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SUBJECT Pesticide literature compilation approach and results (AGR-Pesticide-Literature-Review-FY20)

INTRODUCTION

This memorandum summarizes the methods and results of a literature compilation conducted pursuant to the procurement AGR-Pesticide-Literature-Review-FY20. This compilation is based on readily available, key documents describing the effects of neonicotinoids on pollinators. The principal product associated with this effort is a Microsoft Excel file that summarizes the key features of referenced documents, including document and study type, funding source(s), pollinator species or taxa, contaminant(s), and multiple other characteristics (see "Document Characterization" below). We have also developed an EndNote database of the included articles, which are listed in Appendix A to this memorandum.

The objective of this compilation is to provide a high-level characterization of readily available information on the effects of neonicotinoids on pollinators, with an emphasis on managed and wild pollinators of relevance to the Commonwealth of Massachusetts. As defined by Massachusetts Department of Agricultural Resources (MDAR 2017), managed pollinators in the Commonwealth include honey bees (*Apis mellifera*), bumble bees (*Bombus* spp.), alfalfa leafcutting bees (*Megachile rotundata*), and blue orchard mason bees (*Osmia lignaria*), while wild pollinators include an estimated 380 species of bees and 120 species of butterflies, including monarchs (*Danaus plexippus*).

As described below, since 2010, several hundred research papers, reports, and white papers have been published on the effects of neonicotinoids on pollinators. It is beyond the scope of this review to cover all these documents; instead, we prioritized recent publications and reviews. This compilation may assist MDAR with identifying, planning, and managing future research and policy efforts related to neonicotinoids and pollinators but does not provide any policy recommendations with respect to the management, regulation, or use of neonicotinoids.

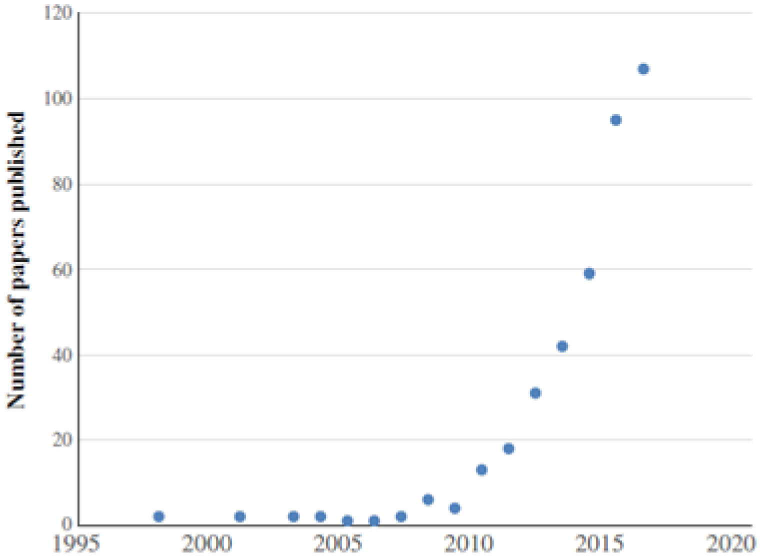
METHODS

DOCUMENT IDENTIFICATION

To identify documents for inclusion in this compilation, we conducted literature searches in PubMed and Google Scholar. PubMed provides a structured search of journal articles, while Google Scholar allows us to additionally identify government reports and other white papers not compiled in PubMed. We also searched for documents associated with the U.S. Environmental Protection Agency's (EPA) reviews of neonicotinoid pesticides (U.S. EPA 2019).

We screened search results based on their titles and abstracts. Because the volume of research conducted on the effects of neonicotinoids on pollinators is large (Exhibit 1) and identifying and reviewing all sources is beyond the scope of this effort, we prioritized recent (≥2015) reviews and meta-analyses. We supplemented these with additional key documents, including several from U.S. EPA's pollinator risk assessments developed to support registration reviews of neonicotinoid pesticides, and articles primarily from 2017 and later, as this timeframe generally post-dates the most recent, comprehensive literature reviews we identified.

EXHIBIT 1 NUMBER OF RESEARCH PAPERS ON POLLINATORS AND NEONICOTINOIDS PUBLISHED SINCE 1998. FROM PISA *ET AL.* (2017).



We include a small number of recent pre-2017 articles for specific reasons. For instance, Lu *et al.* (2016) addresses Massachusetts specifically and is therefore of particular interest. Forister *et al.* (2016) is included because it addresses butterflies, and very little neonicotinoid ecotoxicological literature is available on non-bee pollinators. Stanley *et al.* (2016) is a relatively recent article of relevance, which was not cited in the most recent review articles. Altogether, the resulting set of documents represents varying funding sources, pollinator species, neonicotinoid pesticides, and study designs, which considered endpoints at levels of ecological organization ranging from the molecular and genetic level to the colony, population, and even the community level.

DOCUMENT CHARACTERIZATION

For each document, we populated one or more rows in an Excel spreadsheet to characterize the document and its key findings. Most documents are summarized in a single row; however, EPA risk assessment documents and several other, more complex documents span multiple rows for clarity in presentation of their approaches and findings (see "Approach to EPA Risk Assessment Documents" for more information on our characterization of these reports). Some articles, particularly review articles, provide information on species and/or topics other than the exposure and effects (or the absence of effects) of neonicotinoids on pollinators, and those aspects of such articles are intentionally excluded from this compilation.

Exhibit 2 lists the fields that were populated for each document and briefly describes each. We note that for some study types, certain fields are frequently not applicable and/or are not useful to populate and are therefore shaded grey. Examples include, for laboratory studies, the “Landscape type”, “Plant type/crop”, and “Location(s)” fields. For residue studies, the “Exposed life stage(s)” and “Exposed caste(s) or sex” are generally inapplicable and are shaded grey. Similarly, for review articles it is not feasible (or useful) in many cases to comprehensively populate a field because the number and variety of articles reflected in the review is large, and the underlying studies jointly reflect multiple taxa, contaminants, exposure concentrations, and so forth. For review articles, therefore, a number of fields are intentionally not populated and are shaded grey. In general, the most useful information for review articles appears in the “Notes” and “Key conclusions” fields.

Approach to EPA Risk Assessment Documents

Our summaries of U.S. EPA’s pollinator risk assessments focused on certain aspects of the work. These risk assessments are large documents (hundreds of pages) that report on the results of a combination of registrant-submitted studies and open literature findings, with evidence grouped into “tiers.” Tier I studies are laboratory studies that focus on individual-based endpoints, typically including adult acute contact toxicity, adult acute oral toxicity, adult chronic oral toxicity, larval acute toxicity, and larval chronic toxicity. Tier II studies evaluate are semi-field studies that evaluate colony-level endpoints. These studies are “designed to more closely reflect real world exposures” and commonly include feeding studies evaluating effects on colonies that are sometimes contained in enclosures. Tier III studies are full field studies with free-foraging bees that may include longer-term endpoints such as over-wintering success. Although EPA’s risk assessment documents reflect the findings of many registrant-submitted and open literature studies across all three tiers, not all studies are accorded equivalent weight in the risk assessment. For instance, multiple studies often address Tier I endpoints, and in conducing the risk assessment, EPA “uses the most sensitive toxicity estimates from laboratory studies” that report on that endpoint (U.S. EPA 2018). When summarizing these large documents in this review, we focus on those studies that EPA has indicated it relies on most. These are primarily those that EPA uses to calculate risk quotients; however, we also include others that EPA has characterized as “acceptable” or “supplementary – quantitative” that provide additional information of relevance to this review (e.g., because they address an additional pollinator species).

For a full listing of studies and information considered by EPA in its risk assessments, we refer readers to the full text of these documents, which are publicly available.

EXHIBIT 2 REVIEW FIELDS.

FIELD	DESCRIPTION
Citation	Brief citation; full citations are in Appendix A and in the Endnote Database
Funding source(s)	Funding sources, if any, as identified in the document. This may include study-specific funding and/or general funding for the authors. Any statements made about potential conflicts of interest are also noted here.
Author(s) conflict of interest statement	If the authors identify or explicitly disavow conflicts of interest, they are noted in this column; otherwise, "no statement provided" is entered.
Type of document	These include journal articles and reports.
Study type	Examples of study types include but are not limited to: review (i.e., review articles), laboratory, residue analysis (i.e., study focuses on measuring contaminant concentrations), semi-field, modeling, and risk assessment.
Author-reported pollinator species or taxa	These are identified to the degree of taxonomic specificity provided in the original document and, where possible, are generally described for review articles.
Genus	For ease of sorting, we include the genus of the author-reported pollinator species in a separate column. Where more than one genus is included, the entry is "multiple."
Species	For ease of sorting, we include the scientific name at the species level of the author-reported pollinator species in a separate column. Where more than one species is included, the entry is "multiple."
Exposed life stage(s)	The exposed life stage(s) evaluated in the document are listed (e.g., adults, larvae). When a more specific age is provided (e.g., 1- to 2-day old adults, or newly eclosed adults), then that information is also included. For most semi-field and field studies, the entry is "all."
Exposed caste(s) or sex	For pollinators with castes such as honey bees, the exposed caste is indicated (e.g., workers, queens, drones). For pollinators without castes such as butterflies, the sex is indicated if specified in the source document.
Landscape type	Information on landscape type is often general (e.g., urban, agricultural) but sometimes more detail is provided by the authors and is included here.
Plant type/crop	This field is most commonly applicable for field and semi-field studies where colonies are located in close proximity to agricultural areas.
Region	Where relevant (particularly semi-field and field studies), the study's general region (e.g., Europe, North America, Australia), is identified.
Location(s)	This field the more specific geographic location where the study took place. The level of geographic specificity provided is a function of the information presented in the original source document. This field is applicable to most field and semi-field studies.
Contaminant(s)	This field identifies the contaminant(s) used in toxicology experiments or measured, in the case of residue studies.
Exposure concentration(s)	For toxicology studies, the concentrations are generally presented as a dose range (e.g., control to 6 ppb); more detail is provided for some studies when needed to more fully understand study results. For residue studies, this field summarizes key findings, although more details may be presented in the "key conclusions" field.
Exposure duration	This field reflects the period of time for which organisms were exposed to contaminants. For field studies and modeling efforts, this may be lifetime.

FIELD	DESCRIPTION
Exposure route(s) for pollinators	In review articles that address pathways of contamination, key exposure routes/pathways are identified. For toxicological studies, typical exposure routes include "oral ingestion of sugar syrup" and similar entries. For field studies, an entry might be "pollen/nectar of seed-treated crops."
Endpoints considered	This field identifies key study endpoints. Examples include mortality, colony size, colony weight, pollen composition, residue concentrations, various behavioral metrics, and so forth.
Notes	This field provides information useful in understanding the study's objectives and interpreting its results.
Key conclusions	This field succinctly identifies key conclusions of the document appertaining to neonicotinoid effects on pollinators. Direct quotes are used as possible, although in some cases results are paraphrased in the interest of brevity.

Careful reviewers of the Excel spreadsheet may note some differences in how information is presented across documents within a field. While we strive for a reasonable degree of consistency in the presented information, we also prioritize presenting the information as stated in the original source document. Examples of fields where reviewers may notice differences in how a field is populated across documents include the following. For one, different authors present exposure information in different units. We have elected to present the values and associated units as stated in the cited documents, and we have not conducted unit conversions or any standardization of such values. In addition, with respect to pollinator taxa, in the "author-reported pollinator species or taxa" column, we provide the species' scientific names where stated; however, a small number of documents do not provide a scientific name but merely provide a common name (e.g., "honey bees"). The level of detail provided in some fields (e.g., "Plant type/crop" and "Location (s)" is also generally a reflection of the level of detail provided in the source document.

RESULTS

A total of 70 documents are included in this compilation. Of these, 66 are journal articles and four are EPA risk assessment documents for pollinators (addressing acetamiprid, dinotefuran, imidacloprid, and thiamethoxam/clothianidin jointly). Exhibits 3 through 5 provide a breakdown of the compiled documents by study type, taxon, and neonicotinoid.

EXHIBIT 3 STUDY TYPES IN THE REVIEWED DOCUMENTS.

STUDY TYPE	COUNT OF DOCUMENTS[(A)]	PERCENT OF DOCUMENTS REVIEWED[(A)]
Review	9	13%
Laboratory	29	41%
Semi-field	12	17%
Field	7	10%
Model	6	9%
Residue analysis	9	13%
Other(b)	8	11%

Note:

a. The total count exceeds the total number of documents (70), and the sum of the percentages exceeds 100% because some documents present results for more than one study type.

b. This category includes EPA's risk assessments, several quantitative weight-of-evidence articles, and one methods-only article that is associated with several other included articles that present results.

EXHIBIT 4 TAXA REPRESENTED IN THE REVIEWED DOCUMENTS.

TAXON	COUNT OF DOCUMENTS (A)	PERCENT OF DOCUMENTS REVIEWED(A)
Honey bee (*Apis mellifera*)	44	63%
Bumble bee (*Bombus* spp.)	26	37%
Other bee(s)	7	10%
Non-bee pollinator(s)	3	4%

Notes:

a. The total count exceeds the total number of documents (70), and the sum of the percentages exceeds 100% because some documents present results for more than one taxon.

EXHIBIT 5 NEONICOTINOIDS REPRESENTED IN THE REVIEWED DOCUMENTS.

NEONICOTINOID	COUNT OF DOCUMENTS[A]	PERCENT OF DOCUMENTS[A]
Acetamiprid	10	14%
Dinotefuran	4	6%
Imidacloprid	34	49%
Clothianidin	28	40%
Thiamethoxam	30	43%

Notes:

a. The total count exceeds the total number of documents (70), and the sum of the percentages exceeds 100% because some documents address more than one neonicotinoid. In addition, these numbers do not include eight review articles, one modeling article that is not specific to any particular neonicotinoid (Rumkee *et al.* 2017), and one article that does not identify the specific neonicotinoids about which it gathered application information (Forister *et al.* 2016).

We also conducted a rough count of articles to identify those that found one or more neonicotinoids *to cause or be associated* with one or more effects endpoints. In conducting this count, we excluded 27 of the 70 documents. Excluded documents included summary articles (e.g., review articles, quantitative weight-of-evidence articles, EPA's risk assessments), and articles that did not attempt to investigate or evaluate such associations (e.g., articles that presented information on neonicotinoid concentrations only). Of the remaining 43 documents, 42 identified at least one effect caused by, or associated with, neonicotinoid exposure. In stating this, however, we recognize that this is an extremely broad-brush observation and should be understood in context: publication bias may result in a higher publication rate for studies that identify effects. Not all identified effects were seen at field-realistic concentrations. Some studies found one neonicotinoid to affect an endpoint while another neonicotinoid did not.

That said, recent and more comprehensive reviews point to a large body of evidence documenting the ability of neonicotinoids to adversely affect pollinators. For example, the second Worldwide Integrated Assessment[1] includes an updated analysis of the effect of systemic insecticides on organisms and ecosystems (Pisa *et al.* 2017), dividing its discussion of pollinator literature by study type (field, semi-field, and laboratory), and endpoint (memory, behavior, locomotion, immunity, metabolism, reproduction). The authors conclude:

> Research on bees has revealed new aspects of sublethal effects, including the reduced fecundity of queen bees, impairment of sperm in drones, negative interactions with parasites and the immune system. Our knowledge of acute toxicity has also broadened to include some wild bee species, while the mixture toxicity in combination with other pesticides or infectious agents has reported some synergisms that are more

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[1] The original Worldwide Integrated Assessment (WIA) was an effort undertaken by the Task Force on Systemic Pesticides, a specialist group advising two IUCN Commissions. The first WIA took four years and included the examination of over 800 papers published over two decades (van Lexmond *et al.* 2015). The latest review represents an update to that original effort.

> pronounced than simply additive. Impacts of neonicotinoids and fipronil [a non-neonicotinoid insecticide] at the population level of bumblebees were known to some extent, but have now been compared among countries with different environments. The impacts on other wild bees were unknown and recent studies have shown that they are more sensitive to neonicotinoids than the honey bee.

Wood and Goulson (2017)[2] presents a review of post-2013 evidence (i.e., of evidence collected subsequent to the European Union’s partial ban on neonicotinoids), focusing on wild, non-target organisms. The authors conclude that these pesticides "pose a similar to greater risk to wild and managed bees, compared to the state of play in 2013." Moreover, the post-2013 research points to previously unexplored exposure pathways: bee exposure to neonicotinoids mediated through wild plants may be "much more prolonged" than the flowering period of crops, and the amount of these pesticides in wild plant pollen and nectar is "not trivial." Overall, the new research demonstrates "significant negative effects on free flying wild bees under field conditions, and some laboratory studies continue to demonstrate negative effects on bee foraging ability and fitness using field-realistic neonicotinoid concentrations" (Wood and Goulson 2017).

A review of global trends in bumble bee health describes worldwide patterns of bumble bee population decline and states “There is mounting evidence that widespread use of neonicotinoid insecticides is problematic for wild and managed pollinators, including bumble bees, through sublethal effects of exposure to field-realistic doses” (Cameron and Sadd 2020).[3]

In short, many studies and reviews have documented that neonicotinoid exposure can have deleterious effects on a wide range of endpoints relevant to pollinators and pollination services. The only review (or review-like) articles we identified that draw the opposite conclusion consist of a co-published series of articles that adopt a “quantitative weight-of-evidence” approach. This set of articles concludes that there is “minimal risk to honeybees” to exposure from imidacloprid, clothianidin, and thiamethoxam and that these pesticides do not adversely affect colony viability or survival (Solomon and Stephenson 2017b, a, Stephenson and Solomon 2017b, a). We note that the funding for this suite of articles was provided by manufacturers of neonicotinoids, and moreover that the authors’ analyses relied heavily on unpublished reports provided by these manufacturers, which limits third-party review of the underlying studies.

In conclusion, this memorandum and the associated deliverables present a compilation of current, readily available information on the effects of neonicotinoids on pollinators. Although it is clear that such compounds can adversely affect a range of pollinator species important to the Commonwealth of Massachusetts, it is beyond the scope of this effort to draw conclusions as to the probability or severity of such effects under Massachusetts-relevant field conditions, or to provide policy recommendations with respect to the management, regulation, or use of neonicotinoids.

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[2] The authors do not identify any particular funding sources associated with this review. Author affiliations include Michigan State University and The University of Sussex.

[3] Funding for this effort was provided by the USDA National Institute of Food and Agriculture. Author affiliations include the University of Illinois at Urbana, and Illinois State University.

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