting from all studies. The *P*-values for the heterogeneity test are indicated

Fig. 6b), and Italy, China, and Morocco showed the highest proportion of resistant individuals per population (i.e., 0.43–1.00; Fig. 6b). In contrast, the average incidence of resistant insects among maize weevil populations across the globe was only 12% (Fig. 6c), albeit with a smaller set of studies.

Among the main species of grain external feeders, the overall effect estimated by the meta-analysis model indicated that the incidence of phosphine resistance insects per population ranged from 39 to 48%, which exhibited high variability within species ($I^2 = 100\%$, $P < 0.01$; Fig. 7). The red flour beetle *T. castaneum*, for instance, showed an average of 39% resistant individuals per population (proportion = 0.39; $k = 15$; $P < 0.001$; Fig. 7a), and Australia, the US, Bangladesh, Brazil and Greece exhibited the highest proportion of resistant insects (i.e., 0.42–1.00; Fig. 7a). Similarly, the overall incidence of resistant individuals per population of the confused flour

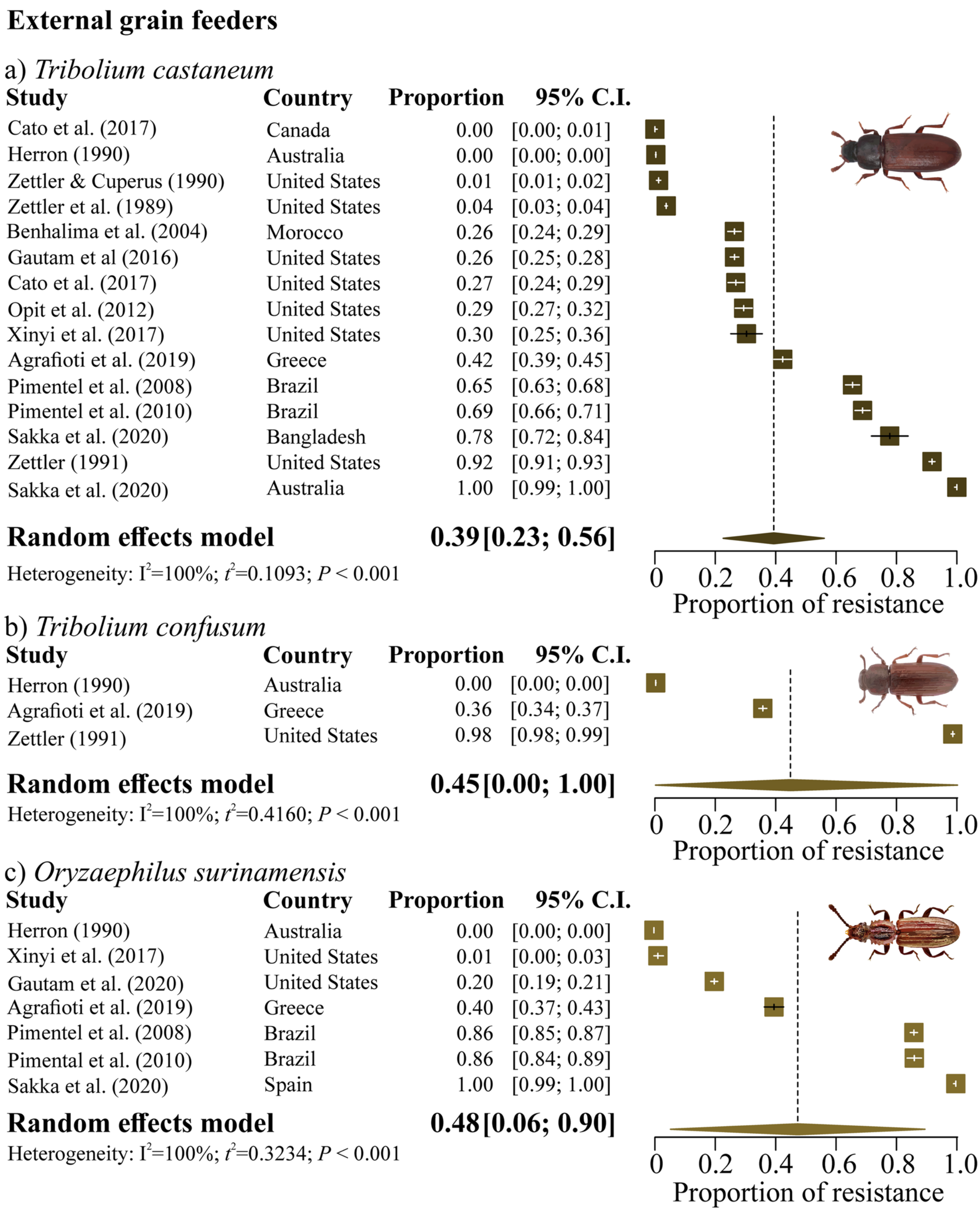

Fig. 7 Forest plot summarizing the results of the frequency of resistant insects in populations of beetle species of external grain feeders, considering the insect species and country. The proportion (95% CIs) is denoted by colored boxes (horizontal lines). The combined frequency of resistance estimate for overall trends is represented by a colored diamond, whose width corresponds to 95% CI bounds. The vertical dashed line shows the overall estimated effect resulting from all studies. The *P*-values for the heterogeneity test are indicated

beetle *T. confusum* (proportion = 0.45; $k = 3$; $P < 0.001$; Fig. 7b) and the saw-toothed grain beetle *O. surinamensis* (proportion = 0.48; $k = 7$; $P < 0.001$; Fig. 7c) were similar and prevalent in the US and Greece for *T. confusum*; and in Spain, Brazil, and Greece for *O. surinamensis*.

The levels of phosphine resistance were subjected to meta-analysis for only three species of internal grain feeders–the lesser grain borer and the rice and maize weevils, and two external-feeding beetles–the red flour beetle and the saw-toothed grain beetle (Fig. 8), as the data from the other species did not adhere to the required criteria for analysis. The interspecies variability was significant ($I^2 = 85\%$, $P < 0.01$), and the maize weevil and lesser grain borer exhibited the highest average levels of phosphine resistance, 123- and 122-fold respectively, followed by the red flour beetle with nearly 98-fold resistance. The levels of phosphine resistance for the rice weevil and saw-toothed grain beetle were 23- and 18-fold, respectively.

In summary, 22 papers used discriminating concentrations in their surveys of phosphine resistance to determine the frequency of resistant individuals per population and were used for quantitative analyses of the literature. Six insect species of internal and external feeders were included in the meta-analyses, but the species from the other (miscellaneous) group of insect pest species of stored products did not meet the eligibility criteria for analyses and were excluded. According to the meta-analyses, phosphine resistance was observed in 12% to 41% of individuals from internal feeder species and in 39% to 48% of individuals from external feeder species (average ranges). In addition, there was a considerable level of variation among species and geographic distribution, and high incidence of phosphine resistance was reported particularly in the US, Brazil, Greece, and Australia.

Meta-analyses: level of resistance in beetle species

The level of resistance to phosphine was reported in a total of 193 populations worldwide, including three beetle species of internal feeders (i.e., *R. dominica*; *S.oryzae*; *S. zeamais*) and two beetle species of external feeders, (i.e., *T. castaneum* and *O. surinamensis*). The meta-analysis model estimated an average resistance rate of 67.26-fold for the species investigated, albeit with significant variability among the species ($I^2 = 85\%$, $P < 0.01$; Fig. 8). Overall, the levels of phosphine resistance vary significantly among species, but the maize weevil, lesser grain borer and red flour beetle exhibited high levels of resistance, reaching near 100-fold, and above (Fig. 8); the rice weevil and saw-toothed grain beetle exhibited moderate levels of resistance (i.e., between 10 and 100-fold) (Fig. 8).

Discussion

Phosphine has a 100-year old history as a fumigant for pest control and noticeable dominance as the prevailing fumigant that continues to be used worldwide for insect pest control, particularly in stored product facilities (Chaudhry 2000; Thoms and Busacca 2016). Such prevalence intensified even further with the phasing out of methyl bromide (United Nations Environmental Programme [UNEP] 1994), which led to overreliance on phosphine for managing stored product insect pests and the issuing problems of phosphine

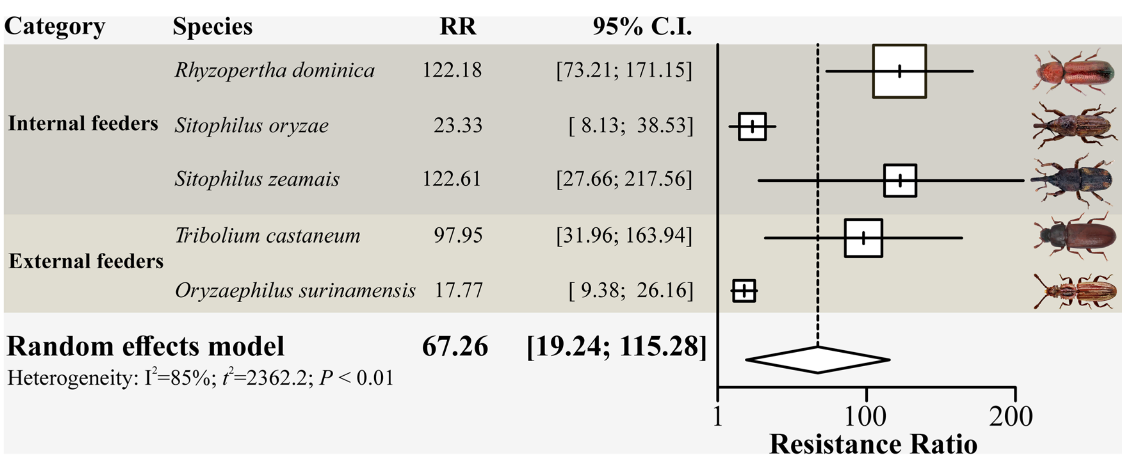

Fig. 8 Forest plot summarizing the results of the level of phosphine resistance (i.e., resistance ratio) of beetle species of internal and external grain feeders. The average resistance ratio (95% CIs) is denoted by boxes (horizontal lines), and the box size refers to the number of populations reported for each species. The combined resistance ratio estimate for overall trends is represented by a diamond, whose width corresponds to 95% CI bounds. The vertical dashed line shows the overall estimated effect resulting from all species. The *P*-values for the heterogeneity test are indicated

resistance due to the increased selection pressure for resistance to phosphine (Champ and Dyte 1976). This problem sparked early worldwide concern that resulted in the development of standardized bioassay methods for the detection of phosphine resistance and the subsequent global-wide survey of the phenomenon whose results were published by the mid-1970's (Food and Agriculture Organization [FAO] 1975; Champ and Dyte 1976). Interestingly, despite the further increasing usage of phosphine in storage facilities and the increased number of reports of phosphine resistance since 1975, there is no global compilation with quantitative analysis of the phenomenon, which justifies the present effort.

A systematic literature survey was carried out aiming to detect general patterns and trends of phosphine resistance, besides quantifying the scale of the problem using meta-analyses. An increase in the number of species and countries of study was expected, as well as an increase in the incidence of the phenomenon and the frequency of resistant individuals in insect populations across stored product insect species. Indeed, such a trend was largely confirmed by the present survey and analyses of the 46 accumulated years of studies on the subject, which points to some convergence and knowledge gaps that deserve attention to improve the management of stored product insects and minimize their losses throughout the globe.

An exponential growth in studies on phosphine resistance has been observed since 1975, and a significant expansion since the 1990's, mirrored by a similar increase in the number of insect populations tested, which reached 980 populations in 2021. The number of species tested also increased, compared with the 1970's survey (Champ and Dyte 1976), which numbered six species with instances of phosphine resistance and reached 13 species of stored product insects in 2021. Interestingly, the main species of concern in the 1970's, the lesser grain borer and the red flour beetle, remain the main concern in the subsequent studies and account for most of the populations tested–260 for the former and 235 for the latter, which totals 50% of the insect populations tested in the 46-year period of the survey. The remaining species, which were addressed by rather few studies, included some of the main beetle species of internal and external feeders, two externally feeding moths (the Indian meal moth and the almond moth), and a psocid species. The latter two groups, however, had a limited number of populations tested (22, 19 and 11, respectively).

The greater the number of populations tested for phosphine resistance within a species, the broader the distribution of the studies. Phosphine resistance in populations of the lesser grain borer and the red flour beetle is rather broadly distributed worldwide. However, Africa remains grossly underrepresented with just a single survey from Morocco and no further data from this continent (Benhalima et al. 2004). It does not mean that Asia and Neotropical America are particularly well-represented, although the coverage in the former is better than in the latter, where the results available are only from Brazil. These Brazilian studies focus on two of the main species of stored product insect pests, which are cosmopolitan, and cause massive post-harvest losses, particularly in warmer climates (Rees 2004; Hagstrum and Subramanyam 2009b; Hagstrum et al. 2013; Tadesse 2020). Therefore, such deficiency needs attention. Most of the other species are also rather important stored product insect pests, which are even less represented. Also noticeable is the shortage of studies on phosphine resistance with stored product mites.

The global distribution and relative importance of the stored product species may explain the biases in the studies with an overemphasis in a few species, and particularly in two species, and a few countries, namely–Australia, Brazil, Greece, and the US. Distribution and importance play a significant role in this scenario, but it does not strictly reflect pest importance or distribution. Grain weevils, for instance, do have ancient and global distribution, and recognized importance (Corrêa et al. 2013, 2017), but prevail in warmer climates, except for the granary weevil (Plarre 2010; Corrêa et al. 2017). Yet, the studies with rice weevil are from Australia, Asia and Europe, while those with the maize weevil are all from Brazil, and those with the granary weevil are from Europe and the Middle-East. Similarly, phosphine use is not restricted to a few countries and continents, but it is very widespread in warmer climates with more intensive use, overuse or used under more unsuitable conditions, such as a deficient airtightness (Champ and Dyte 1976; Nayak et al. 2020). These areas encompass large regions with greater deficiency in phosphine resistance studies. A counterpoint is the continuous and steady attention given by Australian agencies and researchers to the issue of phosphine resistance, which reflects a sustained effort, whose information is centralized in the Australian Grain Insect Resistance Database (AGIRD) (Emery et al. 2011).

The use of standardized bioassays to determine phosphine toxicity and resistance allowed the survey of a representative set of studies from grain and flour beetles, in which the frequency of resistant individuals per population was determined using discriminating concentrations. Thus, among the internal feeders, the lesser grain borer with its 94% of phosphine resistant populations exhibited an average frequency of 41% resistant individuals per population, despite the significant variability found across populations, studies, and countries. Nonetheless, Brazil features at the higher end of the spectrum, exhibiting over 80% of resistant individuals per lesser grain borer population. Such incidence of phosphine resistant individuals was also high among rice weevils, particularly from China and Italy, but the overall average frequency is similar to the lesser grain borer, and higher than that observed for maize weevils, which are still available only from Brazil and the US (Pimentel et al. 2009; Corrêa et al. 2014). High levels of phosphine resistance are observed for grain beetles, particularly for the lesser grain borer, and the maize weevil (i.e., over 100-fold).

Among external feeders, the overall frequency of resistant individuals per population ranges from 30% for the red flour beetle to 45% for the confused flour beetle and 48% for the saw-toothed grain beetle, with significant variation among populations within species and higher frequencies of resistance appearing in Brazil, Bangladesh, Australia, and the US, for the red flour beetle; also, the US, for the confused flour beetle; and Brazil and Spain, for the saw-toothed grain beetle. Fewer studies reported the levels of resistance in individual populations, but the red flour beetle also appears as a highlight for exhibiting high overall level of resistance (nearly 100-fold). Even fewer studies explored the phosphine resistance mechanisms involved (Schlipalius et al. 2012), sublethal effects of this fumigant (Pimentel et al. 2012; Agrafioti et al. 2021), and existing fitness advantages (Daglish et al. 2014), which deserve attention. The lack of alternative fumigants for large scale uses among storage facilities is one likely reason for current phosphine resistance scenario, since it limits the potential tactics for phosphine resistance management. Nonetheless, important progress is being achieved in the understanding of the phosphine mode of action and resistance mechanisms.

Phosphine is recognized as a disruptor of mitochondrial metabolism for compromising electron transport during the oxidative phosphorylation (Chefurka et al. 1976; Ebert et al. 2011; Sciuto et al. 2017). Ironically, the set of studies on phosphine resistance mechanisms started by 2010's in Australia greatly helped to improve the understanding of the mechanism of phosphine toxicity in insects (Ebert et al. 2011; Jagadeesan et al. 2012; Schlipalius et al. 2012), which leads to two phosphine phenotypes–strong and weak resistance. Phosphine toxicity seems to rely on the generation of reactive oxygen species (ROS) by the activity of dihydrolipoamide dehydrogenase (DLD), as a by-product of aerobic respiration. One of the mechanisms of phosphine resistance observed in insects is a single point mutation in the DLD gene, which reduces the production of ROS under phosphine exposure, as observed with the *rph2* gene coding for the strong phosphine resistant phenotype recorded in phosphine resistance populations of the lesser grain borer, red flour beetle, and rice weevil (Schlipalius et al. 2002, 2012, 2018; Oppert et al. 2015; Hubhachen et al. 2020; Nayak et al. 2020). Besides this mechanism, which is associated with the expression of a strong phosphine resistance phenotype (when in homozygosity or even heterozygosity), a weak phosphine resistance phenotype also takes place and it is associated with another gene, *rph1*, and resistance mechanism.

Fatty acid desaturase (FADS) is another important enzyme for phosphine resistance, due to its involvement in the production of desaturated fatty acids. These are also targets of ROS, which increases with phosphine exposure, oxidatively damaging cellular membrane fatty acids. Thus, the *rph1* gene encoding FADS, responsible for the weak resistance phenotype, reduces the vulnerability of cellular (mitochondrial) membranes to ROS associated with phosphine exposure, which is another phosphine resistance mechanism (Schlipalius et al. 2018). Both mechanisms *rph1* and *rhp2,* synergistically interact, leading to high levels of phosphine resistance, also referred to as "strong resistance", which has been consistently observed in different stored product insect species (Schlipalius et al. 2018; Hubhachen et al. 2020; Nayak et al. 2020). Unfortunately, the FAO-based diagnostic dose bioassays cannot detect the strong phenotype as those easily survive the relatively low concentration in these bioassays. Nonetheless, the use of diagnostic concentrations for strong phosphine resistance are possible, if it is enough to kill both phosphine susceptible and weakly resistant populations, but allows the strongly resistant to survive. A high proportion or incidence of strong phosphine resistance in storage facility will compromise phosphine use requiring a switch to a different fumigant.

A word of caution is important though, regarding the phosphine resistance mechanisms described above. The prevalence of these mechanisms should not obscure the recognition that alternative and secondary resistance mechanisms may also be present and further aggravate the problem of phosphine resistance, which deserves attention. Evidences for that do exist (Pimentel et al. 2012), but were little explored. The convergence of studies and the development of targeted molecular tools aimed at detecting the two prevailing mechanisms recorded for phosphine resistance seems to inadvertently lead to such neglect.

In summary, the phosphine resistance survey and meta-analyses reported here quantitatively reveal the escalation of this phenomenon, the further spread around the globe, and its propagation to a broader range of insect species, laying credence to the current perception of the problem (Nayak et al. 2020). A few biases and knowledge gaps were identified in this study; for instance, the steady increase in the incidence of phosphine resistant populations and frequency of resistant insects, and levels of resistance within these populations also demand attention, as well as the circumscribed records of occurrence of the phenomenon with large under-represented geographical regions without any information about the phenomenon. This is observed, despite the intensive use of phosphine throughout the world and particularly in warmer climates, where little information is available. An important geographic variable that may affect the resistance data reported here from certain places in the world may be the presence of public institutions with scientists conducting phosphine resistance research. Further studies recording frequency and level of phosphine resistance are therefore needed in more diverse geographical areas and for a broader range of species, for properly understanding the magnitude of the phenomenon and its consequences. Furthermore, the existing phosphine resistance mechanisms need to be better explored and surveyed, in addition to the sublethal effects of this fumigant and the existing fitness (dis)advantages, which are all important components for the development of suitable tactics of phosphine resistance management, that are still missing.

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Author contribution LMM-M, LMT and RNCG conceived and designed the study. LMT and RNCG provided the materials and tools. LMM-M and LMT gathered and analyzed the data. LMM-M, LMT and RNCG structured and wrote the manuscript draft, which was read, corrected, and approved by all.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Data availability The datasets supporting the conclusions of this article are included within the article and its additional files.

Code availability Not applicable.

Ethical approval All applicable international, national, and institutional guidelines for the care and use of animals were considered in the present investigation.

Consent to participate Not applicable.

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