Neonicotinoids and their substitutes in sustainable pest control

European Academies Science Advisory Council EASAC

EASAC Secretariat, The Royal Society

2023-02-28

European Academies Science Advisory Council EASAC , Smagghe , G , Hayrabedya , S , Hayrabedyan , K , Topping , C , Kahru , A , Hardy , I C W , Mikó , Z , Székács , A , Pennacchio , F , Geissen , V , de Silva , C , Lipiec , J , Mitchell , E A D , Rundlöf , M , Walloe , L & Norton , M 2023 , Neonicotinoids and their substitutes in sustainable pest control . EASAC Secretariat, The Royal Society . < https://easac.eu/publications/details/neonicotinoids-and-their-substitutes-in-sustainable-pest-control >

http://hdl.handle.net/10138/356109

unspecified
publishedVersion

European Academies

easac

Science Advisory Council

Neonicotinoids and their substitutes in sustainable pest control

EASAC policy report 45

ISBN 978-619-92418-0-6 (Printed)
ISBN 978-619-92418-1-3 (PDF)

This report can be found at
www.easac.eu

Science Advice for the Benefit of Europe

EASAC

EASAC – the European Academies' Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

EASAC covers all scientific and technical disciplines, and its experts are drawn from all the countries of the European Union. It is funded by the member academies and by contracts with interested bodies. The expert members of EASAC's working groups give their time free of charge. EASAC has no commercial or business sponsors.

EASAC's activities include substantive studies of the scientific aspects of policy issues, reviews and advice about specific policy documents, workshops aimed at identifying current scientific thinking about major policy issues or at briefing policy-makers, and short, timely statements on topical subjects.

The EASAC Council has 30 individual members – highly experienced scientists nominated one each by the national science academies of EU Member States, by the Academia Europaea and by ALLEA. The national science academies of Norway, Switzerland and the United Kingdom are also represented. The Council is supported by a professional Secretariat based at the Leopoldina, the German National Academy of Sciences, in Halle (Saale) and by a Brussels Office at the Royal Academies for Science and the Arts of Belgium. The Council agrees the initiation of projects, appoints members of working groups, reviews drafts and approves reports for publication.

To find out more about EASAC, visit the website – www.easac.eu – or contact the EASAC Secretariat at secretariat@easac.eu

European Academies

easac

Science Advisory Council

Neonicotinoids and their substitutes in sustainable pest control

February 2023

ISBN 978-619-92418-0-6 (Printed)
ISBN 978-619-92418-1-3 (PDF)

EASAC Publications Office
Bulgarian Academy of Sciences
1 '15 Noemvri' Street
BG-1040
Sofia
Bulgaria

Telephone: +359 2979 5241; +359 2979 5236
E-mail: publications@easac.eu
Web: www.easac.eu
Twitter: @EASACnews
Facebook: www.facebook.com/EASACnews/

Cover image: Communication Works / Felix Sorau.

Copy-edited and typeset in Frutiger by The Clyvedon Press Ltd, Cardiff, United Kingdom.

Printed by Schaefer Druck und Verlag GmbH, Teutschenthal, Germany. Printed on FSC-certified paper.

Contents

Foreword

Since Rachel Carlson's book *Silent Spring* was first published in 1962, we have been aware of the collateral damage that can arise from the use of toxic pesticides in agriculture, and regulators have faced the challenge of striking a balance between protecting agriculture from damaging pests, and adverse effects on the environment and health. More demanding testing protocols have been introduced, foodstuffs monitored and standards set for acceptable daily intakes, but the examples of previously approved pesticides that have been withdrawn shows that it is far from easy to find a defendable balance.

The neonicotinoid insecticides were such a group where the balance between effectiveness and environmental impact has been difficult to strike. Widely welcomed by farmers as providing simple and effective pest control, they soon became a billion-dollar business around the world. However, as adverse side effects appeared, it became clear that the environmental costs were greater than anticipated in the collateral damage to pollinators and other beneficial insects. This was the subject of the EASAC report on neonicotinoids in 2015, and outside use of the main neonicotinoids has since been banned in the European Union.

The recognition that we need to work with nature rather than against it is at the core of the Green Deal and its Farm to Fork strategies. One objective is to have a more sustainable and environmentally friendly use of pesticides—an aim that EASAC academies fully share. However, these noble ideals are not always easy to achieve, as shown by the slow progress following the original 2009 Sustainable Use of Pesticides Directive. This led the European Commission to propose a new regulation to drive agriculture to a more sustainable path. To assist this, we assembled an Expert Group from our member academies which has looked at the current state of the science on neonicotinoids, implications for future regulatory testing, the long list of possible future substitutes, and the challenges in bringing integrated pest management into the mainstream of agriculture.

Since starting this review, the Russian invasion of Ukraine has made food security a primary concern and, as pointed out by some of our academies when reviewing our experts' assessments, increases the pressure for more sustainable agriculture to deliver at least the same yields as conventional agriculture. Our report includes work that shows this can be done, but that the challenges may be substantial and require a range of measures, supported by future research and development. In these challenging times, individual fellows of our member academies may assess the broader political aspects differently against the weight of the evidence of the adverse effects of neonicotinoids. But we hope that our detailed examination of the environmental aspects of sustainable pesticide use will be a useful contribution to this important debate on the future of agriculture.

Wim van Saarloos
EASAC President

Abbreviations

CAP	Common Agricultural Policy
EC	European Commission
EFSA	European Food Safety Agency
EASAC	European Academies' Science Advisory Council
ERA	Environmental risk assessment
EU	European Union
HRI	Harmonised Risk Indicator
IPM	Integrated pest management
IPPM	Integrated pest and pollinator management
IRAC	Insecticide Resistance Action Committee
nAChR	Nicotinic acetylcholine receptor
NASAC	Network of African Science Academies
PPP	Plant protection product
REFIT	Regulatory Fitness and Performance Programme
SUP	Sustainable Use of Pesticides Directive (2009/128/EC)

Summary

Since restrictions on three neonicotinoids were introduced in 2018 in the European Union (EU), other insecticides with similar modes of action have entered the EU market, raising concerns that they may pose similar risks to honeybees and other non-target species. Meanwhile, agrochemical innovation continues to develop new molecules that exploit the same or similar neuroactive mechanisms to the original neonicotinoids. At the same time, debate is underway on the sustainable use of pesticides, on how to evaluate the environmental risk of existing and new pesticides, and on adapting regulations with the European Green Deal, Farm to Fork, and Biodiversity strategies.

As part of the Farm to Fork Strategy to reduce environmental impact of agricultural land, the European Commission has proposed a new Regulation on the Sustainable Use of Plant Protection Products (PPPs) that will seek to better apply integrated pest management (IPM) and reduce pesticide use and risk. In this report, the European Academies' Science Advisory Council (EASAC) reviews recent research into the effects of neonicotinoids and assesses its implications for the current policy debate. The policy proposals are especially important because current climate trends may lead to greater pesticide use with associated health and environmental damage risks, increased pesticide resistance and accumulation of persistent pesticides.

The report summarises the results of research in recent years and strengthens earlier conclusions in EASAC's 2015 review on the wider ecosystem effects of neonicotinoids. This supports the continuation of existing restrictions and of measures to minimise future use—especially to mitigate the threat to future food security from the continued decline in insects (including pollinators).

EASAC notes that although outdoor use has been restricted, many Member States have used provisions for **emergency authorisations** to continue neonicotinoid use—especially for controlling flea beetle in oilseed rape and in sugar beet to avoid yellow leaf virus. The European Court recently ruled that such trends do not meet the Commission's guidance that emergency authorisations should be a last resort.

The restrictions on the original neonicotinoids created incentives to develop **neonicotinoid substitutes** that exploit the same insect neural mechanisms. Two such products, a sulfoximine (sulfoxaflor) and a butanolide (flupyradifurone), have been approved as active substances in plant protection products, but many more chemical molecules are under development. With similar mechanisms, there is a risk that they will become 'regrettable substitutions' whose impacts turn out to be similar to, or worse than, the neonicotinoids they are designed to replace. Caution is thus needed in evaluating new molecules that inhibit nicotinic acetylcholine receptors and it should be assumed that similar broad ecosystem effects may occur unless applicants demonstrate otherwise when applying for regulatory approval.

Work continues to improve the regulatory process. This report describes some of the underlying issues in **environmental risk assessment (ERA)** methods and how to take into account accumulation of pesticides that may be used more than once in a season, exposure to other pesticides and to chemicals present in formulated products (co-formulants), stress factors such as viruses or parasites, uncertainties in applying the results to real field ecological conditions, or abiotic factors (e.g. soil pH or organic content) that can affect the toxicity of the pesticide.

To address these challenges, we support measures under way by the European Food Safety Authority (EFSA) towards a **'Systems-based ERA'** approach. A systems approach requires more data on post-approval use and effects, and EASAC agrees with other observers that the current extent of monitoring concentrations of, and exposures to, approved PPPs is insufficient to estimate their effects on human health and the environment, and for early identification of emerging problems. The Commission should continue to advocate improvements in data availability because this will offer greater protection against environmental damage in Member States' agriculture.

'Low-risk' pesticides can be based on bacteria, fungi and viruses, as well as substances such as blood, limestone or pepper. In principle, low-risk products should be preferred by farmers in managing pests, and should have a higher priority than more toxic synthetic chemicals in the IPM hierarchy. We note proposals to simplify the approval processes for such products but caution that context remains important, and limiting the designation of low risk just to those pesticides' toxicological profile could be misleading from an environmental perspective.

Even with an improved regulatory testing regime, future regrettable substitutions may never be avoidable. Moreover, concerns about leakage of pesticide residues into organic agriculture that the Farm to Fork Strategy seeks to expand, and over the overshooting of planetary boundaries for novel (chemical) entities, add to the urgency of **substantially reducing use of synthetic pesticides** overall.

Concerning the priority given to IPM, this report points out that, despite much historical success, IPM has not prevented a continued growth in the use of pesticides worldwide. The report explores reasons why IPM has not achieved its full potential and concludes that an effective IPM strategy needs support, incentives and regulatory pressures. The following are discussed:

- **Ensuring that there is a common understanding of what IPM is**, and of the IPM pyramid where chemical control is the option of last resort. A clear definition is required and options are given in the report.
- **Education and awareness**. IPM increases the complexity of farming management and requires additional decision-making, and detailed husbandry knowledge and experience, increasing the need for external advice and support.
- **Help for farmers to make new investments**.
- **Providing basic monitoring services**.
- **Incentive-based policies** where EASAC commends the Commission's current actions to support deployment by farmers and encourage further integration of IPM practices and technologies through the incentives in the Common Agricultural Policy (CAP).
- Recognising the potential for **carbon offsetting** in support mechanisms under the CAP.
- **Agrochemical industry** can support the transition to IPM by moving away from mass-market sales of treated seeds and crop protection options, to more target-specific and niche markets that support farmers' moves to increase crop biodiversity and apply biological and other control mechanisms.
- It is important to take a **landscape perspective** that extends beyond the single farm; pest populations migrate across farms and wider areas, so coordinated pest control actions are the optimal approach.

This report asks whether there is a **role for neonicotinoids in IPM**. We confirm that prophylactic or blanket uses such as seed pre-treatment are incompatible with IPM. Where, having applied the non-chemical actions in the IPM pyramid, a final option of chemical control is considered, the question becomes whether neonicotinoids should be automatically excluded from consideration; for instance, in local targeted sprays in precision agriculture. However, the risk of accumulation in soil, their persistence, toxicity to non-target organisms and water solubility argue for continued caution.

Ultimately, **IPM needs to become the mainstream approach** if the objectives of the Green Deal are to be met. The challenge is that IPM may be more expensive in cost, work and manpower and also needs to meet farmers' objectives for crop productivity and income security. Evidence that IPM is not in conflict with food security is thus critical in persuading Member States to support the Commission's proposals, especially following the Russian invasion of Ukraine. In the latter context, in reducing the need for chemical fertilisers and PPPs, IPM could improve agriculture's resistance to such supply shocks.

EASAC agrees with the Commission that support for **IPM should be accompanied by quantitative targets for reducing** the uses of pesticides. Although reduction in actual use can be quantitative, assessing risk requires integrating different aspects (from human health to biodiversity and ecosystem services), and deciding a single indicator will depend on the formula selected. The validity of the current **Harmonised Risk Indicators (HRIs)** in use is discussed and that the current formulae and targets may have the effect of 'locking in' the increases in the toxic load to agricultural landscapes that have occurred in the past 20 years. From an environmental perspective, reduction targets should be substantially increased and a better science-based indicator developed that takes into account a PPP's persistence in the environment, its toxicity to non-target organisms (especially pollinators and natural enemies of pests) and effectiveness in controlling the target pest, as well as concerns over human toxicity.

Finally, the report examines a wide range of new technologies that support and facilitate the application of IPM and point to several programmes (EU-wide and in Member States) that support IPM development.

1 Background

The history of neonicotinoid insecticide use started in 1991 with the introduction of imidacloprid. Neonicotinoids rapidly became the dominant group of insecticides; they are now registered in more than 120 countries, with an estimated market value of US$4752 million in 2018 (Sparks *et al.* 2020). They act by disrupting insect nervous systems, and are effective at controlling a broad range of insect pest species (see Bass *et al.* 2015). Despite their efficacy and ease of use, evidence emerged of adverse effects that were not detected in the regulatory approval process, especially on non-target insects (such as honeybees that provide pollination services). This led to initial restrictions on the use of neonicotinoids in the European Union (EU) in 2013. Since then, scientific evidence has pointed to wider ecosystem effects arising from their systemic nature which leads to their spreading to all parts of the target crop, making it toxic to insects including bees (Goulson 2013). Furthermore, neonicotinoids' solubility and persistence in nature allow them to spread into the wider environment, posing risks that the initial regulatory risk assessment process had not sufficiently addressed.

EASAC reviewed the wider ecosystem effects of neonicotinoids in 2015 (EASAC 2015); the main conclusions of that report are shown in Box 1. Since then, the outdoor use of the three main active substances (clothianidin, imidacloprid and thiamethoxam) has been banned and only use in permanent greenhouses remains permitted unless national governments grant special permissions for their use in 'emergencies' (EC 2018a). Of the other neonicotinoids registered in the EU, acetamiprid remains approved (although the maximum residue levels were lowered in 2019), while approval of thiacloprid was withdrawn in February 2020.

Although four of the five original neonicotinoids on the European market have been restricted or are no longer on the market, new insecticides with similar modes of action (i.e. nicotinic acetylcholine receptor (nAChR) agonists) have been approved, raising concerns that they may pose similar risks to honeybees and other non-target species. Moreover, agrochemical innovation continues to develop new chemical molecules with insecticidal properties that exploit the same or similar neuroactive mechanisms. Concerns over wider ecosystem effects of such insecticides continue.

The issue of the potential adverse effects and regulation of neonicotinoids is part of a wider debate over the implementation of the Sustainable Use of Pesticides (SUP) Directive, how to evaluate the environmental risk of pesticides, and the compatibility of current regulations with the European Green Deal, Farm to Fork, and Biodiversity strategies. In a review of the current regulatory situation, Buckwell *et al.* (2020) reported stakeholder dissatisfaction concerning the risk assessment process, insufficient data on pesticide use, and a lack of implementation of integrated pest management (IPM) as required in the SUP Directive. At the same time, outdoor use of the neonicotinoids that have been 'banned' continues through emergency authorisations granted by Member States. Recent

Box 1 Conclusions of the EASAC (2015) study

1. Ecosystem services provide significant economic benefits to agriculture. Maintaining strong functional ecosystem services is a critical part of a sustainable agricultural system.
2. Biodiversity has significant positive impacts on the provision of ecosystem services but is also an objective in its own right under global and European international agreements.
3. Insects providing ecosystem services have shown major declines in recent decades (pollinating wild bees, natural pest control providers, etc.).
4. Protecting honey bees is not sufficient to protect pollination services and other ecosystem services. Honey bees have been the main focus in assessing the risks from neonicotinoid use, and much debate has focused on whether honey bee colonies are being affected. Yet the honey bee colony structure provides an exceptionally resilient buffer against losses of its foragers and workers. In contrast, bumble bees have just a few hundred workers at most, while solitary bees and other insects have no such buffering capacity.
5. There is an increasing body of evidence that the widespread prophylactic use of neonicotinoids has severe negative effects on non-target organisms that provide ecosystem services including pollination and natural pest control.
6. There is clear scientific evidence for sublethal effects of very low levels of neonicotinoids over extended periods on non-target beneficial organisms. This should be addressed in EU approval procedures.
7. Current practice of prophylactic usage of neonicotinoids is inconsistent with the basic principles of integrated pest management as expressed in the EU's Sustainable Pesticides Directive.
8. Widespread use of neonicotinoids (as well as other pesticides) constrains the potential for restoring biodiversity in farmland under the EU's Agri-environment Regulation.

research has also shown that confining applications to indoor uses does not prevent restricted neonicotinoids from entering the environment (Herbertsson *et al.* 2021). In October 2022, the European Commission proposed that the SUP Directive be replaced by a Regulation on the Sustainable Use of Plant Protection Products (PPPs) (EC 2022a). At the same time, the European Food Safety Agency (EFSA) is working on improvements to the current risk assessment process by developing systems-based methods to assess environmental risks, and establishing new means of assessing ‘low-risk’ pesticides.

With such a wide range of science-based policy issues, EASAC’s Council decided to contribute to the debate within the Commission and European Parliament by evaluating the implications of the latest science. This report includes an overview of many of the more recent research findings on the original neonicotinoids, the evidence on substitutes that are currently in use, and the development of additional chemicals exploiting the same neural pathways. This is placed within the broader framework of environmental risk assessment, the introduction of IPM, and additional tools to reduce or eliminate the need for pesticides. The report has been prepared under the guidance of a group of leading experts nominated by EASAC’s member academies (Annex 1) and is intended to inform debate on the issues introduced above within the European Union as well as Member States.

2 Current developments

2.1 The policy context

The European Union (EU) regulatory and policy background for pesticide management is diffuse, fragmented and complicated. The overall framework for crop protection is provided by Regulation 1107/2009,[1] on the placing of plant protection products on the market; Regulation 396/2005,[2] on the maximum levels of pesticides in food and feed; and the Sustainable Use of Pesticides (SUP) Directive (EC 2009). These aim to reduce the risks and impacts of pesticide use on human health and the environment, and to promote the use of IPM. The SUP Directive introduced IPM principles at the EU level (see section 4.2), and requires Member States to produce their National Action Plans to reduce the risks and impacts of pesticide use, and to encourage the use of alternatives. Following a review (EC 2017), Member States have been asked to improve their National Action Plans and, as noted in chapter 1, a new Regulation on the Sustainable Use of Plant Protection Products is under negotiation (EC 2022a). Buckwell *et al.* (2020) also point to the interaction with the Drinking Water and Water Framework Directives, and the regulation on the transparency and sustainability of the EU risk assessment in the food chain (EC 2019).

As the EU institution responsible for assessing food and feed risks to the environment, animal and human health, the European Food Safety Agency (EFSA) develops and revises scientific methodologies, including guidance documents for pesticide risk assessments, and coordinates Member State peer review of pesticides. This system provides independent scientific advice and scientific opinions to the European Commission, such as on current pesticide risk for non-target arthropods and, more specifically, on the association between pesticide use and mortality rate of wild bees.[3] EFSA is responsible for the peer review of the risk assessment of active substances, the outcome of which is published and forms the basis of the decisions whether active substances are approved or not in the EU.

In addition to the directives listed above, the use of pesticides needs to be consistent with the aims and objectives of other policy areas including the Common Agricultural Policy (CAP), the European Green Deal and its Farm to Fork Strategy (EC 2020), Zero Pollution Action Plan,[4] Biodiversity Strategy to 2030,[5] and the related Birds[6] and Habitats[7] Directives. Increasing organic farming to 25% of agricultural land by 2030 is a goal of the Farm to Fork Strategy,[8] and contributes to sustainable agriculture without the use of neonicotinoids and other synthetic chemicals. Integrating this complex web of regulations and policies, each with its own group of stakeholders, towards specific aims such as protection and enhancement of biodiversity, or a more sustainable and regenerative agriculture, poses a substantial challenge.

The regulation of plant protection products has also been the subject of reviews under the Regulatory Fitness and Performance (REFIT) programme (EC 2016), by the Science Advice Mechanism (SAM 2018; SAPEA 2018), the European Court of Auditors (ECA 2020) as well as analyses by non-governmental organisations (see, for example, Buckwell *et al.* 2010; PAN Europe 2020). In explaining the proposal to replace the SUP Directive with an EU regulation, the Commission notes that the original directive had failed to sufficiently achieve its overall objective, as well as there being deficiencies in implementation in some Member States. A regulation at EU level is expected to have more binding effects on policies in individual Member States and includes a target '*to reduce by 50% the overall use and risk from chemical pesticides by 2030 and reduce by 50% the use of more hazardous pesticides by 2030*' and to promote the use of IPM and alternatives to chemical pesticides.

Continuing European research initiatives on pesticides include the Horizon programme's Sustainable Plant Protection Transition (SPRINT) project, which aims to develop a Global Health Risk Assessment Toolbox to assess impacts of plant protection products on the environment, and animal and human health. Specific objectives called for by the programme are methods of increasing soil biodiversity in agricultural fields, reducing pesticide application and implementing IPM. The implementation of IPM is also the aim of the 'IPMworks' project described in section 5.3.4.

2.2 Recent research on neonicotinoids

The scientific literature on the neonicotinoids approved in Europe exceeds 10,000 papers overall (Clarivate

---

[1] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:309:0001:0050:EN:PDF.
[2] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32005R0396.
[3] https://www.efsa.europa.eu/en/news/pesticides-and-bees-evidence-mortality-rates-reviewed.
[4] https://ec.europa.eu/environment/strategy/zero-pollution-action-plan_en.
[5] https://ec.europa.eu/environment/strategy/biodiversity-strategy-2030_en.
[6] https://ec.europa.eu/environment/nature/legislation/birdsdirective/index_en.htm.
[7] https://ec.europa.eu/environment/nature/legislation/habitatsdirective/index_en.htm.
[8] https://ec.europa.eu/info/food-farming-fisheries/farming/organic-farming/organic-action-plan_en.

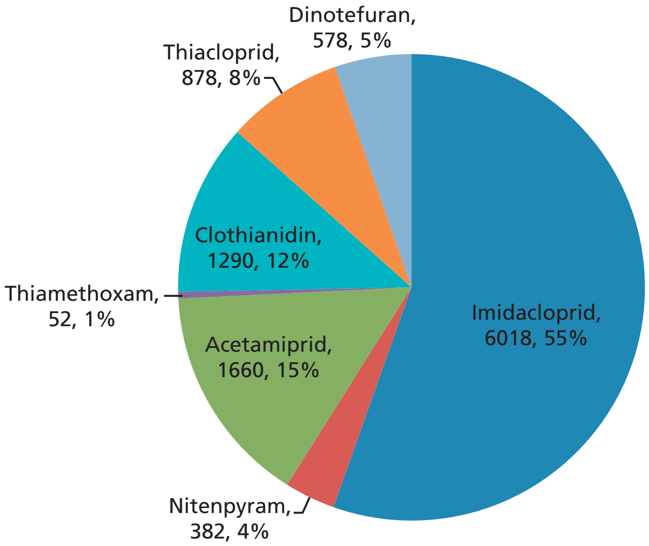

Figure 1 Number of publications indexed by Clarivate Analytics Web of Science (on 22 May 2022) on the seven neonicotinoids shown, and the percentage share. Total number of papers is 10,858.

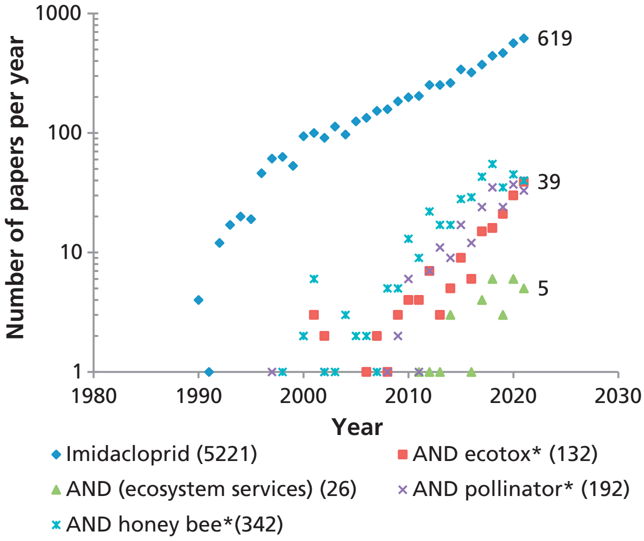

Figure 2 Scientific data on ecotoxicological effects of imidacloprid and its implications on ecosystem services (time frame: 1990–2021). Numbers indicate the number of articles retrieved. Note the logarithmic scale of the y-axis.

Analytics Web of Science statistics in Figure 1). Most of the research concerns imidacloprid (>6000 papers), followed by acetamiprid (1660 papers), clothianidin (1290), thiacloprid (878), dinotefuran (578), nitenpyram (382) and thiamethoxam (52).

Figure 2 follows the papers on imidacloprid, showing that research results started to emerge in 1990 and have increased exponentially since. The adverse effects on the environment apart from those on pollinators were not, however, studied until considerably later and in 2021 comprised about 6% of the total. Very little work has been done on the adverse effects of imidacloprid on **ecosystem services**; the effects were mostly focused on honeybees (403 papers) and aquatic ecotoxicity test organisms including fish (120 papers), *Daphnia* (69) and algae (31). There were 80 papers just on the effects on earthworms.

Figure 2 illustrates the long delay between approval of the original insecticide and studies on their effects on non-target organisms and the ecosystems in which they are used. Moreover, studies on neonicotinoids other than the main one, imidacloprid, are particularly sparse. This emphasises the scale of the challenge facing reforms of the regulatory system to avoid repeated approvals of substances that later turn out to pose unacceptable environmental risks (chapter 3).

At the time of EASAC's 2015 study, detailed reviews that summarised the literature covering the mode of action, fate, toxicity, ecosystem effects and alternatives were available. Notable among these was the Worldwide Integrated Assessment of the Impact of Systemic Pesticides on Biodiversity and Ecosystems, which produced a synthesis of 1121 published peer-reviewed studies spanning the previous 5 years (Bijleved van Lexmond *et al.* 2015). Since then, the same group of scientists has updated their earlier reviews in three further publications on papers published to 2017.

In the first of these, Giorio *et al.* (2021) examined the mode of action and metabolism of neonicotinoids (and fipronil), and synergistic effects from interactions with other insecticides, fungicides, herbicides, adjuvants, honeybee viruses and parasites of honeybees. In the second, Pisa *et al.* (2021) reviewed the lethal and sublethal effects of neonicotinoids. The high toxicity of these systemic insecticides to invertebrates was confirmed and expanded to include more species and compounds. In the third update, Furlan *et al.* (2021) reviewed use in pest management, effects on crop yields, the development of pest resistance, and IPM that relies mainly on natural ecosystem services instead of chemicals.

These updates and other general reviews (e.g. Wood and Goulson 2017; Dicks *et al.* 2021; Hough 2021; Tang *et al.* 2021a; Alsafran *et al.* 2022) have been supplemented by some 300 additional recent papers identified in two studies focused on Africa and Asia performed under the auspices of the InterAcademy Partnership (NASAC 2019; AASSA 2022) and papers known to the Expert Group of this report. A synopsis of these is given in Annex 2 in the following categories: environmental contamination; sublethal and synergistic effects; non-target species and whole ecosystem effects; regulatory processes; vertebrate and human exposure; greenhouse gas emissions; general chemistry and actions; and effectiveness of alternatives to neonicotinoid use. Some representative findings in Annex 2 are summarised here:

- Evidence of **environmental contamination** has continued to grow, reflecting the results of surveys in several regions. In China, for example, imidacloprid and thiamethoxam have been detected in large river systems (Zhang *et al.* 2019a) and in the Eastern Coast ocean waters (Chen *et al.* 2019). Following up on the earlier survey of neonicotinoid contamination in honey samples from around the world (Mitchell *et al.* 2017), a Chinese survey of 693 honey samples showed that 40.8% of them contained at least one of five neonicotinoids at levels previously found to have significant adverse effects on honeybee health (Wang *et al.* 2020a). Marine and estuary waters near the Seto Sea (Japan) contained imidacloprid and fipronil at levels exceeding the freshwater benchmarks for aquatic invertebrates (Hano *et al.* 2019).

- Levels of imidacloprid in Australia's Great Barrier Reef catchment area were estimated to be high enough to cause biological harm to aquatic organisms (Warne *et al.* 2022).

- In South Africa, Curchod *et al.* (2020) and Chow *et al.* (2022) found that, among other pesticides, imidacloprid, thiacloprid and acetamiprid exceeded their environmental quality standard in rivers of three agricultural catchment areas in the Western Cape by up to 58-, 12- and 5-fold respectively.

- In Kenya, acetamiprid, imidacloprid and its degradation product (imidacloprid-guanine) have been detected in snail tissues and sediments within the Lake Victoria South Basin (Kandie *et al.* 2020a) and in freshwater systems in the same region (Kandie *et al.* 2020b).

- In northern Belize, neonicotinoids were found in 68% of soil samples, 47% of sediment samples and 12% of water samples (Bonmatin *et al.* 2019).

- In the USA, neonicotinoid use has grown exponentially in some regions, and is reflected in increased contamination of aquatic systems in New York State (Mineau 2019). In some Californian aquatic systems, imidacloprid has been recorded at levels exceeding ecological damage thresholds defined by the US Environmental Protection Agency by factors of 10–100 (Mineau 2020).

- Analyses of soils from different European countries showed that imidacloprid and acetamiprid persist between cropping periods, which indicates that these neonicotinoids are relatively resistant to degradation in soil (Silva *et al.* 2019). Accordingly, Bonmatin *et al.* (2015) reported that the half-lives of neonicotinoids in soils can exceed 1000 days, and that they can persist in woody plants for periods exceeding 1 year. Furthermore, Pelosi *et al.* (2021) detected higher levels of imidacloprid in the earthworm *Allolobophora chlorotica* than in the soil, demonstrating that imidacloprid has the potential to accumulate in biota. In Switzerland, Riedo *et al.* (2021) found imidacloprid, clothianidin, thiamethoxam and/or thiacloprid in 98.3% (59 out of 60) of conventionally farmed soils and 42.5% (17 out of 40) of organically farmed soils. Bonmatin *et al.* (2015) also detected imidacloprid in organic farms.

- Extensive evidence documenting the **acute and sublethal toxicity effects of neonicotinoids on bees and synergistic effects with other stressors** has been published. Neonicotinoid exposure has been shown to disrupt bumblebee nesting behaviour, social networks and thermoregulation (Crall *et al.* 2018), and synergistic effects have been observed with fungicides (Willow *et al.* 2019) and other pesticides (Wang *et al.* 2020b), in weakening the honeybee immune response to bacteria (Decio *et al.* 2021). Neonicotinoids and ectoparasitic mites act synergistically to weaken bee colonies and contribute to colony collapse (Straub *et al.* 2019). Bees may require multiple generations to recover from a single pesticide application with substantial reductions in reproduction rates (Stuligross and Williams 2021).

- Regarding **ecosystem impacts**, exposure through contaminated honeydew of species that are important for the natural control of pest aphids, mealybugs and whiteflies has been demonstrated (Calvo-Agudo *et al.* 2019, 2021). Neonicotinoids have been identified as a central cause of the decline in damselfly and dragonfly populations because of impacts on mobility, emergence and prey consumption rates (Barmentlo *et al.* 2019). The emergence of aquatic insects has also been found to decline over time in central Saskatchewan sites where neonicotinoids have been applied in high concentrations (Cavalloro *et al.* 2019). The loss of zooplankton biomass following the introduction of neonicotinoids in Japan has led to the collapse of two commercial fisheries in a large Japanese lake (Yamamuro *et al.* 2019). In soils that might retain most of the neonicotinoid contained in treated seeds (Goulson 2013), reproductive harm to earthworms has been observed at very low concentrations (Ge *et al.* 2018) and spiders have been found to have reduced predation rates when their prey are contaminated with neonicotinoids (Korenko *et al.* 2019; Řezáč *et al.* 2019). Gunstone *et al.* (2021) reviewed nearly 400 studies on the effects of pesticides on non-target invertebrates that have egg, larval or immature development in the soil and concluded that neonicotinoids pose threats to soil organisms. Likewise, De Lima *et al.* (2020) and Ritchie *et al.* (2019) found that clothianidin applications led to a predicted soil concentration that was eight times the no-effect concentration for earthworms and springtails (collembolans), while Renaud *et al.* (2018) showed that chronic toxicity of the neonicotinoids thiacloprid and acetamiprid indicated risks to soil biota.

- When invertebrate populations are harmed, **higher trophic-level effects** may result from the loss of food supply. Hallman *et al.* (2014) found an association between the use of neonicotinoids and the decline in insectivorous birds in the Netherlands. Furthermore, Mineau (2019) found that increased neonicotinoid contamination of aquatic systems in New York State was associated with a loss of invertebrate life and ecosystem-wide perturbations affecting insectivorous birds, bats, fish and other vertebrates. Li *et al.* (2020) found that increased neonicotinoid use was associated with reductions in bird biodiversity between 2008 and 2014, with average annual rates of reduction of 3–4%. Differences in trends between insectivorous birds and seed-eaters or generalists suggest that starvation through lack of insect food may be the cause of the collapse in numbers of insectivorous species observed in many farmed landscapes.[9] Neonicotinoids and other insecticides are cited along with habitat loss and climate change as contributing to the drastic decline recorded in insect populations in general and pollinators in particular (see, for example, Hallmann *et al.* 2017; Sánchez-Bayo and Wyckhuys 2019; Wagner *et al.* 2022). One recent study on the deleterious effects of pollinator declines on blackcurrant cultivation (Anstett *et al.* 2019) suggested a decline of 99% over 40 years and the potential to triple yields (Duchet-Annez *et al.* 2022) if pollinator services could be restored to former levels.

- Neonicotinoids have greater affinity and bind more strongly to insect nicotinic acetylcholine receptors (nAChRs) than the mammalian receptors, so their toxic potency in mammals is lower than in insects. However, normal nAChR functioning is also critical for transmission of the nerve impulse in mammalian and vertebrate nervous systems, and disruption of nAChR signalling also has the potential to cause adverse neurological effects in invertebrates and mammals (Pedersen *et al.* 2019). Recent studies have observed toxic effects of neonicotinoids in birds (Eng *et al.* 2019), bats (Wu *et al.* 2020) and deer (Berheim *et al.* 2019). The US Environmental Protection Agency has evaluated the risk to endangered species; in a preliminary assessment it identified potential risks to more than 1000 endangered plants and animals.[10]

- Recent studies demonstrating **human exposure** in areas when neonicotinoids are used in China showed widespread contamination of vegetables (Zhang *et al.* 2019b; Chen *et al.* 2020a) and drinking water (Wong *et al.* 2019). Another Chinese study found imidacloprid in 100% of urine samples taken from workers applying the pesticide, in the urine of their family members, and that levels increased significantly after a spraying event (Tao *et al.* 2019a,b). Urine samples from children also had relatively high levels of imidacloprid and, on the basis of the concentrations in urine, it was estimated that daily intakes of imidacloprid were 1.6 µg per day (Zhang *et al.* 2019c).

2.3 Summary of impacts on humans

The expansion in monitoring described above has helped quantify human exposure to neonicotinoids and thus allowed more detailed risk assessments. Contamination of water spreads from fields into river systems, estuaries and coastal waters; levels of contamination have been measured across Europe, China, Canada and the USA which show it is extensive. Neonicotinoids have been frequently detected in food including rice, tea, honey, and fruit and vegetables, and in drinking water. They have also been detected in urine samples. Trends have indicated an increase in use of acetamiprid, clothianidin, and thiamethoxam, although imidacloprid remains the most detected.

Despite the frequency of detection, estimates of daily intake indicate consumption typically does not exceed established tolerance levels, and maximum residue levels have been established in several countries for tea, grains, fruits, vegetables, dairy and meat. One study in Japan (Harada *et al.* 2016) estimated that the average daily intake of neonicotinoids among Japanese adults was between 0.53 and 3.66 µg per day, with a high of 64.5 µg per day for dinotefuran, well below the acceptable daily intake set by the Japanese Government. Lu *et al.* (2018) estimated the total daily dietary intake of neonicotinoids in the USA and China to be 10.1 and 37.9 µg per day respectively, below the acceptable daily intakes recommended by the World Health Organization. Ospina et al. (2019)

---

[9] For example, https://www.vogelwarte.ch/fr/shop/livres/atlas-des-oiseaux-nicheurs-de-suisse-2013-2016.

[10] https://cen.acs.org/environment/pesticides/Neonicotinoids-likely-adversely-impact-endangered/99/web/2021/08.

found that approximately half of the US population is exposed to at least one neonicotinoid on a regular basis, while the US Environmental Protection Agency estimates that intake ranged from 2% to 38% of the acceptable daily intake, but that infants up to 1 year old are exposed through diet (food and water) to roughly 70–80% of the maximum acceptable limit for *each* of acetamiprid (69% of acute population-adjusted dose, 0.071 μg/kg per day) *and* imidacloprid (84% of acute population-adjusted dose, 0.08 μg/kg per day). Thus, when considered on a cumulative basis, exposure to infants of all neonicotinoids would exceed the US EPA's acceptable limit. In addition, neonicotinoids may form compounds that are more toxic when chlorinated during water treatment (Klarich Wong *et al.* 2019). However, the annual surveys by the EFSA (e.g. EFSA 2022c) do not report such proximity between exposure through food and European acceptable daily intakes.

Limited animal research available indicates long-term potential for genotoxicity, cytotoxicity, impaired immune function, reproduction (sperm count and motility) and birth defects; and acute health effects ranging through respiratory, cardiovascular and neurological symptoms. Subacute intoxication from food consumption, especially fruit, vegetables and tea, has been documented in Japan (Taira *et al.* 2011) with symptoms including finger tremor, impaired short-term memory, fever, general fatigue, headache, palpitation/chest pain, abdominal pain, muscle pain/ weakness/ spasm and cough. Marfo *et al.* (2015) found an association between *N*-desmethyl-acetamiprid concentrations in urine and increased prevalence of similar neurological effects. Other studies have reported a variety of respiratory, cardiovascular and neurological symptoms such as shortness of breath, coma, and irregular heartbeat, low blood pressure and dilated pupils following acute exposure. Several case reports have also detailed fatalities due to acute exposure, although mortality is generally considered uncommon. Studies reviewing incidents of acute neonicotinoid poisoning indicate that death occurred in fewer than 5% of cases. Overall, as stated by Thompson *et al.* (2020), the widespread exposure due to the heavy use of neonicotinoids leads to '*potential for cumulative chronic exposure*' and '*these insecticides represent novel risks and necessitate further study to fully understood their risks to humans.*' Further study is required to better understand toxicity to humans, but the existing evidence suggests that the precautionary principle should be applied.

Other papers described in Annex 2 have documented the **spread of resistance** and explored **alternatives to neonicotinoid use**, options for **revising the regulatory process** to better assess the real risks to non-target species and the environment, and challenges in providing **objective advice** independent of pesticide manufacturers. The high **carbon intensity** of pesticide manufacture, transport and application, accounting for a similar proportion of global emissions to that from aviation (Heimpel *et al.* 2013; Wyckhuys *et al.* 2022; Cech *et al.* 2022), has also been pointed to as offering climate benefits through the reduction of greenhouse emissions, if pesticide use can be reduced by IPM.[11]

Finally, on **efficacy**, studies indicate that some uses are neither effective nor cost-effective from the farmer's point of view. Mourtzinis *et al.* (2019) showed that neonicotinoid treatment in soybean seed seems to have little benefit for most soybean producers, and Labrie *et al.* (2020) found neonicotinoid seed treatments in field crops in Quebec useful in fewer than 5% of cases. A comparison of pest control methods in soybean production in Brazil showed no differences between prophylactic use of imidacloprid and an IPM approach (Bueno *et al.* 2001). There are thus concerns that the growth in use of neonicotinoids has been driven by convenience and industry marketing, rather than any real risks of crop losses. Before the introduction of seed pre-treatment, less than 10% of soybean and less than 50% of corn was treated with any type of insecticide. After the introduction of the pre-treatment approach, however, Thompson *et al.* (2020) pointed out that 50% of soybeans, nearly 100% of corn and 95% of cotton globally are treated with neonicotinoids. Together with the studies above that show few or no benefits, this suggests a strong influence of factors other than the real threat posed by pests.

In terms of efficacy of the active ingredient in reaching the target pest, Mörtl *et al.* (2020a) showed that the environmental loads from neonicotinoids based on recommended dosages are practically the same in the case of seed coating as in spray or granule application. However, less than 10% of the active ingredient in pre-treated seeds enters the plant so most is released into the environment where it can reach non-target species (Goulson 2013). Efficacy in reaching the target pest species is thus likely to be higher when used as a spray than in seed dressing. In addition, seed coating is not compatible with IPM as it does not allow application to be limited to periods of pest population densities above the damage threshold (section 4.2).

2.4 Candidates to replace neonicotinoids as insecticides

The restrictions on the original neonicotinoids created incentives to develop alternatives, some of which exploit the same insect neural mechanisms and therefore can

---

[11] They estimate that the carbon footprint of pesticide production, supply and application is equivalent to 3.1% of global cropland emissions.

also be labelled as 'neonicotinoids'. Currently two products that are also nAChR agonists are a sulfoximine (sulfoxaflor) and a butanolide (flupyradifurone); however, as summarised in Annex 3, many more chemical molecules are under development. This raises the question to what extent these 'new neonicotinoids' affect non-target organisms and the wider environment, and how they differ from the insecticides they replace. With similar mechanisms, there is a risk that they will become 'regrettable substitutions' (Maertens *et al.* 2021) whose impacts turn out to be similar to, or worse than, the original neonicotinoids they are designed to replace.

Sulfoxaflor was first approved in the EU in 2015 (Annex 3). It can be used as a seed treatment for bee-attractive crops but is more commonly applied as a foliar spray (Siviter and Muth 2020). Its insecticidal chemical is absorbed and systematically distributed throughout the plant and so can expose bees either via the crop or indirectly through flowering weeds that are present in fields or orchards. Some studies show that field-realistic doses of sulfoxaflor affect egg-laying rates and reproductive success of bumblebees (Siviter *et al.* 2018) but not their foraging and cognitive performance (Siviter *et al.* 2019a). A semi-field study on honeybees found increased mortality during the exposure phase but no overall effects at the colony level (Cheng *et al.* 2018). In oral toxicity studies on bees, sulfoxaflor was found to be less toxic than imidacloprid, thiamethoxam and clothianidin, but much more toxic than acetamiprid and thiacloprid, while it was found to have negative effects even at low doses when bees were simultaneously exposed to the fungicide fluxapyroxad (Azpiazu *et al.* 2021). De Lima *et al.* (2020) showed that the worm *Eisenia fetida* and the springtail *Folsomia candida* were very sensitive to most neonicotinoids, and the limited data available for sulfoxaflor reported by Lewis *et al.* (2016) suggest similar toxicity to both species of soil invertebrates.

Post-approval assessment by EFSA concluded that there is a high (acute) risk to honeybees and bumblebees from sulfoxaflor in the field and in non-permanent structures/greenhouses, and that insufficient data were available to finalise the assessment of the chronic risks for bumblebees, or the acute and chronic risks to solitary bees (EFSA 2020). As a result, the Commission regulated in 2022 to restrict the use of sulfoxaflor to permanent greenhouses.[12]

Flupyradifurone has lethal and sublethal effects on honeybees, and synergistic effects with other pesticides (Tosi and Nieh 2019; Chakrabarti *et al.* 2020; Tosi *et al.* 2021). Initially it was considered substantially less toxic to bees than thiamethoxam, clothianidin and imidacloprid, but exposure to sublethal doses significantly reduces survival of both larval and adult honeybees and alters the expression of several immune and detoxification genes. It has also been found (Siviter and Muth 2020) to have a significant negative effect on the mortality, fitness and behaviour of other beneficial insects (pollinators and predatory insects). Flupyradifurone is persistent, lasting in soil for several months, and has the potential to reach the aquatic environment through runoff, erosion and leaching to groundwater. It presents moderate risk to earthworms (EFSA 2016).

Following calls for the authorisation of flupyradifurone to be reviewed, EFSA concluded recently that there was insufficient new evidence on human health and environmental risks to justify revoking its regulatory approval. It did, however, recommend (*inter alia*) that an assessment be undertaken of the chronic toxicity to honeybee adults and larvae in line with new OECD (Organisation for Economic Co-operation and Development) standards and that a risk assessment be undertaken for solitary bees (EFSA 2022a). Reviews have also been requested by the Dutch and French authorities.

The potential for new 'regrettable substitutions' remains given the wide range of chemical adjustments that are available within the same general toxicological mechanism, and more neonicotinoid analogues could make their way onto the global market over the next few years. Those that appear at an advanced stage of development (triflumezopyrim, flupyrimin, cycloxaprid, paichongding, imidclothiz and guadipyr) are described in Annex 3, but have only limited information available in the open literature to enable an assessment of potential environmental risks. There is, however, no *a priori* reason to expect their direct effects, or their side-effects, to be substantially different from the restricted neonicotinoids.

This challenge to the regulatory process brings to the fore the long debate on how to adapt the system to better recognise the effects of prolonged exposure to lower levels of pesticides, effects of combinations of pesticides, potential interactions with other stressors and side impacts on non-target species and biodiversity, as well as to how to apply the precautionary principle (which emphasises caution in the face of uncertainty). These aspects are discussed in chapter 3.

---

[12] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R0686.

3 Challenges for the regulatory testing regime

Debate about the adequacy of the regulatory system for pesticides has been prolonged and intense. Following the discovery of widespread and cumulative effects of previous generations of pesticides, such as organochlorines, testing was revised to identify risks from properties such as persistence and bioaccumulation. Such improvements were intended to avoid the authorisation of chemicals with significant deleterious effects on the environment and human health but have not prevented the registration of substances that were subsequently withdrawn as evidence of effects emerged. Maertens *et al.* (2021) argue that such 'regrettable substitutes' are a result of failures during the pesticide design, hazard identification, risk management and regulatory processes. Such concerns have led to widespread calls for further revisions of the testing regime to try to prevent harmful substances entering the market in the first place. Here, some of the shortcomings in the current risk assessment regime are summarised and the challenges that face attempts to reform the current system discussed.

3.1 Current environmental risk assessment

Testing and risk assessment guidelines agreed at EU level[13] are regularly updated; for instance, methods for testing in-soil organisms (EFSA 2017). Risk assessments are thus evolving but the current regulatory procedure still evaluates each product separately for each agronomic use (a single-product, single-crop assessment) resulting in an essentially binary decision: approve or not. Protection for the environment is assumed to be due to the conservative nature of the overall evaluation using a realistic worst-case scenario and assessment factors for tests performed in the laboratory. Existing environmental risk assessment (ERA) procedures have come under criticism as out of step with ecological and practical reality (Topping *et al.* 2020). Not only do the assumptions behind the risk assessment not match the reality of the ecological systems, but also the current system may not properly assess all the risks associated with neonicotinoid-like modes of action, including their persistence, systemic mode of action, long-term irreversible and cumulative effects, high mobility and application versatility (Sglolastra *et al.* 2020).

3.1.1 Exposure to multiple chemicals

Even for a single crop across the EU, multiple pesticide applications are the norm (e.g. up to nine substances mixed in the tank for apple pest management; Table 1). This results in exposure to multiple compounds and may also increase the frequency of exposure (Brühl and Zaller 2019; Weisner *et al.* 2021). Assessing single active substances alone leads to a disconnect between official risk assessments and reality in the field, where mixtures can have additive or synergistic actions. Environmental risk may be increased even when only one or a few compounds are present at the same time, by exposure to different compounds over a season. This situation is not covered by the plant protection product (PPP) registration process and, according to Weisner *et al.* (2021), can lead to an underestimation of risk for freshwater systems by a factor of 3.2. This tendency is also found in the scientific literature, which often presents the results of toxicity of single active substances to a single species, ignoring the potential effect of mixtures. In addition to mixtures of the active substances, the formulations that are actually applied contain many other additives that are not included in the initial assessments.

Table 1 Some common crops and average number of pesticide applications in Europe

Crop	Country examples	Number of active substances	Number of applications
Apples	Italy, Poland, UK	24.9–40.6	3.4–25.6
Potatoes	Belgium, Lithuania, the Netherlands	6.1–36.3	3.4–19.1
Wheat	Lithuania, Poland, UK	5.5–18.3	2.9–6.1
Maize	Belgium, Italy, Poland	2.7–7.3	1.4–3.3
Onions	Spain, the Netherlands, Poland	4.0–41.8	2.0–20.8

Source: adapted from Garthwaite *et al.* (2015).

3.1.2 Spatial dynamics

Non-target and beneficial organisms may move within and between fields and to habitats outside the crop areas. Mobile species such as bees, birds and some mammals are thus exposed to multiple chemicals by virtue of their movement between crops. Bees are an extreme case, existing as a super-organism (colony) with many thousands of foragers returning with potentially contaminated resources from many locations

---

[13] https://food.ec.europa.eu/plants/pesticides/approval-active-substances/guidelines-active-substances-and-plant-protection-products_en.

simultaneously. This effect probably synergises with mixture application.

Further, if the crop does not support the net reproduction of beneficial organisms (for instance because of the toxicity of pesticide treatments), then their in-field populations ('sink-population') will decline unless there is sufficient migration from off-field ('source populations'). Some agricultural landscapes suffer a lack of biodiversity reservoirs such as hedgerows that provide both a source of beneficial organisms and shelter from field applications of pesticides (Gossner *et al.* 2016). Where such untreated areas are small in proportion to treated field areas, then source populations may become greatly depleted, with the supply of migrants into the crop being insufficient to deliver the desired ecosystem services (EFSA Scientific Committee 2016).

3.1.3 Long-term effects

Currently, ERA considers effects occurring only within a single season. However, year-on-year effects are known to be important, especially when related to long-term population dynamics, as small annual changes can accumulate to have major effects. For instance, multigeneration tests on the effects of imidacloprid, thiacloprid and thiamethoxam on the springtail *Folsomia candida* in soils showed that there was an increase in toxicity for the soils and that following generations would disappear (van Gestel *et al.* 2017; De Lima *et al.* 2018). Long-lived organisms may also accumulate damage by repeated exposure with long-term consequences not seen in field studies. If the organism moves between fields over time, exposure to mixtures can also be a function of time. Note here that the current recovery approach based on field testing will not only fail to detect small effects that may become large over time, but also misrepresent effects of use in both space and time (Topping *et al.* 2014).

3.1.4 Toxicological issues

From a toxicological perspective there are three main criticisms of the current approach. The first is that the unrealistic one-substance assumption fails to measure the potential for combined (additive or interactive) effects in mixtures. The second is how to supplement the acute toxicity tests for arthropods with effective evaluations of the ecologically important chronic (sublethal including hormonal) effects. The third is the inherent uncertainty relating to the use of a small sub-set of species to predict the sensitivity of all organisms. For instance, the risk assessment for soil invertebrates is based on single-species testing, with a second tier in the event of risks being detected, of a field test with earthworms.[14] Given the complexities of the soil biota, relying on just one or two species that are not always found in agricultural fields leads to questions as to how realistically these results can be translated to the field.

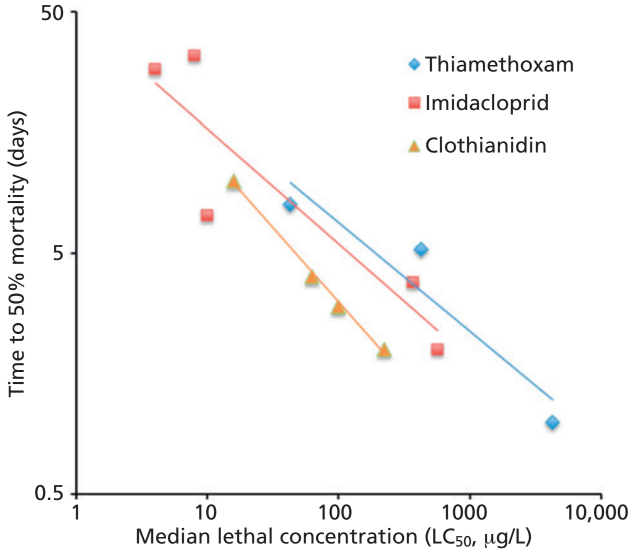

Figure 3 Median lethal concentrations of three neonicotinoids against exposure time (Figure 1 of Pisa et al. 2021).

On the second point (acute toxicity), with systemic and cumulative effects of substances such as the neonicotinoids, the length of exposure is a critical issue. Testing the effects of exposure over 1–2 days fails to measure the cumulative effects of prolonged and repeated low-level exposures. As an example, Figure 3 shows that exposure to low concentrations over 25 days increases the estimated toxicity by a factor of 1000.

3.1.5 The shortcomings in context

In brief, the criticisms of the current ERA methods are that they do not sufficiently consider the accumulation of effects from the following:

1. The potential for accumulation of pesticides that may be used more often in a season than assumed in the risk assessment.

2. Exposure to other pesticides and chemicals present in the formulated products.

3. Stress factors such as viruses or parasites.

4. Inherent uncertainties in the choice of test species or test procedures in applying the results to real field ecological conditions or abiotic factors such as pH or organic matter content in soils, which can influence the toxicity of the pesticide. Moreover,

---

[14] https://www.efsa.europa.eu/sites/default/files/consultation/160503.pdf.

effects on biodiversity, food-web interactions and ecosystem functions are not considered (e.g. Brühl and Zaller. 2019).

Given the ecological and toxicological complications of the real world, both the environmental relevance and ability to effectively manage the risk assessment are affected by such limitations. The current approach of assessing focal species assumed to be representative, sensitive and, therefore, protective of the system, provides scope for key interactions to be missed (De Lima *et al.* 2021). The resulting decision (safe/unsafe) does not account for the sensitivity of the receiving environment, nor the potential for change with time. Most critically, this assumption ignores effects associated with scale of use: the widespread use of a borderline 'safe' product may be much more damaging to the ecosystem than the restricted use of a borderline 'unsafe' product.

3.2 New approaches suggested

To address such criticisms, Topping *et al.* (2020), among others, advocate a change to a 'systems-based ERA'. This would comprise a more holistic approach, addressing the spatio-temporal scale, context, spatial dynamics and mixture effects. This approach was also suggested by EFSA as a way forward for evaluating effects on bees (More *et al.* 2021) and is the subject of a roadmap project to define the steps to such a systems ERA (EFSA 2022b). Specific challenges to the risk assessment of PPPs for in-soil organisms are also under evaluation. A systems approach would use modelling to simulate real conditions of use and would be followed, after authorisation, by monitoring of real-world exposure, fate and impacts. The monitoring results would not only provide a post-market check for unexpected effects but also feedback to model improvement. New approaches to mixture toxicity are also under development following the EFSA guidance for humans (More *et al.* 2019), and could be expanded to the environment and combined in the systems ERA. Such substantive reforms would need to gain wide acceptance in the EC and Member States and entail changes to the data requirement (EC284/2013) and uniform principles (EC 546/2011) regulations.

An additional regulatory complication is that chemicals can be registered under multiple frameworks owing to their multiple uses (e.g. use of imidacloprid for veterinary use and plant protection use), resulting in incoherent assessments of similar chemicals (van Dijk *et al.* 2021). This has led to the suggestion for adopting a 'one substance – one assessment' approach in the Green Deal, supported by EFSA and the European Chemicals Agency. Although this would eventually harmonise regulatory evaluations across use categories, currently this approach is developing separately from the systems ERA thinking.

4 Reducing the demand for neonicotinoid use

4.1 Emergency authorisations

When neonicotinoids were restricted, the lack of a viable alternative for some uses led farming or agrochemical organisations to seek emergency authorisations to continue their use. These are allowed under Article 53 of the Plant Protection Regulation (1107/2009) which '… *allows Member States, in special circumstances, and for a period not exceeding 120 days, to authorise the placing on the market of plant protection products for limited and controlled use, where it appears necessary because of a danger which cannot be controlled by any other reasonable means*'. Authorisations are publicly available[15] but their justification has been questioned (e.g. PAN Europe 2017).

A review by EFSA focused on the 2020 sugar beet growing season, and the 11 Member States that had repeatedly used Article 53 since 2017. EFSA's mandate was to review whether the authorisations were '*necessary and due to a danger, which could not be contained by any reasonable means, and whether research programmes had been established to find alternative solutions*'. EFSA found that, while not always consistent with IPM principles, the emergency authorisations had been largely justified, either because no alternative products or methods were available at the time, or because there was a risk that the use of available alternatives would increase pest resistance.

Since then, questions have been raised over the review process used by EFSA and the basis on which the 'emergency' of each case had been assessed. Some Member States' submissions seemed to have prioritised the use of chemical over non-chemical methods of control, and some had relied on pesticide producers and/or farming organisations to submit the case for emergency use. Questions have been raised whether foreseeable, common or cyclical threats to plants, such as annual pest occurrence, can constitute an 'emergency' (Epstein 2021; Epstein *et al.* 2022). The European Court (case number C/162-21) has just ruled to restrict Member States' ability to issue such authorisations.[16]

4.2 Integrated pest management

The Farm to Fork Strategy includes the aim of increasing organic farming to 25% by 2030 which would exclude the use of synthetic chemicals. For the rest of agriculture, the concept of IPM has been widely supported for decades but, as pointed out by Deguine *et al.* (2021), its implementation has not prevented a continued growth in the use of pesticides worldwide. In the European context, the SUP Directive aimed to reduce the risks and impacts of pesticide use on human health and the environment through promoting the use of IPM, yet evaluations of Member State actions conclude that the implementation of IPM was a weakness in the application of the SUP Directive.[17] Since IPM maintains its priority in the proposed new Regulation on Plant Protection Products, understanding why IPM has not achieved its full potential is important.

The SUP Directive focuses on long-term prevention of pest damage through a combination of techniques such as biological control, habitat manipulation, modification of cultural practices and use of resistant varieties (Barzman *et al.* 2015). Pesticides are used only after monitoring indicates they are needed according to established guidelines, and treatments are made with the goal of removing only the target organism. Pest control materials are selected and applied in a manner that minimises risks to human health, beneficial and non-target organisms, and the environment. The key is an ecosystem approach that maximises the natural enemies and seeks to create an environment that is unfavourable to the pest. For instance, Khan *et al.* (2014) intercropped the main cereal crop with a forage legume that repels the target pest (stemborer moths) and attracts natural enemies, while planting borders with grasses that attracts the pest away from the main crop (a 'push–pull' approach). In contrast, relying on pesticide applications may *increase* average pest densities throughout a growing season when effective natural enemies are present (Janssen and van Rijn 2021). IPM is information-intensive and science-based, but often built on experience, and requires interaction with farmers to adapt its approach as far as possible to their existing practices. The aim is to manage pests rather than eliminate them completely—especially because, if pests are eliminated, populations of natural enemies also decline or die out, allowing pests to re-invade from surrounding areas.

While each situation is different, six stages are common to IPM programmes:

1. Pest identification.
2. Monitoring and assessing pest numbers and damage.

---

[15] https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/ppp/pppeas/screen/home.

[16] https://curia.europa.eu/jcms/upload/docs/application/pdf/2023-01/cp230012fr.pdf.

[17] Report on the experience gained by Member States on the implementation of national targets established in their National Action Plans and on progress in the implementation of Directive: COM/2020/204 final.

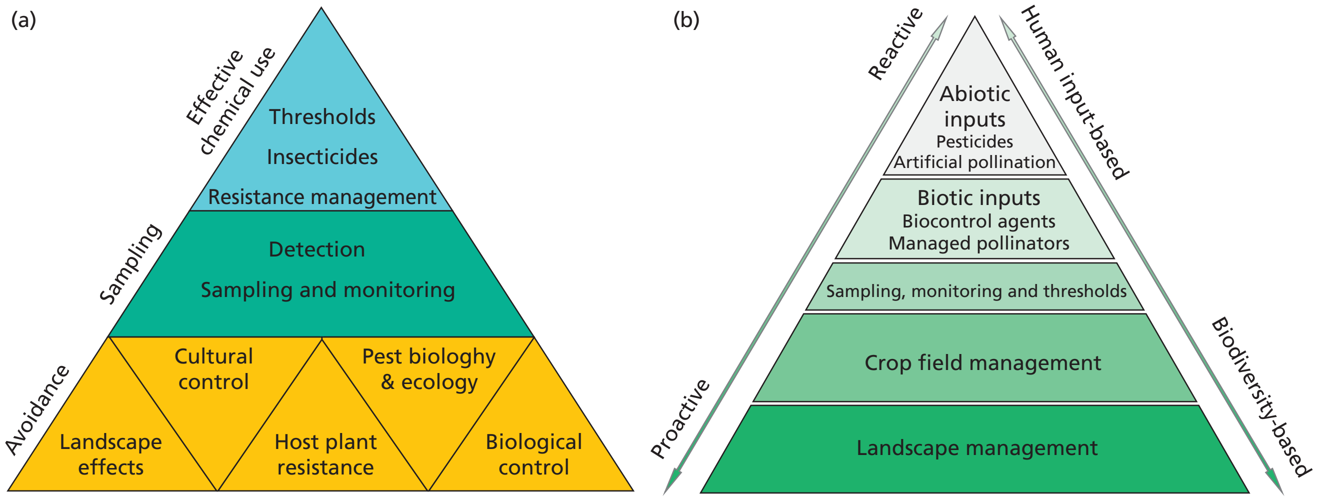

Figure 4 IPM pyramids. (a) Classic pyramid concept of IPM (source: Hutchison et al. 2014). (b) The IPPM pyramid (source: Lundin et al. 2021).

3. Guidelines for when management action is needed.
4. Preventing pest problems.
5. Using a combination of biological, cultural, physical/ mechanical and chemical management tools.
6. After action is taken, assessing the effect of pest management.

The concept of IPM is often expressed in the form of the 'IPM pyramid' to reflect that there should be a hierarchy or prioritisation of practices in which chemical pesticides are listed as a measure of last resort (Figure 4a). While protection of pollinators is one of the implicit objectives of IPM, Lundin *et al.* (2021) advocate a more explicit inclusion of pollinators in IPM through Integrated Pest and Pollinator Management (IPPM), which aims to co-manage the ecosystem functions driven by pests, natural enemies and pollinators (Figure 4b). This prioritises the first layer of actions through landscape and crop field management to directly suppress pests and support diverse and abundant communities of natural enemies, thus promoting biodiversity-based pest control (Gurr *et al.* 2017) while supporting pollinators and pollination services.

A key component of IPM is that of biological rather than chemical control, through the use of biopesticides made from microorganisms including bacteria, cyanobacteria and microalgae, plant-based compounds and recently applied RNAi-based technology (Kumar *et al.* 2021). These are increasingly available although concerns remain over their weaker effects than synthetic chemicals and sensitivity to weather. Another component is **conservation biological control** which seeks to integrate naturally present beneficial insects back into crop systems by encouraging the habitats that support pest predators and parasitoids.[18] Examples include the use of adjoining flower strips to support wild bee reproduction and mitigation of negative effects of pesticide exposure (Rundlöf *et al.* 2022) in accordance with the IPPM pyramid.

Another component of biological control is to use botanical pesticides derived from plant-based products (Leather and Pope 2019). Botanicals can have various modes of action against target pests, which reduces the risk of pest resistance, and may have other favourable properties, such as low human toxicity, rapid degradation and environmental safety. Botanicals constitute around 5.6% of all biopesticides (and <0.05% of all pesticides) applied worldwide, although their use seems to be increasing in some developing countries where the source plant species may be locally abundant and the preparation of extracts is inexpensive. One plant of interest is the neem tree (*Azadirachta indica*), a source of azadirachtin, an active ingredient known to adversely affect oviposition, feeding and growth of more than 540 insect pest species. Azadirachtin is registered for commercial use in many countries but it can also affect non-target organisms. For instance, one study found it is equally toxic to bees as the neonicotinoid imidacloprid (Bernardes *et al.* 2017).

IPM involves the setting of thresholds: pests are monitored and action, such as insecticide application, is only taken if the pest exceeds some predetermined density, usually based on counts per plant or similar. These are termed action thresholds or economic thresholds which define the lowest pest density for

---

[18] Parasitoids are a very useful class of natural enemy but with relatively little literature on how they are affected by agrochemicals (Hassell 2000).

which action must be taken to avoid reaching the economic injury level, which is the lowest pest density that incurs financial loss as a result of crop injury that exceeds the cost of the control action. In addition, a more sophisticated approach, dynamic thresholds, incorporates the density of natural enemies that are present. Taking account of natural enemies through the dynamic threshold approach will typically reduce pesticide applications compared with using action thresholds or economic thresholds.

4.3 Implementing IPM

The SUP Directive established IPM as a central component but delegated the choice of actions to Member States. A recent review (Helepciuc *et al.* 2021), however, showed that, even though the adoption of IPM principles is compulsory, there is considerable variation among EU Member States' commitment to implementing them. While some Member States' National Action Plans have been assessed (see, for example, Cech *et al.* 2023), the lack of any quantifiable means to assess progress and of specific mandatory targets has contributed to the limited implementation, and few crop-specific guidelines have been developed.

This patchy and slow implementation in the EU reflects several fundamental weaknesses in IPM that were examined globally by Deguine *et al.* (2021). They noted that there has been a plethora of different definitions of IPM (as well as overlap with terms such as agroecology, sustainable agriculture, organic agriculture), leading to inconsistencies between IPM concepts, practice and policies. Despite this, there were many examples of successful IPM strategies. In Southeast Asia, farmer training programmes attained a 92% pesticide reduction in rice cultivation (Bangladesh), 50–70% reduction in tea and cabbage crops (Vietnam), while the International Rice Research Institute attained 50–80% cuts in insecticide use on millions of rice farms without any noticeable yield loss. In the USA, the Huffaker project for IPM and the IPM consortium (1972–1985) attained a 70–80% reduction in a wide set of pesticides on more than 5 million hectares, resulting in annual savings greater than US$500 million (Pimentel and Peshin 2014). In a review of more than 500 IPM programmes from across the world, 13% and 19% respective increases in crop yields and farm profits were logged (Waddington and White 2014), with even partial adoption of IPM delivering concrete benefits. Studies on the effectiveness of IPM and IPPM continue. For instance, Pecenka *et al.* (2021) found that, in IPM corn, the absence of a neonicotinoid seed treatment had no impact on yields, whereas IPM watermelon increased yields by 29% owing to more frequent flower visitation by pollinators; similar findings were reported by Leach *et al.* (2022) in beetle control where IPPM increased melons during harvest by 49%. In New Zealand, an IPM approach was even used to eradicate invasive species (Voice *et al.* 2022)

The above successes were the result of specific initiatives; however, once supportive policies and funding were removed, pesticide use surged again, indicating an inherent bias towards a 'default option' of pesticide use. Identifying the key roadblocks to IPM adoption is thus critical to effective implementation. According to Lechenet *et al.* (2017) and Deguine *et al.* (2021), the barriers to overcome include the following:

- A weak farmer knowledge base and insufficient engagement of farmers in IPM technology development.
- Risk aversion, because the benefits of IPM are often unclear or unquantified and there is frequently a lack of basic understanding of its underlying ecological concepts.
- The complexity of using threshold-based IPM decisions compared with the simpler options offered by insecticide-coated seeds or calendar-based spraying.
- The strength of industry campaigns to maintain and increase markets for pesticides through extensive lobbying, marketing and manipulation (Goulson 2020). In many locations, farm advisers are paid (or decision-support tools are designed) by the agrochemical industry, or the local pesticide supplier is the most accessible source of pest management information.

As a result, implementation has often diverged from fundamental IPM principles, so that chemical control remains the basis of most plant health programmes. Furthermore, IPM research[19] has sometimes paid insufficient attention to the ecological functioning of agroecosystems. To counter the degradation of IPM concepts, the concept of agroecological crop protection was proposed which is consistent with the original concept of IPM to promote the growth of a healthy crop with the least possible disruption to agroecosystems (FAO Agroecology Knowledge Hub: https://www.fao.org/agroecology/newsletter-archive/2020/en/).

---

[19] With its dependency on designing strategies to address each individual combination of pest and crop, IPM application may be hindered by scarcity of human expertise, lack of knowledge transfer into practice, communication gaps within and between countries, and lack of multi-, inter- and transdisciplinary IPM research. These were reviewed in a Coordinated Integrated Pest Management in Europe study (CORDIS 2016) which established a consortium of 34 partners from 21 countries to identify IPM research needs and gaps, strengths and weaknesses, and future direction to overcome the existing IPM challenge.

In theory, IPM provides farmers with a low-cost way to reduce the risk of losing their crop because it allows them to buy fewer pesticides and reduces environmental and health risks. However, Parsa *et al.* (2014) found that IPM remains severely under-adopted even in poorer countries and faces many obstacles from a lack of training, outreach and technical support, and interference from the pesticide industry. Surveys of farmers found more than 50 reasons why IPM was not applied. These included '*The costs of IPM are much more apparent than benefits*', '*Farmers have low levels of education and literacy*' and '*IPM is too difficult to explain and understand.*' Participants in developing countries rated the statement '*IPM requires collective action within a farming community*' as the most important obstacle. This ranking reflects the fact that IPM is most effective when implemented collectively at the regional level.

As noted by Deguine *et al.* (2021), the lack of a clear definition of IPM contributes to the difficulties with its implementation. The Commission's proposal for a new regulation contains the definition as '*careful consideration of all available means that discourage the development of populations of harmful organisms, while keeping the use of chemical plant protection products to levels that are economically and ecologically justified and minimise risks to human health and the environment*'. This lacks the priorities implicit in other definitions, for example that of PAN Europe (2021): '*IPM is an iterative process that places preventative agronomic measures at the heart of agricultural plant production's pest control. When these fail, cultural practices and physical pest treatment is favoured, before using biocontrol and, as a last resort, chemical alternatives can be used*'. Although IPM remains focused on the ecological aspects of pest management, business aspects that consider changing consumer trends and increased awareness for sustainably produced food systems suggest that the definitions also need to recognise the full spectrum of human, environmental, social and economic factors that influence the food production chain (Dara 2019).

4.4 IPM and neonicotinoids

Annex III of the SUP Directive sets out the general principles of IPM, which seem incompatible with the prophylactic use of neonicotinoids in seed dressing because of the following:

- Only a small proportion of the insecticide enters the plant, most being released into the environment.
- Neonicotinoids may be applied proactively, not reactively on the basis of monitoring the need for pest control; with the first priority thus placed on chemicals rather than as a last resort.
- Principle 5 (which states that '*the pesticides applied shall be as specific as possible for the target and shall have the least side effects on human health, non-target organisms and the environment*') is also inconsistent with the toxic effects on non-target organisms and wider ecosystem effects.

Moreover, the establishment of chemically prophylactic use as standard practice has rendered redundant the necessary monitoring, threat assessment and menu of non-chemical responses to pests inherent in applying IPM. Many farmers thus lack the necessary resources, skills or experience to apply an IPM approach, which should consider all relevant and available information and provide pest control options based on actual need.

Continued calls for emergency authorisations (section 4.1) suggest that many farmers continue to see neonicotinoids as their preferred solution to some pest problems. A key question is thus 'what are the IPM options for replacing their use?'. There have been several reviews on this aspect. Furlan and Kreutzweiser (2015) and Furlan *et al.* (2021) note that a diverse range of pest management tactics is already available, all of which can achieve efficient pest control below the economic injury level, while maintaining the productivity of the crops, as well as avoiding growth in pest resistance. Risk assessments adapt the IPM strategy to the real risk (which often may be very low and not require insecticides at all). One option was an insurance scheme to compensate farmers suffering above a given threshold of damage. In the area of Italy in which it was applied, the costs of insurance against corn pest damage were below those of the insecticide use avoided, and thus contributed to farm profitability.

A recent study by Veres *et al.* (2020) assessed the actual risks posed by arthropod pests in four major crops (maize, winter wheat, rice and cotton) and the readiness of six kinds of IPM approach. These were (1) biological control; (2) cultural (e.g. sanitation, crop rotation, nutrition or water management) or mechanical control; (3) innovative pesticides and application regimes (e.g. attractants, reduced product doses, anti-resistance strategies); (4) host plant resistance; (5) decision-support tools (e.g. monitoring schemes, predictive models, early-warning systems); and (6) other tools such as farming systems adaptations and multi-faceted IPM packages. The status of each IPM approach differed with the pest, ranging from techniques that were still at the research stage, through those that were ready for application to those that were already in use. Overall, the authors concluded that cost-effective alternatives to neonicotinoids were available for cereals and to maize farmers.

In a review, Jactel *et al.* (2019) evaluated available alternatives to five neonicotinoids in terms of efficacy, applicability, durability and practicability in a wide range of crops and pest species. Of the 2968 case studies analysed, they found that effective alternatives to neonicotinoids were available in 96% of the cases, although not all complied with IPM principles. In 78% of cases, at least one non-chemical alternative method could replace neonicotinoids, as summarised in Figure 5. The most promising methods involved the use of microorganisms (e.g. *Bacillus thuringiensis*) for biological control. Physical (e.g. coating the fruit with paraffin oil or clay) and semiochemical methods (mating disruption with sex pheromones) have also proved effective. Farming practices designed to conserve biological control (Heimpel and Mills 2017; Gardarin *et al.* 2018) also had potential. Many of the promising non-chemical methods, however, required further field evaluation before their introduction into routine use by farmers, emphasising the importance of funding to establish efficient alternative methods for reducing pesticide use.

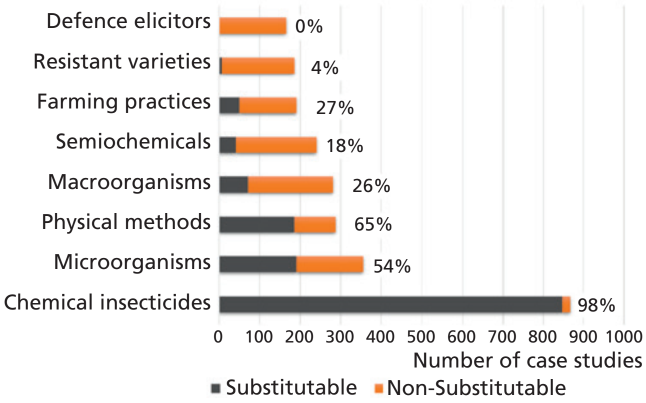

Figure 5 Number of substitutable and non-substitutable chemical and non-chemical alternatives to neonicotinoids for pest control, for the 2968 case studies considered (Jactel et al. 2019).

Another study examined how IPM technologies such as biological control can replace neonicotinoid insecticides (Wyckhuys *et al.* 2020). Artificial intelligence, remote sensing and precision agriculture for reducing or eliminating pesticide use are also suggested as alternative methods (Filho *et al.* 2020). A barrier to applying such alternatives is that a single, simple solution may not be generally available and that a combination of approaches will often be required, adding to manpower demands and increasing costs.

In view of the number of emergency exemptions involving sugar-beet yellow virus and oilseed rape flea beetle, examples of how IPM can apply to these two cases are provided in Box 2.

Box 2 IPM case studies

Sugar-beet yellow virus and other related viruses cause leaf yellowing and can reduce yields by as much as 50%. The viruses are spread by aphids (especially the peach-potato aphid, *Myzus persicae*, which overwinters and feeds on growing beet plants the following spring), as well as by machinery, people or animals passing through the crop. It has long been a serious disease and in the 1970s led to some farmers in Europe giving up growing sugar beet. It was an early candidate for seed pre-treatment with neonicotinoids which provided an efficient vector control. Since the withdrawal of neonicotinoids in 2019, emergency exemptions have been frequent owing to the lack of an equivalent replacement insecticide (the aphid has developed resistance to some of the earlier foliar sprays and only flonicamid remains effective).

The mild winters associated with global warming increase the threat of early infestation and have driven emergency exemption pressures. Publications on alternatives include recommendations by the French Agency for Food, Environmental and Occupational Health & Safety[20] such as synthetic and natural PPPs, microorganisms, aphid insect predators and parasitoids, vegetable and mineral oils to provide physical protection, methods for stimulating the plants' natural defences, selection of beet varieties resistant to yellowing viruses, and combining the cultivation of beets with that of other plants whose role is to keep aphids from accessing the beet plants or to encourage the action of aphid predators or parasitoids.

Current advice given to farmers is typified by the four-point plan (https://www.fwi.co.uk/arable/sugar-beet/4-point-plan-to-control-virus-yellows-in-sugar-beet).

1. Good crop hygiene, limiting sources of infection such as spoilage heaps, weeds and root remnants, and avoiding cover crops that provide a good host for aphids.
2. Rapid establishment of the growing plant to the stage when natural resistance in the mature plant sets in. For instance, by growing seedings under controlled conditions and then transplanting. The seed bed should be of good quality to ensure rapid germination and growth.
3. Monitoring. Typically, 10 plants across the field will be counted, and if the threshold of one green wingless aphid per four plants up until the 12-leaf stage is met, treatment is justified. After the 12-leaf stage, just one green wingless aphid per plant justifies treatment. After the 16-leaf stage, there is no need to spray. Farmers' organisations may provide aphid forecasts to inform this decision.
4. Timely targeted treatments. To reduce the risk of resistance, it is vital only to use the remaining effective insecticides at the specified threshold for green wingless aphids. Application of pyrethroids or carbamates serves no useful purpose, as more than 80% of aphids are resistant to these chemicals.

The above regime conforms to IPM in understanding the ecological role of the pest, monitoring and only using the insecticide when needed and in the minimum quantity. Research into sugar-beet varieties that are resistant to the yellow virus is under way, with varieties expected to be available within 3 years. The approach is also consistent with the conclusions of McNamara *et al.* (2020) on post-neonicotinoids approaches to a similar challenge against yellow-dwarf disease which affects cereals, and with Hauer *et al.* (2017) on options for alternatives to neonicotinoid seed pre-treatments.

Oilseed rape flea beetle. The cabbage-stem flea beetle (*Psylliodes chrysocephala*) is a serious pest of crops in the brassica family. As a flowering crop, there are particular risks to pollinators of neonicotinoid treatment. For example, Woodcock *et al.* (2016) found evidence of increased population extinction rates among wild bees in response to neonicotinoid seed treatment on oilseed rape in the UK, while Goulson (2015) showed reduced colony growth and queen production in the presence of neonicotinoids used in oil seed rape. Foliar sprays using pyrethroids are only partly effective since they do not reach larvae already inside the stems, and because of pest resistance. The effects of neonicotinoid withdrawal were estimated by Noleppa (2017) to be an average yield loss of 4% (ranging from 0.5% to 22%) across six EU countries which, together with a need for extra foliar sprays, had a total economic impact of €512 million per annum. On the other hand, a review by Lundin *et al.* (2020) reported large yearly natural variation in crop damage caused by flea beetles, and that seed pre-treatment decreased yield and profit loss in only one year in three. Viable alternatives included early sowing and higher sowing rates. Overall, Lundin (2021) found that in Sweden the neonicotinoid ban did not have major impacts on total cropping area or yields per hectare for either winter or spring oilseed rape, in contrast to reports from the UK and Germany.

As with aphids, the beetle is susceptible to frosts, so numbers increase with milder winters. Overwintering adults emerge in mid- to late spring and move into fields, searching for emerging host plants using visual and chemical/olfactory cues; they deposit their eggs in the soil at the base of a host plant. Larvae feed on below-ground portions of the plant, pupate in the soil, adults emerge to feed on above-ground foliage and then overwinter under protective plant debris in field borders.

IPM strategies based on the life cycle above can seek to strengthen the crop's resistance to beetle attack, reduce beetle numbers overwintering, and interfere with the pest's ability to locate the crop. In the first approach, a combination of only drilling when there is soil moisture, selecting the right variety and giving seedlings a nutritional boost can ensure that seedlings are actively growing by the time the adults attack. Varieties that provide larger plants in an autumn sowing and grow faster in the spring cope better with beetle attack.

Sanitation practices such as mowing and tilling weeds (especially early in the season) and removing plant debris help reduce flea beetle populations by minimising food sources and overwintering habitats. Lengthening crop rotations may reduce attacks, with some recommending that oilseed rape should be grown no more than once in 5 years. Other techniques include trap crops (a separate stand of plants grown to attract pest insects away from the cash crop and/or to intercept the pest as it migrates into a cropping field).

Another approach is to disguise the crop so that the highly mobile beetles fail to detect its presence. Stubble or companion crops such as buckwheat can hide the emerging seedlings. Applying sewage sludge or other manures can overwhelm the beetle's olfactory senses. Other treatments recommend applying diatomaceous earth. Lundin (2019) found that no-till approaches offer effective flea beetle control without the need for seed treatments, with 74% fewer flea beetles found after two no-till cycles. In Switzerland, intercropping winter oilseed rape with legumes (faba bean and grass pea) lessened the impact of the beetle by reducing larval density, egg laying and damage (Breitenmoser *et al.* 2022). Similar reductions in larval abundance in intercropping with legumes were also found in Sweden (Emery *et al.* 2021). Intercropping with legumes is increasingly used to provide atmospheric nitrogen and soil coverage and prevent weed growth, erosion and leaching losses as well as increase plant biodiversity.

Despite the range of measures described above, Ortega-Ramos *et al.* (2022) concluded that full IPM strategies that can also respond to increased pest resistance are still lacking, and IPM will continue to rely on combining methods of limited individual effectiveness. As a result, research ranging from monitoring methods to non-synthetic alternatives is urgently needed to widen the IPM options available.

Agrochemical companies have offered products contributing to this IPM approach. Some help with early establishment by stimulating root formation, or anti-fungal treatments that improve rooting. Biological treatments include bacteria that form a film around roots to help promote health. Where the above preventive measures fail to avoid infestations, thresholds for treatment by foliar sprays can be set, for example when there are five pest larvae per plant.

A major point to emerge from this description of IPM approaches is that they are more complex than chemical methods, and more information is required on which to base decisions. IPM may face difficulties because of trends to reduce staffing on the farm and outsource tasks such as planting, spraying and harvesting. Farm advisory services have an important role to play in promoting multi-actor interactions, information flow and the production of locally pertinent knowledge, while services such as monitoring may need to be provided by external sources. The fundamental challenge is that busy and risk-averse farmers may prefer to avoid laborious monitoring and apply routine approaches (e.g. calendar-based sprays) or convenient applications such as insecticide seed coating. Farmers' actions may also be guided by their beliefs and perceptions rather than by actual pest numbers. In this respect, Wyckhuys *et al.* (2019) found many farmers lacked an understanding of insect-killing fungi or viruses, endoparasitoids or predatory mites, although most were open-minded towards insect-friendly measures if financially compensated (Busse *et al.* 2021). Thus, basic communication initiatives are required on the underlying principles of IPM, and on low-cost, labour-saving IPM alternatives. These issues are explored in section 5.3.

4.5 IPM, conventional agriculture and food security

Studies generally find that yields in organic agriculture are less than for conventional farms (e.g. 67% across

---

[20] https://www.anses.fr/fr/system/files/PHYTO2016SA0057Ra-Tome1.pdf.

a range of crops (Kniss *et al.* 2016); 70–75% in the meta-analysis of Alvarez (2022)) although, as pointed out by Seufert and Ramanketty (2017), yields are highly context dependent and can be much closer to those of conventional agriculture. With the IPM studies mentioned earlier (section 4.3), yields are generally similar or even enhanced relative to conventional agriculture. However, the greater complexity of IPM can make it hard for farmers to choose the strategy that matches their circumstances and goals, and the resulting uncertainty involves risks which may discourage some farmers from adopting IPM. This was found to be the case found in IPM cropping systems in Norway (Lavik *et al.* 2020), where farmers who were only moderately risk averse preferred the IPM approach, but highly risk-averse farmers were more likely to continue with conventional farming practices.

With the Russian invasion of Ukraine and crop losses due to more extreme weather caused by climate change, as well as the continued growth in global population, the issue of food security has risen on the political agenda. This has led to criticisms of the Green Deal by some agronomists who cite studies that suggest savings in crop losses greatly exceed the costs of the pesticides used (Popp *et al.* 2012) and prefer to continue with the routine use of pesticides in conventional agriculture (e.g. Hornok 2022). This increased attention to food security places a high priority on research and technical demonstrations to show that different cropping systems and IPM approaches can be as effective as conventional agriculture, and to provide the technical support needed to allow farmers to apply IPM effectively. Recent studies such as Redhead *et al.* (2022) are encouraging in showing enhancement of wildlife conservation while maintaining or increasing crop yields as a result of planning, implementation and management of agri-environment measures.

5 Policy issues

5.1 General observations

The previous chapters have focused particularly on recent evidence of effects of neonicotinoids, the challenges to the regulatory system in avoiding 'regrettable substitutions' when assessing new products, the high rates of emergency authorisations, and the intent to steer farmers towards full IPM implementation and away from reliance on chemicals, so that risks to health, the environment and biodiversity are substantially reduced while maintaining yields. These are urgent challenges as evidenced by the current situation where pesticide risk globally is widespread: Tang *et al.* (2021a) calculated that pesticide residues in the environment have placed 64% of global agricultural land (approximately 24.5 million km^2) 'at risk' and 31% is 'at high risk' from multiple active ingredients.[21] With continued warming of the climate, Deutsch *et al.* (2018) estimated that if average global surface temperatures increase by 2 °C, the median increase in yield losses from pests would be 46%, 19% and 31% for wheat, rice and maize respectively. To combat the estimated future increase in pest pressure without increasing the use of pesticides, there is thus an urgent need for a change to a more sustainable use of crop protection products.

The Science Advice for Policy by European Academies (SAPEA)/Science Advice Mechanism study (SAM 2018) pointed to the fundamental conundrum that while the objectives in plant protection regulations are that '*substances … do not have any harmful effect on human or animal health, or any unacceptable effects on the environment*', pesticides are designed to have biologically toxic effects and only those with such efficacy can be approved! So, with zero risk likely to be unachievable, risk management becomes the critical step and should be based on clear criteria and levels for acceptable risk. EASAC concurs and stresses the need for a more systems-based approach, as discussed in section 5.2.

The Science Advice Mechanism also recommend that the current approach for the re-authorisation of individual PPPs should be replaced by the assessment of groups of PPPs according to type of active substance, mode of action and/or use pattern. This could be relevant to neonicotinoids where substantial research (Annex 3) is aimed at finding alternative chemical molecules that act on the same insect neural pathways. As has been demonstrated in the case of sulfoxaflor (and is under examination for flupyradifurone), a default assumption based on the precautionary principle should be that the properties that led to the banning of the original neonicotinoids are likely to be found in other chemicals exploiting the same mechanism of toxicity. It may be that differences in binding affinities could reduce toxicity despite targeting the same receptors, or provide an active substance that would not leak into the environment, but the existence of such significant differences should be clearly demonstrated.

EASAC also concurs with the conclusion of the Science Advice Mechanism (SAM 2018) and European Court of Auditors (ECA 2020) that the current extent of monitoring concentrations of, and exposures to, approved PPPs is insufficient to estimate their effects on health and the environment, and for early identification of emerging problems. Milner and Boyd (2017) suggested that post-use monitoring of pesticides could learn from that deployed for pharmaceutical products, where approval is followed by long-term monitoring to determine unexpected effects, using national and global reporting systems and pharmacovigilance regulations. For pesticides, there are some controls to protect human health (such as by monitoring maximum residue levels in food), but reporting of incidents is *ad hoc*, with no organised system for post-approval long-term monitoring of residues in the environment or deleterious effects. As a result, there is little information about where, when and why pesticides have been used, making it difficult to quantify potential environmental effects; nor can Member States' National Action Plans be properly evaluated. To resolve this, Mesnage *et al.* (2021) recommend reporting of products applied, adjuvants, active ingredients, rate and timing of application, target crop variety, and at a spatial scale that allows fine-scale granular analyses. EASAC concurs with this, and notes the Commission's proposals to require currently available data on farm usage to be provided annually and made more readily accessible (EC 2021). The Commission should continue to advocate improvements in data availability because this will offer greater protection against environmental damage in Member States' agriculture.

5.2 Improving the ability of regulatory testing to evaluate real environmental impacts

Chapter 3 described shortcomings in the tests used for regulatory purposes, and noted that they failed in several cases (including the neonicotinoids) to identify risks to the environment that later led to withdrawal. There is no shortage of suggestions on how to

---

[21] Land 'at risk' is where pesticide concentrations exceed the no-effect level and 'high-risk' is where concentrations exceed this by three orders of magnitude.

improve the testing regime. However, the framework of the possible reforms is still under debate between stakeholders. On the one hand, it was argued in the recent REFIT evaluation of the EU regulations on plant protection products and pesticides residues[22] that the EU system is already the most stringent in the world. Opponents to this argument (e.g. Jensen 2015) argue that regulators should treat PPPs like antibiotics and limit them to a prescription-style use. There are also logistical and resource issues to consider, with the current approval system already overloaded and the REFIT evaluation identifying a lack of resources and capacity in Member States to implement the current system efficiently. Adding additional or more complex testing may thus be opposed on practical grounds.

Many suggestions for improvement are based on expanding current test systems by increasing the number of test species, extending the number of environmental pathways considered, adding longer exposure tests and so on. The testing system for soils could also gain from adding species (surrogates) that are present in or close to actual agricultural landscapes. Nevertheless, concerns remain that merely adding more steps to the current list of tests will not be sufficient to ensure that the actual use of the pesticide is compatible with environmental and biodiversity constraints. In addition, there is no consensus on how the precautionary principle should be applied. As pointed out by Schäfer *et al.* (2019), the current system lacks consideration of the ecological, landscape and management contexts. The context related to scale of use of a pesticide is critical for the ecological outcome and this may far outweigh toxicological considerations (a more toxic compound used on a small scale may have much less impact than a less toxic compound that is used across a wide range of crops). This has been understood scientifically for a long time, but is often ignored owing to the difficulty in taking a systems approach.

As a result (section 3.2), there is increasing interest in a systems approach which would allow the risk assessment process to consider broader knowledge than that emerging from the testing protocols, considering agronomical reality at a landscape level, while including ecological effects in monitoring. For instance, it is known (e.g. Ward *et al.* 2022) that bee-attractive field border plants in agricultural areas harbour many pesticides, despite pesticides not being applied directly, so that bees can be exposed to many more pesticides than assumed. Such multiple exposures can be included in models to simulate real conditions of use and would be followed after authorisation, by monitoring real-world exposure, fate and impacts to allow checking on whether impacts are as expected. Models would allow inclusion of multiple stressors, and larger/longer spatio-temporal scales (year-on-year effects to be taken into account, and larger scales). The monitoring results would also provide early warnings on where the precautionary principle may need to be applied. A major advantage of a systems view would be the ability to take context dependency into account, allowing for a differentiated approach.

The Partnership for Environmental Risk Assessment (PERA) and Insect Pollinator Environmental Risk Assessment (IPol-ERA) are the current fora for developing the systems approach (EFSA 2022d). The systems approach may be built on complex models and processes, but this does not make the risk assessment itself more complicated, since an integrated perspective will allow a streamlining of existing procedures to avoid the complexities of having to align different approaches across testing protocols. We thus support a staged transition of the current testing regime to one based on this systems approach (EFSA 2022b). Initially system-based assessments should be complementary to the current testing regime which may still benefit from further reforms (such as testing additional species, inclusion of greater safety margins; e.g. Schäfer *et al.* (2019)), but as data and experience improve, the regulatory system should evolve to a more nuanced approval process where authorisation allows more specific approvals limited to particular pests or crops, and takes into account landscape and mitigation options. The latter approach might, however, pose challenges for enforcement and governance.

A separate issue relates to the regulation of ‘low-risk’ pesticides (approval criteria are found in Annex II (5) of Regulation (EC) 1107/2009) whose use is encouraged in the Green Deal. The Commission’s list of low-risk substances (EC 2018b) covers insecticides, fungicides, repellents, attractants, plant growth regulators, pheromones, nematicides and acaricides, with the active substances including bacteria, fungi and viruses, as well as substances such as blood, limestone or pepper. In principle, because of their low-risk, such products should be preferred by farmers in managing pests and should have a higher priority than more toxic synthetic chemicals in the IPM hierarchy.

Until 2022, pesticides considered to be of low risk had to be subjected to the same regulatory processes and tests as synthetic chemical pesticides. However, recently new guidance to facilitate the approval of microorganisms for use as active substances have been introduced to help farmers protect their crops in a more sustainable manner.[23] These may reduce the data

---

[22] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020SC0087.

[23] https://food.ec.europa.eu/plants/pesticides/micro-organisms_en.

requirements for some active substances, but potential impacts beyond those measured in acute toxicity tests should still be considered. For example, the potential of microbial agents to affect the microbiome of insects could be important (as shown with bees by Hotchkiss *et al.* (2022)) or for some bacterial symbionts involved in pesticide detoxification to increase pesticide resistance (Blanton and Peterson 2020; Gupta and Nair 2020). Moreover, a plant origin in botanical pesticides does not preclude negative effects on pollinators (Giunti *et al.* 2022). The risk analysis related to these products should therefore take a wider contextual view, taking into account the amounts and means by which the 'low-risk' PPP is applied. Although the importance of replacing chemical pesticides with less damaging products should be stressed, risks inherent to the modes of action of alternatives should still be included in risk assessments.

Even with an improved regulatory testing regime, it remains the reality that, to be effective, pesticides need to be toxic substances and that future 'regrettable substitutions' may never be completely avoidable. This emphasises the importance of implementing IPM (section 5.3) and the parallel deployment of overall reduction targets (section 5.4).

5.3 The role of IPM

5.3.1 Overcoming the barriers

Chapter 4 summarised the strengths and weaknesses of IPM and barriers to its implementation, pointing out that IPM approaches are more complex than routine use of chemical pesticides, and that more information is required on which to base decisions. Busy and risk-averse farmers who encounter continued pressures to reduce labour input and increase productivity through outsourcing to specialised contractors may see laborious monitoring and complex decisions as a step back and prefer routine approaches (e.g. calendar-based sprays) or convenient applications such as seed coating. How to overcome such barriers is the challenge the Commission faces in trying to convert the ambitions of the Green Deal and Farm to Fork strategies into concrete actions that allow food production to be maintained while achieving environmental and biodiversity objectives.

In the latest proposals (EC 2022b), Member States are required to adopt legally binding '*effective and enforceable*' crop-specific rules based on IPM controls and covering at least 90% of the utilised agricultural area. Professional users have an obligation to follow the IPM hierarchy of options before resorting to the use of chemical products, and must document the decision-making process in a nationally centralised electronic register. Monitoring and reporting requirements are set out, and the two pre-existing Harmonised Risk Indicators (HRIs) have been retained, although HRI 2 on emergency authorisations will be replaced in 2027 by one that measures the areas covered by emergency authorisations.

Achieving these objectives will require that the barriers discussed in sections 4.3 and 4.4 are overcome through support, incentives or regulatory pressures, as follows:

- **Ensuring that there is a common understanding of what IPM is**. In the IPM pyramid (Figure 2a), a fundamental aspect is that chemical control is the option of last resort. As mentioned in section 4.3, the current definition of IPM offered by the Commission does not explicitly mention this hierarchy of priorities, although users are required to explain why chemicals were used. This leaves ambiguity about how far IPM is linked to reduction in use, and effective IPM would be strengthened if the definition were to explicitly recognise that chemical treatment should be the option of last resort.

- **Education and awareness**. Providing education, training and advice to farmers, farm advisors and support for knowledge transfer. Agricultural colleges and advisory services need to shift to IPM as the primary focus of their agricultural courses.

- **Help for farmers to make new investments**. IPM requires more data collection and decision systems and may also trigger a need for changes in product marketing and diversification. New techniques may be required (e.g. to shift from synthetic chemicals to biocontrol). Techniques such as precision farming, robotics and use of big data all require investment.

- **Providing basic monitoring services**. As noted by Lundin *et al.* (2021), monitoring and sampling are fundamental components of IPM that are used with thresholds to determine how and when (if at all) to act against pest damage. The most commonly used is the economic threshold (section 4.2), but thresholds vary between specific pests and cropping systems, and are often unavailable, outdated or lack scientific support. In addition, other more sophisticated thresholds can be considered such as the dynamic threshold. Determining such thresholds is beyond the capacity of individual farmers and should be provided collectively—either through government agricultural services or joint actions between farming and agricultural research and monitoring organisations.

- **Incentive-based policies**. Taxes and subsidies can influence decisions that would otherwise fail to take into account the externalities of pest control practices (Lefebre *et al.* 2015). Taxes on pesticide use have been introduced in some countries (e.g. Denmark and France), but the price elasticity of pesticide use is low and thus high tax rates are needed to achieve significant reductions in use. The pesticide tax in Norway is differentiated by toxicity so that encouraging substitution between pesticides may reduce overall toxic impact (Popp *et al.* 2012). Another approach is to see a pesticide tax as a source of income allocated to supporting research and technical support for IPM.

It will be important to ensure that Common Agricultural Policy (CAP) payment schemes follow IPM principles as a precondition for receipt of related CAP subsidies. One potential measure would be to include reduction in pesticide use in the formula that determines CAP subsidies. The new CAP for 2023–27 (Greening European Union, https://agriculture.ec.europa.eu) will support biodiversity-friendly practices by allocating more funds to green direct payments (specific objective 6), and the Commission makes provision for some form of financial support to farmers complying with the new PPP regulation (EC 2022c). These incentives should be designed to achieve a rapid transition to IPM.

- The high carbon footprint of pesticide manufacture and use means that IPM may offer a mechanism for **carbon offsetting**, or at least for its mitigation potential to be recognised in mechanisms under the CAP that reward farmers for reducing emissions.

- **The agrochemical industry** has the potential to support the transition to IPM by moving away from mass-market sales of treated seeds and crop protection options, to more target-specific and niche markets that support farmers' moves to increase crop biodiversity and apply biological and other control mechanisms. Such a fundamental shift in the business model may need to be supported through regulation and incentives.

- **IPM and agricultural culture/diversity of approach**. With IPM, one solution does not fit all, and tailored solutions are required. Different countries approach farming in different ways; in some, farming is strongly interlinked with local culture. Developing support for IPM thus requires a multi-actor approach and respecting the local culture, so that farmers will be more likely to embrace the solution and make it their own.

5.3.2 The landscape level

It is important to take a **landscape perspective** that extends beyond the single farm; pest populations migrate across farms and wider areas, so coordinated pest control actions are the optimal approach. In contrast, landscape simplification in the past has reduced ecosystem services including pollination and biological pest control by removing natural or semi-natural reservoirs for beneficial insects (see, for example, Dainese *et al.* 2019). As pointed out by Lundin *et al.* (2021), the first stage of the IPM/IPPM pyramid (Figure 2) is for actions at the landscape scale that directly suppress pests and support diverse and abundant communities of natural enemies and pollination, such as reducing field size and diversifying cropland so that at least 20% of the landscape area is semi-natural habitat (Khan *et al.* 2014; Tscharntke *et al.* 2021). Thus, just as regenerative agriculture (EASAC 2022) needs to be applied at the landscape level to maintain agricultural productivity, increase biodiversity and enhance ecosystem services including carbon capture and storage, IPM also needs to be applied at these larger scales.[24]

Broader regional IPM strategies may be more costly to implement as they require additional societal acceptance, coordination and cooperation among farmers (Brewer and Goodell 2012), so different forms of incentives may be necessary to encourage their development; financial schemes should not only benefit individual farmers but also communities and associations of farmers managing landscapes in a coordinated way.

5.3.3 IPM and neonicotinoids

Given the subject of this report, the question arises whether there is a role for neonicotinoids in IPM. We pointed out in section 4.4 the reasons why prophylactic or blanket uses such as seed pre-treatment are fundamentally incompatible with IPM. However, the IPM framework neither bans nor allows chemical pesticides as a final option: that is for the risk assessment in each specific case to assess, taking into account both advantages and disadvantages. Where, having applied the non-chemical actions in the IPM pyramid, chemical control seems to be the best option, the question remains whether neonicotinoids should be automatically excluded from consideration. With specific pests under local and targeted applications (precision agriculture), it could be argued that neonicotinoids should be an option; however, the risk of neonicotinoids accumulation in soil, and their persistence, toxicity to non-target organisms and water solubility, argue against routine or repeated use if the precautionary principle is to be applied. Moreover, the extent to which emergency authorisations have been applied by some Member States raises the question whether use allowed only for highly restricted applications could be effectively monitored under current governance mechanisms.

---

[24] Agroforestry is often seen as one working example of such synergies (Varah *et al.,* 2020; Sollen-Norrlin *et al.,* 2020).

5.3.4 Practical considerations and knowledge gaps

A key challenge of the new Regulation is to develop crop-specific rules for the most economically harmful pests; rules that specify effective non-chemical methods, and the thresholds that must be exceeded before chemical intervention is considered. Non-chemical methods mentioned include crop rotation, modern cultivation techniques, use of resistant/tolerant cultivars and high-quality/certified seed and planting material, balanced fertilisation, liming and irrigation or drainage, use of hygiene measures to prevent spread of harmful organisms, protection and enhancement of beneficial organisms and pest exclusion. Developing such rules will depend very much on appropriate funding and support from agricultural research at both European and Member State levels. As noted by Jacquet *et al.* (2022), research offers progress in five major areas: (1) redesigning cropping systems to enhance prophylaxis; (2) diversifying biocontrol strategies and associated business models; (3) broadening the scope of plant breeding to include functional biodiversity and evolutionary ecology concepts; (4) setting new goals for agricultural machinery and digital technologies; and (5) supporting development of public policies and private initiatives for the transition towards pesticide-free agri-food systems. Horizon-funded activities are already underway, including the webinars on **Crop Protection and Scenarios for the Future of Agriculture** organised by the Institut National de la Recherche Agronomique (INRAE) which bring together European researchers working on the future of agriculture on the one hand and on crop health and crop protection practitioners on the other. Other collaborative work is planned under the biodiversity and ecosystem services call to identify the obstacles faced by farmers to transition to sustainable agriculture practices, such as intercropping.

Ultimately, IPM needs to become the mainstream approach if the objectives of the Green Deal are to be met. The challenge is that IPM may be more expensive in cost, work and manpower and needs to meet farmers' objectives for crop productivity and income security. Evidence that IPM is not in conflict with food security is thus critical in persuading Member States to support the Commission's proposals, especially following the Russian invasion of Ukraine (potentially, in reducing the need for chemical fertilisers and PPPs, IPM could improve agriculture's resistance to such supply shocks). In this context, projects such as the 'IPMworks' initiative (Box 3) are important.

5.4 Quantitative reduction targets

As noted above, there are strong grounds for associating support for IPM with quantitative targets for a reduction in the use of pesticides. Additional pressure to substantially reduce the quantities of synthetic pesticides in general arises from the projected expansion in organic agriculture to 25% of agricultural land, where cross contamination from non-organic farms would pose an increasing risk at current rates of use (e.g. Linhart *et al.* 2021; Zaller *et al.* 2022; Cech *et al.* 2023). In addition, Persson *et al.* (2022) have concluded that humanity has already exceeded the likely planetary boundary for novel entities (which include synthetic chemicals used in agriculture), and that the annual production and releases are increasing at a pace that outstrips the global capacity for assessment and monitoring. These trends have the potential for large-scale impacts that threaten the integrity of Earth system processes.

The current Farm to Fork strategy includes two targets: '*Target 1: to reduce by 50% the use and risk of chemical pesticides by 2030. Target 2: to reduce by 50% the use of more hazardous pesticides by 2030.*' While actual use statistics are quantitative, risk must be based on a formula that integrates different aspects (from human health to biodiversity and ecosystem services) into a single indicator, and the outcome is thus dependent on the formula selected. At present, the first Harmonised Risk Indicator (HRI 1) comprises the quantity of the product of each active substance in each of four groups from 'low-risk' to 'unapproved', multiplied by weighting factors in each group (1 for low-risk to 8 for category 2, 16 for category 3 to 64 for unapproved)

Box 3 Demonstrating the viability of IPM

A major research programme (IPMworks) is underway led by the Agency for Food, Environmental and Occupational Health & Safety (INRAE) to demonstrate that 'holistic IPM' not only reduces pesticide use but is also efficient and cost-effective. Case studies based on the practical experience of pioneer farmers cover 250 success stories in 16 countries (https://ipmworks.net/).

Holistic IPM is defined as '*combinations of non-chemical approaches, including a stronger use of ecology-based processes, more diversity and more biodiversity, eventually combined with innovative technologies (robotics, precision agriculture, Decision Support Systems, biocontrol) to develop sector-specific and site-specific solutions*'. It comprises five components:

1. Redesigning landscapes to decrease pest pressure (diversity, hedgerows, grass strips, etc.).
2. Redesigning cropping systems to decrease pest pressure (rotation, cultivars, fertilisation, cover crops, sowing dates, etc.).
3. Non-chemical pest control (mechanical weeding, robotics, protective nets, biocontrol agents, etc.).
4. Increased chemical efficiency (precision treatments using drones, etc.).
5. Improved decision making (to avoid unnecessary treatments, etc.).

and is intended to reflect the risks to human health and the environment of each group. There is also a second indicator, HRI 2, based on the number of emergency authorisations of active substances also weighted by the same factors, which show a 50% increase over the period 2011–17 (Buckwell *et al.* 2020). Some questionable outcomes of the current system have been pointed out by Burtscher-Schaden (2022) who noted that the same HRI weighting factor of 8 is given to one kilogram of a nerve agent, such as the highly bee-toxic insecticide deltamethrin, as one kilogram of quartz sand used as a deterrent to wildlife in organic agriculture.

An objective evaluation of progress against the 2030 targets depends very much on the correct assessment of risks. HRI 1 has shown declines since it was first calculated in 2011. In contrast, a different indicator (Di Bartolomeis *et al.* 2019) measuring the 'acute insecticide toxicity loading' suggested that the toxic load delivered in modern US agriculture had increased substantially (4- to 48-fold between 1992 and 2014) as a result of the combination of neonicotinoids' acute toxicity and environmental persistence. Similarly, Goulson *et al.* (2018) estimated that the toxic load on honeybees of insecticides applied in Great Britain over the period 1990–2015 had increased 6-fold as a result of the increasing use of neonicotinoids. Silva *et al*. (2022) also pointed to the difficulty in quantifying the hazards of active substances in pesticides. They noted that EC data classify 61% of the 2018 approved substances as being of intermediate hazard, 37% of low hazard and the other 2% of high hazard. Silva *et al*., however, found that all 230 of the active substances they examined had the potential to cause adverse effects on human or non-target organisms, and that more than half were in one of the top use or top hazard positions. Moreover, there were major gaps in the data available for many of the active substances on the market, leaving risk assessments incomplete.[25] In addition, there was a lack of clarity over which databases should be used among the wide range of sources available,[26] on how to rank effects on non-target organisms and whether to consider metabolites or pesticide adjuvants. Given that the 230 active substances studied have 414 known soil metabolites, including them in risk assessments would have substantial implications.

This emphasises the importance of the selection of the indicator in determining whether 2030 targets are to be met, as well as the baseline dates. Current use of baseline years from 2015 to 2017 has the unfortunate effect of 'locking in' the huge increases in toxic load found in earlier studies, so that even achieving the 50% reduction target leaves agriculture exposed to many times the toxic load of 20 years ago. From an environmental perspective, reduction targets should thus be substantially increased and/or baseline dates before the sudden surge in toxic load selected. As the Commission makes provision for the HRIs to be evaluated scientifically within 1 year of the new regulation being implemented, such factors should be considered in developing new indicators. A revised indicator should include data on a PPP's persistence in the environment, its toxicity to non-target organisms and biodiversity (especially pollinators and natural enemies of pests) and the effectiveness in controlling the target pest.

EASAC, while recognising that the selection of the HRI is a complex matter, encourages the Commission to rapidly conduct its planned review of the basis of the HRIs to provide more credible indicators. Open debate with the scientific community should be encouraged and supported by transparency. The outcome should be for an indicator that reverses the drastic increase in toxic load of recent decades. Greater efforts should also be made to allow public access to available data, so that the current gaps that restrict abilities to assess risks are minimised.

5.5 Innovations that enable IPM

In current conventional agriculture, pesticides are applied at a uniform rate throughout the field irrespective of the actual distribution of pests. In contrast, precision pest management identifies the pest risk at a microlevel and applies a pesticide only where required. This can substantially reduce the quantities of active substances applied, reducing costs and environmental impact. The key is detecting the areas at risk, and the controlled and targeted response.

There are several sensor-based approaches that can detect where the crop is stressed or damaged by pest outbreaks that can provide the required detailed data and precision response. Sensors can now detect airborne natural 'info-chemicals' (e.g. pheromones, allelochemicals, volatile organic compounds) produced by crops and pests (Ivaskovic *et al.* 2021). Advances in designing biochemical sensors mimicking the olfactory system, chemical sensors and sensor arrays (e-noses) offer precise detection and quantification that can be used in IPM pest control. Filho *et al.* (2020) also describe the use of small drones that measure canopy reflectance, transmitted as a digital map to guide an actuation drone that can address the pest hotspots by

---

[25] The proportion of species with moderate or high toxicity or no data was 100% for mammals, 76% for bees, 68% for birds, 86% for aquatic life and over 90% for soil organisms.

[26] For example, the EU Pesticides Database/EU dossier reports, EFSA OpenFoodTox database, US-EPA ECOTOX database, PubChem database, eChemPortal.

releasing natural enemies or applying precision-sprays of pesticides.

For the pesticide delivery itself, Singh *et al.* (2020) describe innovative controlled release systems such as nano-systems, microcapsules, microemulsion, hydrogels, environmental/stimuli-responsive materials of polymeric origin, and improved foliar adhesion. These targeted and efficient releases substantially reduce the amount of active substance leakage into the environment. Another approach to reduce leakage outside the targeted plant is described by Söftje *et al.* (2020), where the insecticide molecule is modified to reduce its aqueous solubility and prevent it leaching out of woody materials to which it has been applied. These approaches may not reduce the risk of non-target damage from exposure to the crop (as is the concern with bees in contact with contaminated pollen, nectar or guttation fluids), but lessen the wider spread into aqueous and out-of-field environments.

Other innovative approaches are based on geostatistical analysis. In a study by Li *et al.* (2021a), the spatial distribution of the diamond-back moth (*Plutella xylostella*, the most destructive pest of cruciferous crops worldwide) derived from pheromone traps placed in and around fields allowed precise targeting and localised control of the pest in IPM. Using a machine learning technique, Liao *et al.* (2020) developed a method for the semi-automatic identification of a biological control agent (a phytoseiid mite) for small pests. For pests other than insects, multispectral imagery classification combined with unmanned vehicle systems identified a common vole (*Microtus arvalis*) population, the number of active burrows and damage to an alfalfa field (Plaza *et al.* 2022). These techniques are also effective for precision pest control of possums in inaccessible areas (Morley *et al.* 2017).

As a general guide to future research, the reduction of pesticide use in agriculture requires a truly multidisciplinary approach, to promote the integration of different tools and approaches in crop protection that are sustainable from an ecological and socio-economic point of view. In particular, three complementary areas can be highlighted in most agriculture that does not apply organic methods:

1. Tools to support agroecology and landscape management and reinforce ecosystem services. This area would assist in developing and adopting agroecology and IPM principles that promote functional biodiversity (both at farm and landscape levels) and enhance the action of natural providers of ecosystem services such as control of pests, pollination and recycling of nutrients. It would include landscape features that can minimise habitat for pests while protecting predator populations and providing habitat for pollinators.

2. Alternative tools and strategies to reduce the use of synthetic pesticides. Pest populations still need to be controlled through novel alternatives to the use of synthetic pesticides. Plant defence barriers can be reinforced through genetic improvement and/or with the use of beneficial microorganisms and their metabolites as inducers of plant resistance barriers. The study of plant multitrophic interactions can pave the way towards a rational management of natural food webs to optimise the impact of natural biocontrol. Biocontrol agents can be used both as organisms and as sources of biopesticides and bio-stimulants. Formulation nanotechnologies (Abdollahdokht *et al.* 2022) can be developed to enhance efficacy and reduce environmental degradation of biopesticides. Some pest control technologies can be based on a physical mechanism that impairs pest survival and behaviour (e.g. disruption of mating behaviour based on vibrations transmitted through the substrate).

3. Smart technologies towards sustainable IPM in agriculture. The delivery of pesticides must be timely and targeted, preventing pesticide off-target drift. To this end, it is necessary to develop (a) monitoring strategies of both biotic and abiotic components of the environment, which are based on sensing technologies and data management to allow predictive models for crops and pests, and (b) precision agriculture technologies for targeted delivery of agrochemicals. End-users should have access to geospatial decision support systems, which will guide the access and use of the needed information to reduce the use of agrochemicals and environmental pollution.

6 Conclusions

1. The research published since our 2015 report confirms and strengthens earlier conclusions (Box 1) on the wider ecosystem effects of neonicotinoids. This not only supports the continuation of existing restrictions but also of measures to minimise future use even in emergency situations. Evidence on the severity of biodiversity and insect decline (including pollinators) continues to accumulate and, while multiple factors are involved, reducing the role that neonicotinoids may play in agricultural landscapes remains a priority in maintaining food security.

2. Caution is needed in evaluating new insecticide molecules that exploit the mode of action of inhibiting nicotinic acetylcholine receptors (neonicotinoids) and it should be assumed that similar broad ecosystem effects will be associated with such molecules unless applicants demonstrate otherwise when applying for regulatory approval.

3. EASAC shares concerns about the inadequacy of post-approval data on actual use and monitoring of residues in the environment. We urge the European Commission to continue to encourage Member States to collect and disseminate such data. The role of the Commission in monitoring pesticide application data and implementing IPM in Member States is important.

4. EASAC supports the measures taken and under way in improving regulatory testing by the European Food Safety Authority (EFSA) towards a systems approach. However, these measures should not be seen as sufficient to deliver on the objectives of protecting the environment and human health. We especially caution about the risk posed by undesirable neonicotinoid substitutions and emphasise that remaining knowledge gaps (e.g. on cumulative and synergistic effects between plant protection products (PPPs) and their adjuvants and other co-formulants; sensitivity of a wider range of non-target organisms including non-*Apis* bees and other pollinators) lead to a continued potential to overlook environmental risks.

5. We support the Commission’s overall objective to reduce pesticide use and risk to the environment, health and biodiversity, and support measures to encourage an agricultural system that regards integrated pest management (IPM) as its main tool to manage pest risk for most agriculture that does not use organic methods.

6. We confirm that the prophylactic use (e.g. seed coating) of neonicotinoids is inconsistent with IPM. Inclusion of neonicotinoids in the options for the final (last resort) tier of the IPM pyramid should be avoided under the precautionary principle.

7. Substantial economic and cultural barriers exist to the widespread deployment of IPM and will require coordinated action ranging from research, training, information and advice, extension services, common monitoring and other services, to financial incentives or regulations.

8. Maintaining and increasing food security remains a priority, and support for effective IPM that achieves this should be a priority too.

9. The evidence on the drastic increase in toxic load as a result of new-generation pesticides in recent decades argues for a more substantial reduction in the Commission’s 2030 target to reduce pesticide use and risk. EASAC agrees that current risk indicators should be revised and we advocate development of indicators that properly assess toxic load to the environment and ecosystems, and aim for an order of magnitude reduction in toxic load. Indicators should include data on a PPP’s persistence in the environment, its toxicity to non-target organisms (especially pollinators and natural enemies of pests) and effectiveness in controlling the target pest.

10. Many new technologies are emerging that support and facilitate the application of IPM. EASAC commends the Commission’s current actions to support and encourage deployment by farmers, and encourages further integration of IPM practices and technologies through the incentives in the Common Agricultural Policy.

Annex 1 Membership of the Expert Group

The Royal Academies for Science and the Arts of Belgium
Guy Smagghe, University of Ghent

The Bulgarian Academy of Sciences
Soren Hayrabedyan and Krassimira Hayrabedyan, Institute of Biology and Immunology of Reproduction "Acad. Kiril Bratanov"

The Royal Danish Academy of Sciences and Letters
Chris Topping, Aarhus University

The Estonian Academy of Sciences
Anne Kahru, National Institute of Chemical Physics and Biophysics

The Council of Finnish Academies
Ian C.W. Hardy, University of Helsinki

The Hungarian Academy of Sciences
Zanett Mikó, Plant Protection Institute, Center of Agricultural Research, Eötvös Loránd Research Network
András Székács Hungarian University of Agriculture and Life Sciences

The Accademia Nazionale dei Lincei
Francesco Pennacchio, University of Napoli Federico II

The Royal Netherlands Academy of Arts and Sciences
Violette Geissen and Claudia de Silva, Wageningen University

The Polish Academy of Sciences
Jerzy Lipiec, Institute of Agrophysics, Lublin

The Swiss Academy of Arts and Sciences
Edward Mitchell, University of Neuchâtel

The Royal Swedish Academy of Sciences
Maj Rundlöf, University of Lund

Chair of the Environment Programme
Lars Walløe

Director of the Environment Programme
Michael Norton

Annex 2 Overview of the literature since the EASAC (2015) report

Some 300 papers identified through searches on Google Scholar for neonicotinoids and papers known to members of the Expert Group (up to September 2022) are summarised here. They are sorted into the categories of environmental contamination; sublethal and synergistic effects with other pesticides (e.g. fungicides); effects on non-target species and whole-ecosystem effects; the regulatory process; vertebrate and human exposure; general chemistry, new chemical structures and degradation; effectiveness and alternatives to neonicotinoid use. As before, most research has come from Europe or the USA, but increasing attention is being given in Asia (China and Japan), especially to environmental contamination and the intake of neonicotinoids by humans. Each category is arranged in the order of the surnames of the primary author. An overview of the main results is provided in section 2.2.

Environmental contamination

Several papers show the extent of leakage from the point of use to the surrounding environment; for instance the following:

Freshwater and marine

- Bonmatin *et al.* (2019) found neonicotinoids in soil (68% of samples), sediment (47%) and water (12%) in a survey of northern Belize. Thirty-one per cent of sediment samples may pose a risk to aquatic invertebrates by chronic exposure. Imidacloprid was the most common residue, highest in melon fields and lowest in banana and sugarcane fields.

- A review of neonicotinoids in aqueous environments is given by Borsuah *et al.* (2020). Fifty-five articles on the occurrence or fate and transport of neonicotinoids in aquatic environments were reviewed, alongside 22 articles on toxicity to insects and invertebrates. The USA had significantly higher concentrations of insecticides than other reviewed regions.

- Chen *et al.* (2019) analysed water from all 16 rivers along the east coast of China for nine neonicotinoids. The results suggested use had shifted from old types (i.e. imidacloprid and acetamiprid) to new types (i.e. dinotefuran and nitenpyram) in some areas. The estimated annual quantity of neonicotinoids released into the adjacent seas totalled 1256 ± 780 tons, and 27% and 84% of samples exceeded the thresholds for acute and chronic ecological risks respectively.

- In South Africa, Curchod *et al.* (2020) and Chow *et al.* (2022) found that imidacloprid, thiacloprid and acetamiprid exceeded their environmental quality standard in rives of three agricultural catchment areas in the Western Cape by up to 58-, 12- and 5-fold respectively.

- Marine and estuary waters near the Seto Sea (Japan) contained imidacloprid and fipronil at levels exceeding the freshwater benchmarks for aquatic invertebrates (Hano *et al.* 2019).

- Herbertsson *et al.* (2021) screened pesticides in streams adjacent to commercial greenhouses in southern Sweden and identified imidacloprid as one of the most common pesticides in the water despite spray application and soil treatment never having been allowed for outdoor use. The concentrations of imidacloprid found in surface water downstream of greenhouses were up to two orders of magnitude higher than those found in high-intensity agricultural areas. They detected imidacloprid in wild plants growing adjacent to the contaminated streams and concluded that bees and other insects were being exposed through pollen from these wild plants.

- Hladik *et al.* (2018a) found five neonicotinoids detectable in 10 major tributaries to the Great Lakes for every month between October 2015 and September 2016; most frequently detected was imidacloprid (53% of samples), followed by clothianidin (44%), thiamethoxam (22%), acetamiprid (2%) and dinotefuran (1%). The maximum concentration for an individual neonicotinoid was 230 ng/L and the maximum total neonicotinoids in an individual sample was 400 ng/L. Neonicotinoid concentrations generally increased in spring through summer, coinciding with the planting of neonicotinoid-treated seeds and broadcast applications.

- Kandie *et al.* (2020a) detected imidacloprid and its degradation product imidacloprid-guanidine at concentrations ranging up to 32 and 152 ng/L respectively, in freshwater systems within the Lake Victoria South Basin, Kenya.

- Kandie *et al.* (2020b), measured contamination by a range of chemicals in snails and sediments collected from 48 sites within the Lake Victoria South Basin, Kenya. Acetamiprid, and imidacloprid were present in the snail tissues in concentrations up to 27ng/g by mass and 21 ng/g by mass respectively.

- Neonicotinoid concentrations in drinking water in China showed widespread contamination, particularly by acetamiprid and imidacloprid. Urban areas had higher concentrations than rural areas. Some levels exceeded the acceptable value (100 ng/L) recommended by the European Union (Mahai *et al.* 2021).

- Mineau (2019) found exponential growth in neonicotinoid use in New York State and increased contamination in aquatic systems, with loss of invertebrate life and ecosystem-wide perturbations affecting consumer species such as insectivorous birds, bats and fish.

- Mineau (2020) reviewed data on California's aquatic systems and found that some in agricultural areas using neonicotinoids contained levels of imidacloprid exceeding ecological damage levels set by the US Environmental Protection Agency by factors of 10–100.

- Mörtl *et al.* (2019a) demonstrated neonicotinoid active ingredients and their formulating agents (linear alkylbenzenesulfonates) may mutually affect the decomposition rate of each other. Mörtl *et al.* (2020a) reviewed maximum and the corresponding average concentrations in surface waters reported worldwide, benchmarked to national quality reference values. Imidacloprid and fipronil were found in most English rivers at concentrations often exceeding chronic toxicity limits. Sources were postulated to be prophylactic pet treatments for fleas (Perkins *et al.* 2020).

- Median levels of imidacloprid in Florida's water resources were found to exceed the US Environmental Protection Agency chronic freshwater Invertebrate Aquatic Life Benchmark of 10 ng/L, ranging from 2 to 660 ng/L (Silvanima *et al.* 2022).

- Warne *et al.* (2022) measured the imidacloprid concentrations in waterways adjoining the Great Barrier Reef and leaching from use in banana and sugar cane cultivation. It was detected in 0–99.7% of samples from different waterways. While average levels were below likely adverse effect levels, some 42% of aquatic species were likely to be harmed by some of the discharges in the Great Barrier Reef catchment area.

- Transfer of neonicotinoids from agricultural use to large river systems was observed in China. Imidacloprid and thiamethoxam were most often detected; and the total amount of neonicotinoids in surface water and sediment ranged from 24.0 to 322 ng/L, and from 0.11 to 11.6 ng/g respectively. Sources were agricultural run-off and effluent from wastewater treatment plants. An ecological risk assessment suggested a threat to sensitive non-target invertebrates (Zhang *et al.* 2019a).

Soils

- The distribution of neonicotinoids in China (Chen *et al.* 2022) was associated with cropland coverage and crop type. The concentration of neonicotinoids in soil samples ranged from 13.4 to 157 ng/g and imidacloprid was dominant (10.4–81.3 ng/g). The lowest concentrations were in tea croplands and the highest were in fruit croplands.

- Mörtl *et al.* (2016) demonstrated soil mobility and leaching characteristics of clothianidin and thiamethoxam in different soil types (sand, clay or loam) and in pumice. Both compounds were retained by loam and clay, while they readily passed through sand.

- Potts *et al.* (2022) found that mineralisation of acetamiprid formulations in a sandy loam was less than 23% (over 60 days of incubation). The highest mineralisation rates were recorded with the highest additions of organic matter from farmyard manure. The results also showed that 82.9% of acetamiprid was leached from the soil during rainfall. The combination of low sorption and low mineralisation indicates that acetamiprid is highly persistent and mobile within sandy soils.

- In Switzerland, Riedo *et al.* (2021) found imidacloprid, clothianidin, thiamethoxam and/or thiacloprid in 98.3% (59 out of 60) of conventionally farmed soils and 42.5% (17 out of 40) of organically farmed soils.

- Silva *et al.* (2019) and Pelosi *et al.* (2021), who analysed soil samples throughout Europe and France, identified neonicotinoids (e.g. imidacloprid and acetamiprid) in their soil samples, indicating that these compounds can be resistant in soil, posing a threat for the agricultural landscape, years after being applied.

- Šunta *et al.* (2020) found under laboratory conditions with agricultural soil that microplastics including polyester and polypropylene have the ability to adsorb acetamiprid and other pesticides. Microplastics decreased the soil's intrinsic capacity to retain pesticides, making them more available for migration through the soil. Microplastics may carry pesticides and other organic pollutants over long distances, causing combined toxic effects on soil flora and fauna and increasing pollution of aquatic systems (Gateuille and Naffrechoux 2022; Sajjad *et al.* 2022).

- Yu *et al.* (2021) measured concentrations in soils of six neonicotinoids in a typical agricultural zone. At least one of these neonicotinoids was detected in 95% of the soil samples. While no human risks were suggested, sublethal or acute effects to non-target terrestrial organisms such as earthworms were likely. Sorption affinities of neonicotinoids in soils are mainly governed by organic carbon. Biodegradation did occur and their presence influenced the soil nitrifying process (Zhang *et al.* 2018b).

- Soils in five types of land (greenhouse, orchard, farm, park and residential area) showed that imidacloprid, acetamiprid and thiamethoxam were most frequently detected in the following order of declining concentrations: greenhouse, followed by orchard, park, residential area and farm. Levels in soils planted with different crops varied greatly with high levels (>1 part per million) in soils planted with watermelon, tomato and peach in greenhouses (Zhou *et al.* 2021).

Plants and products

- Abafe and Chokwe (2021) found neonicotinoids in 50% of 115 samples of honey in South Africa, with the average concentration ranging from 0.062 to 6.50 µg/kg. Acetamiprid was the most detected (24.35%) but imidacloprid presented the highest concentration (16.945 µg/kg) in a sample.

- Assad *et al.* (2017) used mosquito larvae as a bioindicator in bioassays of okra fruit wash water, and showed levels below the acceptable daily intake for malathion and cypermethrin, but above the acceptable daily intake for imidacloprid residues.

- Devi *et al.* (2021) summarised effects of pesticides on honeybees in India noting that 98% of sprayed pesticides reach a destination other than their target species, including non-target species, air, water and soil.

- Girolami *et al.* (2022) show that honeybees tend to avoid sugar solutions laced with higher concentrations of the neonicotinoid clothianidin and hence reduce the risk of toxic effects spreading into the hive. Such avoidance effects could be detected from 10 ng/L which would be comparable to levels observed in pollen and nectar of flowers close to open fields sown with seeds coated with insecticides. While this reduces the risk to the hive, in the absence of an alternative energy source, reduced feeding can compromise colony health.

- Han *et al.* (2022) analysed 94 honey samples from a Chinese market for eight neonicotinoids and four metabolites. Neonicotinoids and their metabolites were detected in 97.9% of honey samples. Acetamiprid, thiamethoxam and imidacloprid were the top three dominant neonicotinoids, with detection frequencies of 92.6%, 90.4% and 73.4% respectively. For honeybees, 78.7% of honey samples had a hazard index above one based on a safety threshold value of sublethal effects.

- Kavanagh *et al.* (2021) found that neonicotinoids were most frequently detected in honeys from hives in Irish agricultural habitats, and 70% of all samples contained at least one neonicotinoid. Imidacloprid was most frequently detected followed by clothianidin and thiacloprid.

- A survey by Mitchell *et al.* (2017) of neonicotinoids in honey showed contamination across all continents, with 75% of samples containing one or more neonicotinoid, 45% containing two to five of the five tested, and 48% above 0.1 ng/g (lowest concentration known to have negative effects on bees).

- Maize-seed-coating neonicotinoids occur in the guttation drops of maize plants that emerged from uncoated seeds in close proximity (Mörtl *et al.* 2017, 2020b) and of common weeds nearby (Mörtl *et al.* 2019b). Although the levels of these neonicotinoids were substantially lower in the guttation liquid of the weeds than in that of maize plants from coated seeds, the compounds were detected up to 36th day after planting (Mörtl *et al.* 2017).

- In 693 honey samples from across China, Wang *et al.* (2020c) found that 40.8% contained at least one of the five neonicotinoids tested. The concentrations in honey overlapped with those that have been found to have significant adverse effects on honeybee health.

Sublethal and synergistic effects

- Annoscia *et al.* (2020) showed how clothianidin has a negative impact on immune responses, which can boost the proliferation of honeybee parasites and pathogens, and that immune suppression from clothianidin is associated with enhanced fertility of *Varroa destructor*, as a possible consequence of higher feeding efficiency.

- Crall *et al.* (2018) showed that neonicotinoid exposure disrupts bumblebee nest behaviour, social networks and thermoregulation.

- Decio *et al.* (2021) showed that thiamethoxam exposure deregulates the short *ORF* gene expression in the honeybee and compromises immune response to bacteria.

- Flores *et al.* (2021) performed a 3-year study of honeybee colonies to determine any effects of exposure to sunflower blooms grown from seeds treated with thiamethoxam, clothianidin and a non-treated control. In the first week of exposure, the number of adult bees and the amount of brood were slightly lower in the beehives exposed to neonicotinoids, although such differences disappeared in subsequent evaluations.

- Gill *et al.* (2021) reported that imidacloprid altered the activity of antioxidant enzymes in earthworms, although the magnitude of effect was dependent on time and concentration.

- Two literature reviews (O'Neal *et al.* 2018; Harwood and Dolezal 2020) document the harmful interactions between pesticides (including neonicotinoids) and immunity to pathogens and parasites.

- Hatfield *et al.* (2021) reported the largest documented pesticide kill of bumblebees in North America following the application of dinotefuran on ornamental plantings in the parking lot of a shopping mall. Analysis of the concentration of pesticide on flowers revealed that the minimum reported concentration was 737% above the median lethal concentration (LC_{50}) of *Apis mellifera*.

- Karedla *et al.* (2021) found that no effects on brood mortality occurred at level of 25 grams of active ingredient per hectare but significant mortality was observed at 50 grams.

- Thiamethoxam spraying reduced the foraging activity of *A. mellifera* on mustard blooms, as well as brood area, nectar and pollen stores (Karedla *et al.* 2021; Kumar and Mall 2021).

- Merga and van den Brink (2021) found that mayfly nymphs are more sensitive to imidacloprid than other macroinvertebrates, and that tropical species were more sensitive than temperate ones. Concentrations greater than or equal to 0.02 μg/L may cause long-term structural alterations in ecosystems.

- Negi *et al.* (2021) found that thiamethoxam under semi-field conditions reduced the foraging activity of *A. mellifera* on mustard bloom significantly on the 2nd day after spray; decreases in brood area (7th to 21st day), nectar stores (7th to 28th day) and pollen stores (7th to 21st day) were also recorded after the spray, while bee mortality was significantly higher on the 1st and 2nd day after spray, and average bee activity remained statistically low up to the 12th day.

- Paleolog *et al.* (2020) showed the effects of imidacloprid can affect proteolysis, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and global DNA methylation in honeybees.

- Řezáč *et al.* (2022) found that, despite spiders having differences in the sequence of their acetylcholine receptors to those in insects, the maximum and minimum concentrations recommended for foliar applications for thiamethoxam, acetamiprid and thiacloprid disrupt the locomotion of the spider *Pardosa lugubris*.

- Song *et al.* (2021) investigated the acute toxicity and sublethal effects of several different insecticides on the bee pollinator *Osmia excavata* and found that clothianidin was one of the most toxic of the insecticides to larvae and had significant sublethal impacts on larval weight and development.

- Straub *et al.* (2019) showed that neonicotinoids and ectoparasitic mites act synergistically to weaken honeybee colonies and contribute to colony collapse.

- Stuligross and Williams (2021) found that the effects of honeybee exposure to imidacloprid could be detected on reproduction over multiple generations. Repeated exposure across 2 years additively impaired individual performance, leading to a nearly 4-fold reduction in bee population growth. Thus, carryover effects had profound implications for population persistence and must be considered in risk assessment.

- Tasman *et al.* (2020) found that imidacloprid disrupts bumblebee foraging rhythms and sleep.

- Synergistic effects recorded of thiamethoxam with other pesticides (λ-cyhalothrin, β-cypermethrin and abamectin) by Wang *et al.* (2020b) and imidacloprid with the miticide thymol (Colin *et al.* 2020).

- The importance of undertaking combined toxicity studies was highlighted by Wei *et al.* (2021) who found that a mixture of imidacloprid with the fungicide azoxystrobin caused oxidative stress and lethality in *Chironomus dilutes*. Synergistic effects were observed at environmentally relevant concentrations, while antagonistic effects were observed at high concentrations.

- Willow *et al.* (2019) provided further evidence of the significance of synergistic effects between neonicotinoids and fungicide when co-applied. The general reinforcing effect from multiple stressors also features in Wade *et al.* (2019).

- Woodcock *et al.* (2017), in studies conducted on different crops and on two continents, confirmed that neonicotinoids diminish bee health under realistic agricultural conditions. Bees near corn crops were exposed to neonicotinoids for 3 to 4 months via non-target pollen, resulting in decreased survival and immune responses, especially when co-exposed to a commonly used agrochemical fungicide. This reduced overwintering success and colony reproduction in both honeybees and wild bees.

- Zhang *et al.* (2021a) found dinotefuran had exceptional toxicity to adult *Apis mellifera*, and that sublethal doses caused changes to their messenger RNA expression profile. Their results indicated that bees may respond to dinotefuran by regulating key genes, metabolites and signal transduction pathways.

Non-target species and whole-ecosystem effects

- Barmentlo *et al.* (2019) showed that environmental levels of neonicotinoids reduce prey consumption, mobility and emergence of the damselfly *Ischnura elegans* and indicate neonicotinoids play a central role in odonate decline in general.

- Becker *et al.* (2020) found that selection pressure from contamination by imidacloprid (and diazinon) caused insensitive snails to dominate over their less tolerant competitors, increasing a pathway for transmission of schistosomiasis.

- Calvo-Agudo *et al.* (2019) show that honeydew is an important route for exposure by beneficial insects that are predators for aphids, mealybugs, whiteflies or psyllids. Moreover Calvo-Agudo *et al.* (2021) show that soybean aphids survive exposure to neonicotinoids from coated seeds and excrete honeydew containing neonicotinoids, even 1 month after sowing. Consuming this contaminated honeydew in turn reduced the longevity of two biological control agents (a predatory midge and parasitic wasp), thus exacerbating the aphids' initial ability to survive.

- Cavallaro *et al.* (2019) examined the multiple stressors affecting aquatic insects in wetlands near neonicotinoid-treated canola in Saskatchewan. Variables included neonicotinoid concentration, turbidity, vegetation disturbance and continuity of a vegetative grass buffer zone. Higher neonicotinoid concentrations negatively affected insect emergence over time.

- De Lima *et al.* (2017) compared the toxicity of imidacloprid and thiacloprid to soil invertebrates and found imidacloprid was more toxic than thiacloprid for all species tested. *Folsomia candida* and *Eisenia andrei* were the most sensitive species, with LC_{50} values of 0.20–0.62 and 0.77 µg/kg dry soil for imidacloprid and 2.7–3.9 and 7.1 µg/kg dry soil for thiacloprid. This was extended in De Lima *et al.* (2020) to imidacloprid, thiacloprid, thiamethoxam, acetamiprid and clothianidin. The most toxic compound to *E. andrei* was acetamiprid and the most toxic to *F. candida* was clothianidin. De Lima *et al.* (2021) also showed that *F candida* was a good model organism for assessing ecotoxicity in soil.

- Eng *et al.* (2019) reported sublethal effects on white-crowned sparrows, which lost weight when given field-realistic does of imidacloprid-treated seeds, delaying migration.

- Ewere *et al.* (2021) reviewed the impacts of neonicotinoids on mollusc species. Studies have shown that neonicotinoids cause stress to terrestrial molluscs and build up in the tissues at concentrations that could cause mortality in mollusc-eating arthropods; a wide range of behavioural, biochemical and physiological impacts had also been reported.

- As an indication of sublethal aquatic toxicity, Farkas *et al.* (2022) demonstrated physiological activation of metabolic activity (cytochrome P450 monooxygenase) and depression of physiological functions (thoracic limb activity, heart rate) in the great water flea (*Daphnia magna*).

- Gao *et al.* (2020) reported sublethal doses of neonicotinoids can alter honeybee immune systems increasing pathogen loads and parasite infections. Clothianidin and imidacloprid, for example, can enhance proliferation of deformed wing virus. They found that exposure to sublethal doses of imidacloprid significantly affected the physiological performance of *Apis cerana* (Asian honeybee) in China.

- Ge *et al.* (2018) found that earthworms exposed to neonicotinoids (six types tested) responded by avoidance behaviour; this and reproduction harm were observed at very low concentrations.

- In an experimental study comparing the effects of chlorfenapyr, acetamiprid and dimethoate on the freshwater carp species *Cirrhinus mrigala*, Ghayyur *et al.* (2020) found all three pesticides caused rapid swimming, surface activity, convulsions, loss of balance and other abnormal behaviour with severe effects on the gills and liver.

- Gunstone *et al.* (2021) reviewed nearly 400 studies on the effects of pesticides on non-target invertebrates that have egg, larval or immature development in the soil. This review encompassed 275 unique species, taxa or combined taxa of soil organisms and 284 different pesticide active ingredients or unique mixtures of active ingredients. Of the various parameters measured, 70.5% showed negative effects, whereas 1.4% and 28.1% showed positive or no significant effects from pesticide exposure. Non-*Bombus* ground-nesting bees, although less-studied, were particularly sensitive to neonicotinoids. Regulations currently ignore pesticides' harm to soil species and should be adjusted to include soil organisms in any risk analysis of a pesticide that has the potential to contaminate soil.

- Hasan *et al.* (2021) found thiamethoxam caused histopathological alterations in the gills of banded gourami (*Trichogaster fasciata*) in Bangladesh.

- Huang *et al.* (2021) found in crayfish that imidacloprid reduced crawl velocity, and attenuated their dark preference, aggressiveness and reversal ability.

- Humman-Guilleminot *et al.* (2019) showed that sparrows from farmed areas had four to five times the concentrations of neonicotinoids compared with organic farms.

- Many surveys such as those by Bowler *et al.* (2019) and Jactel *et al.* (2021) show that insectivorous birds in farmlands show the most precipitous declines, symptomatic of the decrease in insect food for birds in farm landscapes.

- Korenko *et al.* (2019) found that spiders were repelled from eating captured flies when these were contaminated with neonicotinoids.

- Lennon *et al.* (2019) looked for correlations between neonicotinoid use and changes in the populations of 22 farmland bird species between 1994 and 2014 in England but found no detectable correlation with dietary preferences (secondary effects of pesticide use on insect food supply were not considered).

- Li *et al.* (2020) found increased neonicotinoid use led to significant reductions in bird biodiversity between 2008 and 2014, with average annual rates of reduction of 3–4%. The rates were 5–12% when the dynamic effects of bird population decline on future population growth were considered.

- Li *et al.* (2021b) identified the molecular mechanisms of toxic effects of thiamethoxam on the pupation and survival of honeybee larvae at sublethal concentrations.

- Liess *et al.* (2021) reported a study across 101 sites of small lowland streams in Germany and found that 83% of agricultural streams did not meet pesticide-related ecological targets, and that nonpoint-source pesticide pollution was the major driver in reducing vulnerable insect populations in aquatic environments, more so than other anthropogenic stressors such as poor hydrological conditions and nutrients. Dominant contributors were thiacloprid, imidacloprid and clothianidin.

- Macaulay *et al.* (2019) found that imidacloprid and clothianidin exerted strong chronic toxicity effects on *Deleatidium* nymphs, whereas thiamethoxam was the least toxic.

- Mahmoudi-Dehpahni *et al.* (2021) found that soil application of thiamethoxam did not adversely affect the predatory bug *Orius albidipennis.* But foliar application had severe effects through ingestion of its aphid prey.

- Merga and Van den Brink (2021) found that mayfly nymphs were more sensitive to imidacloprid than other macroinvertebrates, and that tropical species were more sensitive than temperate ones. Concentrations greater than or equal to 0.02 μg/L may cause long-term structural alterations in ecosystems.

- Miotelo *et al.* (2022) evaluated the differentially expressed genes in the stingless bee (*Melipona scutellaris*) after 1 and 8 days of exposure to thiamethoxam and found effects on processes such as detoxification, excretion, tissue regeneration, oxidative stress, apoptosis and DNA repair, demonstrating the types of damage to cells at the molecular level.

- Oumaima *et al.* (2020) reviewed the use of insecticides (both neonicotinoids and other insecticides) and found use by some farmers to be excessive. Concerns were expressed about persistence in the environment and effects on soil microorganisms and aquatic organisms.

- Laboratory tests (Renaud *et al.* 2018) showed chronic toxicity of the neonicotinoids thiacloprid and acetamiprid to soil invertebrates exceeded European Commission trigger values and pointed to risks to soil biota from thiacloprid and acetamiprid use.

- Řezáč *et al.* (2019) found that imidacloprid, thiamethoxam, acetamiprid and thiacloprid had adverse effects on the predation rate of spiders, with imidacloprid associated with the most severe effects. Even acetamiprid caused strong effects, despite being subject to less strict regulations in the EU because of claims of its negligible off-target toxicity.

- Ritchie *et al.* (2019) found that the observed toxicity for *Folsima candida* adult survival and reproduction and for *Eisenia andrei* reproduction occurred at environmentally relevant concentrations of clothianidin and thiamethoxam,

- The acute toxicity of neonicotinoids to the great water flea (*Daphnia magna*) is potentially affected by formulating agents. The toxicity of clothianidin was found to be enhanced, while that of thiacloprid or thiamethoxam was reduced, in the formulated product compared with the pure active ingredient (Takács *et al.* 2017).

- Vanderpoint *et al.* (2022) evaluated the effects of thiamethoxam runoff into wetlands using a mesocosm, and concluded that exposure at environmentally relevant concentrations probably did not represent a significant ecological risk to abundance and community structure of wetland zooplankton and emergent insects.

- Van Hoesel *et al.* (2017) found that neonicotinoid seed dressings significantly reduced the surface activity of earthworms and that these effects were intensified by application of the herbicide glyphosate.

- Vehovszky *et al.* (2015, 2018) demonstrated cholinergic neurotransmission disruption by thiacloprid, imidacloprid and clothianidin in a molluscan (*Lymnaea stagnalis*) nervous system, and possible emergence of multixenobiotic resistance by thiacloprid, imidacloprid, clothianidin and thiamethoxam in the quagga mussel (*Dreissena bugensis*).

- Wu *et al.* (2020) reported the neurological effects of imidacloprid on the echolocation ability of insectivorous bats.

- Yamamuro *et al.* (2019) studied the collapse of two commercial fisheries on a Japanese lake after the introduction of neonicotinoid use and attributed this to the loss of zooplankton biomass resulting from the use of the insecticide.

- Zaller *et al.* (2016) studied how neonicotinoid insecticides in treated wheat seeds influenced the activity and interaction of earthworms, collembola, protozoa and microorganisms in a soil microcosm.

The regulatory process

- Brühl and Zaller (2019) analysed the weaknesses in current environmental risk assessments against the background of biodiversity decline.

- Gunstone *et al.* (2021) concluded that regulations currently ignore pesticides' harm to soil species and should be adjusted to include soil organisms in any risk analysis of a pesticide that has the potential to contaminate soil.

- Liess *et al.* (2021) showed the extent to which regulatory tests fail to properly assess ecological risk-underestimating it by factors of 5 to 40. Reasons are (1) measured pesticide concentrations exceed regulatory acceptable concentrations and (2) the inertia of the authorisation process impedes the incorporation of new scientific knowledge. Regulatory evaluations also fail to consider that the multitude of pesticides present in streams may act in a synergistic manner so that toxic effects may increase by a factor of up to 660 (Liess *et al.* 2020).

- Although based on the case of glyphosate, Mie and Rudén (2022) found that the legal obligation for industry to submit all potentially relevant data to European Union authorities was not fulfilled and relevant research funded by industry was excluded from safety documentation submitted by the applicant companies. They note that authorities cannot reliably pursue a high level of protection of human health, if potentially relevant evidence is withheld from them and suggest that lists of studies performed by test laboratories should be checked to ensure all relevant studies are submitted to regulatory authorities. Moreover, that future toxicity studies should be commissioned by authorities rather than by companies, to prevent economic conflicts of interest affecting the reporting of study results and their conclusions.

- Sánchez-Bayo and Tennekes (2020) reviewed evidence that neonicotinoid toxicity increases with exposure time as much as with the dose (time-cumulative toxicity). This pattern of toxicity, also found among carcinogenic compounds, has far-reaching implications for the impacts on non-target organisms in both aquatic and terrestrial environments. Neonicotinoids are incompatible with integrated pest management (IPM) and regulatory assessments cannot be based solely on exposure doses but need also to take into consideration the time factor.

- Sgolastra *et al.* (2020) pointed out that pesticide regulation failed to detect the ecological threats posed by neonicotinoids, owing to properties such as high efficacy, long persistence, high systemicity, high mobility and application versatility. A more holistic approach is needed.

- Topping *et al.* (2020) pointed to the weaknesses in the regulatory systems caused by managing risks through single-product, single-crop assessments. This provides insufficient ecosystem protection and needs to move to a more holistic view.

Vertebrate and human exposure

- Al-Awar *et al.* (2021) found that imidacloprid caused a range of effects on the testes and prostrate tissues in male rats that reduced fertility.

- Anai and Nisada (2021) found that thiamethoxam and clothianidin were detected in most participants in a survey of neonicotinoid levels in pregnant women in Japan (83.4% and 80.9% respectively), with intake most likely from ingestion of pulses.

- Acetamiprid was also found to be a potent epigenetic modifier, reducing brain and liver DNA methylation and DNA methyltransferase expression in a rat model of chronic non-genotoxic stress (Aricam *et al.* 2019). The authors noted that the possibility of epigenetic modifications, even in sub-toxic or sub-threshold doses, implies a high risk and an increased potential for impairment of embryo development and later stages of live genome instability-caused pathologies, such as cancer.

- Chen *et al.* (2020a) found widespread contamination of vegetables by residue levels of multiple neonicotinoids. Imidacloprid and acetamiprid were most frequently detected with thiamethoxam and clothianidin increasingly found. Exposure was much lower than the current chronic reference dose, but risks should not be overlooked owing to the ubiquity of neonicotinoids in food and the environment.

- Chen *et al.* (2020b) reported the results of a study examining neonicotinoids in breastmilk and nursing infants in China and concluded from 97 samples (2017–2019) from 23 provinces that there was a miniscule risk to infants from neonicotinoid exposure through breastfeeding. The metabolite of acetamiprid (acetamiprid-*N*-desmethyl) was the most common of the neonicotinoids identified in breastmilk followed by imidacloprid.

- Cimino *et al.* (2017) reviewed publicly available literature on unintentional human exposure to neonicotinoids and found some concerns about exposures and malformations of the developing heart and brain. However, overall, there was a need for more studies.

- A review by Costas-Ferreira and Faro (2021) found that exposure to neonicotinoids at an early age alters correct neuronal development, with decreases in neurogenesis and alterations in migration, and induces neuroinflammation. In adulthood, neonicotinoids induce neurobehavioural toxicity, these effects being associated with their modulating action on nicotinic acetylcholine receptors (nAChRs), with consequent neurochemical alterations. These alterations include decreased expression of nAChRs, modifications in acetylcholinesterase activity, and significant changes in the function of the nigrostriatal dopaminergic system. All these effects can lead to the activation of a series of intracellular signalling pathways that generate oxidative stress, neuroinflammation and, finally, neuronal death.

- Craddock et al. (2019) analysed levels of neonicotinoids in fruit and vegetables in the USA from 1999 to 2015. They found amounts below recommended safe intake levels but that residues could be detected in cherries (45.9%), apples (29.5%), pears (24.1%) and strawberries (21.3%) for acetamiprid; and cauliflower (57.5%), celery (20.9%), cherries (26.3%), cilantro (30.6%), grapes (28.9%), collard greens (24.9%), kale (31.4%), lettuce (45.6%), potatoes (31.2%) and spinach (38.7%) for imidacloprid. Neonicotinoids were also detected in organic commodities.

- Han *et al.* (2021) reviewed human exposure and harmful effects of neonicotinoids. Neonicotinoid residues were widespread in fruits and vegetables of which imidacloprid was most often found. In general, levels did not exceed national food safety standards but cases of excessive neonicotinoid detection did occur. Ingestion was the main route of exposure and the levels in Asian countries seemed higher than those in Europe and America. Exposure after spraying led to exposure in rural areas being higher than those in neighbouring urban areas.

- Thiacloprid was recently shown to be a potent endocrine disruptor, affecting both spermatozoa count and inflicting telomere damage in mice models. Moreover, it was shown to act through thyroid hormone receptors in embryonic testis, and, even more importantly, causing global histone methylation genes dysregulation, thus disrupting epigenetic regulation in embryos and later in adults (Hartman *et al.* 2021). The effects were significant even in doses several times below the allowed threshold. Imidacloprid was also found to induce neurological dysfunction and abnormalities in sperm, immune response and whole-blood composition, after *in utero* and early life exposure (Burke 2016).

- Hoshi (2021) reviewed evidence on exposure effects of neonicotinoids and developmental disorders. He concluded that no effect levels could still be associated with adverse effects on cognitive-emotional behaviour and immune system functions, revealing the existence of a major flaw in current toxicity tests.

- Ichikawa *et al.* (2019) reported the first evidence worldwide of neonicotinoid exposure in newborn babies in the early phase after birth, suggesting a need to examine potential neurodevelopmental toxicity of neonicotinoids and metabolites in human foetuses.

- Ikenaka *et al.* (2019) showed that children living in communities where thiacloprid was used to control pine wilt disease were exposed to multiple neonicotinoids on a daily basis.

- Khovarnagh and Seyadalipour (2021) investigated the effects of acetamiprid on rats and found that it induced liver injuries and brain damage through gliosis, hyperaemia and necrosis.

- Laubscher *et al.* (2022) found two or more neonicotinoids in the spinal fluid of children which correlated with blood and urine concentrations, showing that the neonicotinoids pass the blood–brain barrier.

- Imidacloprid and thiacloprid were among pesticide contamination at public playgrounds and other public sites near intensively managed agricultural areas in Austria (Linhart *et al.* 2019, 2021), and among those detected in non-agricultural land, despite measures designed to reduce spray drift (Cech *et al.* 2023). Thiacloprid was among the 109 substances detected in ambient air in Germany (Kruse-Plaß *et al.* 2021), and in a survey of ambient air exposure in Austria (Zaller *et al.* 2022). These authors concluded that the widespread pesticide air pollution detected indicates that current environmental risk assessments, field application techniques, protective measures and regulations are inadequate to protect the environment and humans from potentially harmful exposure.

- Liu *et al.* (2021a) found that thiamethoxam decreased the ovarian coefficient and disrupted the expression of female hormone receptors, subsequently affecting follicle development in mice.

- Neonicotinoid residues have been found in human samples, including urine, blood, breast milk and hair. To better understand mechanisms of hepatotoxicity, Li *et al.* (2021c) exposed male mice to three neonicotinoids (dinotefuran, nitenpyram and acetamiprid), leading to morphological damage in the liver.

- A recent study by Maeda *et al.* (2021) addressed concerns about transfer from mother to child of neonicotinoids and their potential effects on the next generation. They exposed mice to no-observed-adverse-effect doses of clothianidin during the foetal and lactational periods, and then evaluated the neurobehavioural effects in juvenile and adult mice. Their results suggested that foetal and lactational exposure may inhibit neurogenesis and cause different behavioural abnormalities at different developmental stages in the offspring of exposed adult mice.

- Osaka *et al.* (2016) collected urine samples from 223 children (108 males and 115 females) in the summer and winter months. The detection rates of neonicotinoids were 58% for dinotefuran, 25% for thiamethoxam, 21% for nitenpyram and less than 16% for all other neonicotinoids. The median and maximum concentrations of the sum of the seven neonicotinoids were 4.7 and 370.2 nmol/g creatinine respectively.

- Perananthan *et al.* (2020) explained the low human toxicity relative to insects. Although acute exposure to imidacloprid is usually associated with mild non-specific symptoms, since the introduction of new formulations in 2007, the toxic profile had changed with reported cases of death reported in Sri Lanka as well as an increase in cases requiring mechanical ventilation. The median amount ingested was 15 millilitres and the increased toxicity could have been due to the solvents used in the newer formulations and to higher doses of imidacloprid.

- Shah (2020) explained the exposure routes for human health impacts as being through occupational exposure during manufacturing, transportation, sale and application; or passively through ingestion due to contaminated food and water or inhalation of pesticides from air through drift from point of release.

- Sriapha *et al.* (2020) found that patients with imidacloprid poisoning mostly developed only mild toxicity, but a few with mild initial severity died. Symptoms included cardiovascular effects, central nervous system effects, dyspnoea and diaphoresis.

- Tao *et al.* (2019a) found that the concentration of imidacloprid in the urine of people in the vicinity of sprayed orchards (pesticide applicators, their family members, children nearby) significantly increased after a spraying event. Human exposure was confirmed, with imidacloprid detected in 100% of urine samples from rural applicators (Tao *et al.* 2019b).

- Thompson *et al.* (2020) reviewed the environmental fate and toxicity of neonicotinoids and their metabolites and the potential risks associated with exposure. Overall, exposure from drinking water and food was low-level, commonly documented below acceptable daily intake levels. Available toxicological data from animal studies indicated possible genotoxicity, cytotoxicity, impaired immune function, and reduced growth and reproductive success at low concentrations, while limited data from epidemiological studies identified acute and chronic health effects ranging from acute respiratory, cardiovascular and neurological symptoms to genetic damage and birth defects. Owing to the heavy use of neonicotinoids and potential for cumulative chronic exposure, these insecticides represent novel risks and necessitate further study to fully understand their risks to humans.

- Wan *et al.* (2019) analysed raw water, finished water and tap water samples originating from the Han River and the Yangtze River in Wuhan during 2018. Neonicotinoids were found in all raw water samples with a median sum concentration of 27.7 ng/L (range 13.4–186 ng/L). Most were not effectively removed during water treatment, except for acetamiprid and thiacloprid which decreased by 40.1% and 20.0% respectively. At least three were detected in all tap water samples with the highest sum concentration observed in July. The estimated daily intake of neonicotinoids through tap water ingestion in July was 8.66 ng/kg bodyweight per day for infants, about four times higher than that for adults.

- Wang *et al.* (2019) compiled and examined publicly available hazard data for neonicotinoids, and knowledge gaps on mammals were identified. Initial thresholds of toxicological concern were derived for rat, dog, mouse and rabbit. Generally, exposure levels were at or below the default values used by regulators.

- Wang *et al.* (2020c) measured exposure of Chinese school children to neonicotinoids in Shanghai. Neonicotinoids (thiamethoxam, clothianidin, imidacloprid, acetamiprid, nitenpyram and dinotefuran) and three metabolites (*N*-desmethyl-thiamethoxam, *N*-desmethyl-clothianidin and *N*-desmethyl-acetamiprid) were detected in 81.3% of urine samples. Thiamethoxam and clothianidin were more likely to be detected in children consuming more fresh vegetables, while *N*-desmethyl-acetamiprid was more likely to be detected in children who drank more tap water. The maximum hazard quotient and hazard index were 0.3522 and 0.5187 respectively, and 2.8% of children had a hazard index between 0.1 and 1, posing a low risk to children's health.

- Wong *et al.* (2019) detected residues of neonicotinoid pesticides in drinking water that had transformed through chlorination and alkaline hydrolysis during water treatment. Such metabolites and potential novel disinfection by-products during treatment are relevant to evaluating the potential impacts of neonicotinoids on human health.

- Yuan *et al.* (2019) examined the possible effects of different kinds of widely used pesticide on the gut microbiota and analysed their possible subsequent effects on the health of the host. They found evidence that the gut microbiota of animals plays a very important role in pesticide-induced toxicity.

- Zhang *et al.* (2018a) reviewed peer-reviewed articles published before 2017 that addressed potential human exposures through ingestion and inhalation, as well as results from human biomonitoring studies. In addition, they proposed the use of a relative potency factor approach to facilitate the assessment of concurrent exposure to a mixture of neonicotinoids with similar chemical structures and toxicological endpoints.

- Zhang *et al.* (2019c) measured urinary levels of six neonicotinoids in 324 individuals from 13 cities in China. Most common were clothianidin (median: 0.24 ng/ml), imidacloprid (0.21 ng/ml), thiamethoxam (0.15 ng/ml) and dinitrofuran (0.14 ng/ml), collectively accounting for 98% of the concentrations. On the basis of urinary imidacloprid levels, a median daily intake of 1.6 µg per day, or 0.034 µg/kg bodyweight per day, was calculated.

- Zhang *et al.* (2019b) found in Hangzhou that foods such as carrots, green vegetables, baby cabbage and apple were contaminated with up to six neonicotinoids. Although daily intakes were below the chronic reference doses, concern was raised about the health risk of neonicotinoids to children through dietary exposure because of their increased use and ubiquitous presence in fruit and vegetables.

- Zhang *et al.* (2021b) measured contamination in drinking water of neonicotinoid insecticides in China, finding that young children were particularly exposed between the ages of 9 months and 2 years and between 9 and 12 years.

- Zhang (2021c) reported that while neonicotinoids were originally considered to be less toxic to mammals than insects, several studies *in vitro* and *in vivo* showed they could have adverse effects on mammals such as reproductive toxicology, neurotoxicity, genotoxicity, hepatotoxicity and endocrine disruptive effects. By looking at saliva and periodontal blood samples, they found evidence of extensive exposure to neonicotinoids and their metabolites in the South China population, with dinotefuran the most abundant.

- Zhang and Lu (2022) reviewed the extensive data on levels of neonicotinoids in human samples and found urinary levels in Asian populations were substantially higher than those in the USA and Europe. Moreover, where measured, metabolites exhibited higher detection frequencies and levels than their parent compounds. Current available data were insufficient to assess longer-term health outcomes, requiring large-scale epidemiological studies and long-term monitoring not only for urine but also for hair, nail and other alternative samples.

General chemistry, new chemical structures and degradation

- Anjos *et al.* (2021) discussed microbial biodegradation and bioremediation processes (for 12 commercial neonicotinoids), which use isolated microorganisms (bacteria and fungi), consortiums of microorganisms, and different types of soil, bio-bed and mixture. Degradation of neonicotinoid insecticides (imidacloprid, imidaclothiz, thiacloprid, nitenpyram, sulfoxaflor, dinotefuran, thiamethoxam, paichongding, cycloxaprid and clothianidin) in soil enriched with microorganisms resulted in bioremediation of pesticides with good efficiency and in short times.

- Azpiazu *et al.* (2021) investigated interaction of sulfoxaflor with fungicides. This study showed only weak synergistic effects on three bee species: *Apis mellifera*, *Bombus terrestris* and *Osmia bicornis*. Overall, sulfoxaflor was less toxic than the recently banned neonicotinoids imidacloprid, thiamethoxam and clothianidin, but much more toxic than other neonicotinoids (acetamiprid, thiacloprid).

- Di Bartolomeis *et al.* (2019) used the measure of 'acute insecticide toxicity loading' to assess the relative environmental load of neonicotinoids. This increased substantially (4- to 48-fold between 1992 and 2014) as a result of the combination of neonicotinoids' acute toxicity and environmental persistence. Such a significant increase contributes to declines in beneficial insect populations as well as insectivorous birds and other insect consumers.

- Goulson *et al.* (2018) calculated the toxic load on honeybees of insecticides applied to the 4.6 million hectares of arable farmland in Great Britain over the period 1990–2015, finding that it had increased 6-fold as a result of the increasing use of neonicotinoids from 1994 onwards which more than offset the effect of declining organophosphate use.

- Ihara and Matsuda (2018) examined detailed structures on molecules and receptors to identify the potential for research to deliver more selectivity.

- Krishna and Reddy (2020) reviewed a range of insecticides and reported that sulfoxaflor had a high degree of efficacy against a wide range of sap-feeding insects including those resistant to the neonicotinoids.

- Kumari *et al.* (2020) compared the effectiveness of different concentrations of imidacloprid with flupyradifurone and flonicamid for controlling pests (whitefly and leafhoppers) of okra. They concluded flupyradifurone was a better alternative to the neonicotinoids as it controlled nymph and egg stages owing to adult knockdown effects, and that it was 'highly effective against a wide range of sucking insects'.

- Liu *et al.* (2021b) assessed acute and chronic toxicity of sulfoxaflor in *Chironomus kiinensis* and found that sulfoxaflor elicited lower toxicity than traditional neonicotinoids but inhibited growth and emergence, and caused mitochondrial dysfunction and impaired energy metabolism.

- Matsuda *et al.* (2020) pointed to the complex interactions between neonicotinoids and receptors, so that different bee species can exhibit different effects. This makes extrapolation between species (e.g. honeybees, bumblebees and solitary bees) difficult.

- Pang *et al.* (2020) summarised the microbial degradation and biochemical mechanisms of neonicotinoids.

- Siviter *et al.* (2018, 2019b, 2020) showed that chronic exposure to sulfoxaflor, at dosages consistent with potential post-spray field exposure, has severe sublethal effects on bumblebee (*Bombus terrestris*) colonies. Field-based colonies that were exposed to sulfoxaflor during the early growth phase produced significantly fewer workers than unexposed controls, and ultimately produced fewer reproductive offspring, suggesting that direct or indirect effects on a small cohort may have cumulative long-term consequences for colony fitness. Sufoxaflor exposure at 5 parts per billion (the lowest exposure tested) reduced the number of eggs found within the microcolonies. The microcolony-based protocols used in this study could be a useful tool in European Food Safety Agency assessments of ecotoxicology. Combining sulfoxaflor exposure on bumblebee larvae with exposure to *Nosema bombi* found an additive, negative effect when larvae received both stressors in combination.

- Söftje *et al.* (2020) adapted the molecule of imidacloprid to fix itself through covalent bonding to the wood when used as a preservative, thereby reducing its propensity to leak into the environment.

- Zhang *et al.* (2021d) showed that circadian rhythm in *Spodoptera litura* larvae was important for determining insecticide sensitivity (imidacloprid).

Effectiveness and alternatives to neonicotinoid use

Overall use

Agricultural research continues on the efficacy of neonicotinoids on different applications: for instance for the control of termites in groundnut crops in India (Baloda *et al.* 2021, Nakrani and Sevak 2021), on improving availability of the clothianidin active agent (Liu *et al.* 2021c), improving effectiveness on tackling aphids on soybeans (Zhang *et al.* 2021e), extending to new pests such as chive maggots (Gul *et al.* 2021) and wood-boring pests (Sunamura *et al.* 2021), and selective use of a less toxic neonicotinoid (thiacloprid) to control aphids that had become resistant to other insecticides in pepper plant cultivations (Lin *et al.* 2021).

On the other hand, there is evidence that some uses are neither effective in absolute terms nor cost-effective from the farmer's point of view; also, that farmers are restricted in the choices they have in whether to use neonicotinoids in prophylactic treatments.

- Hladik *et al.* (2018b) contrasted the evidence that pollinators and aquatic insects seem to be especially susceptible to the effects of neonicotinoids with evidence that clear and consistent yield benefits from the use of neonicotinoids remain elusive for most crops. Decisions on neonicotinoid use should weigh crop yield benefits against the environmental impacts to non-target organisms and consider more environmentally benign alternatives.

- In terms of the general use of pesticides, Janssen and van Rijn (2021) modelled pest resurgence after chemical pesticide application and showed that pesticide applications will *increase* average pest densities throughout a growing season when effective natural enemies are present. Overall, pesticide applications did not reduce pest densities significantly when natural enemies were present, suggesting that pest control by natural enemies deserves more attention.

- Labrie *et al.* (2020) found that neonicotinoid seed treatments in field crops in Quebec were useful in fewer than 5% of cases. Given the very low level of pest-associated pressure and damage, they should not be used prophylactically.

- Mörtl *et al.* (2019a) indicated that the environmental loads by neonicotinoids on the basis of recommended dosages are practically the same in the case of seed coating and in spray or granule application. From this aspect, seed coating is not favourable for IPM as it does not allow application timing only to periods of pest population densities above the damage threshold, while it does not lead to reduced mass release either. Corresponding worldwide surface water contamination by neonicotinoids was also summarised.

- Mourtzinis *et al.* (2019) showed that the widespread use of neonicotinoid seed treatment on soybean seed yield seems to have had little benefit for most soybean producers.

Pesticide resistance

- Barman *et al.* (2021) discussed the molecular mechanisms underlying insecticide resistance: metabolic detoxification occurs because of gene amplification, overexpression or modification of the gene coding proteins of major detoxifying enzymes including cytochrome P450.

- Castellanos *et al.* (2019) reported imidacloprid resistance in the neotropical brown stink bug *Euschistus heros*, an important pest in soybean in South America; specifically on the selection and associated fitness costs.

- Datta *et al.* (2021) found the brown planthopper *Nilaparvala lugens* in China to have high levels of resistance to imidacloprid, thiamethoxam, dinotefuran and sulfoxaflor. In Bangladesh, high levels of resistance were also found to imidacloprid and thiamethoxam.

- In Turkey, Erdogan *et al.* (2021) found samples of greenhouse whitefly (*Trialeirodes vaporariorum*) populations exhibited up to 8.1-, 16- and 11.4-fold resistance to acetamiprid, imidacloprid and thiamethoxam respectively.

- Fujii *et al.* (2019) studied resistance in the brown planthopper in East Asia and Vietnam. Initially this was with imidacloprid, but this had spread to thiamethoxam and clothianidin, but not to dinotefuran and nitenpyram.

- Gong *et al*. (2021) looked at sensitivity of the aphid *Metopolophium dirhodum* in seven provinces in China and found resistance to thiamethoxam.

- Kaur and Kumar (2020) found that neonicotinoids (imidacloprid and thiamethoxam) resulted in an increase in the incidence of whitefly (*Bemisia tabaci*) while dinotefuran caused a decrease in incidence.

- Krishna and Reddy (2020) noted that several insect pests of Indian Bt cotton had potential for the development of resistance; and that imidacloprid, acetamiprid and thiamethoxam were not effective against the cotton leafhopper. In their investigation they concluded that novel neonicotinoids (nitepyram, dinotefuron and clothianidin) were more effective than the older neonicotinoids acetamiprid, imidacloprid and thiamethoxam.

- Li *et al.* (2021d) showed the effects of acetamiprid on reducing silkworm resistance against pathogens.

- Makoni (2020) found that the increased use of clothianidin in indoor mosquito control had already led to increased resistance in mosquitoes in Cameroon, generating concern that its usefulness may be short-lived.

- Munkhbayar *et al.* (2021) emphasised the importance of understanding the genotypes and phenotypes of target pest organisms when developing resistance management strategies. The cotton aphid (*Aphis gossypii*) in the major cotton planting region of China had developed multiple resistance to neonicotinoids (and pyrethroids).

- Priyadharshini *et al.* (2020) noted that reports of the brown planthopper (*Nilaparvata lugens*) collected from across Asia showed that its resistance factors to imidacloprid were 600- to 800-fold greater after a decade of indiscriminate use, and in China resistance had developed to thiamethoxam (resistance ratio of 13.0- to 36.7-fold in 2011). They concluded that resistance to neonicotinoids is one of the greatest challenges facing the scientific community.

- Saeed *et al.* (2018) found in Pakistan that there was very high resistance to acetamiprid (433-fold) and imidacloprid (173-fold) in the crop pest *Dysdercus koenigii.*

- Ullah *et al.* (2019) noted that the melon aphid *Aphis gossypii* (Hemiptera: Aphididae) is a cosmopolitan sap-sucking pest that infests plants of the Cucurbitaceae family worldwide. It has been reported to be resistant to neonicotinoid insecticides, with increased resistance against imidacloprid documented in China.

- In Brazil, a large survey of rice stinkbugs by Vieira *et al.* (2022) demonstrated thiamethoxam resistance and failure of control.

- Wang *et al.* (2021) looked at the genotype of the melon aphid (*Aphis gossypii*) from Chinese Shandong populations to determine levels of resistance to imidacloprid, acetamiprid and λ-cyalothrin and found significant upregulation of genes in populations with moderate resistance.

- The molecular basis for resistance to neonicotinoids in the whitefly *Bemisia tabaca* was investigated by Yang *et al.* (2021), focusing on the cytochrome P450 *CYP6CM1* and *CYP4C64* genes. Laboratory studies have shown resistance to thiamethoxam is associated with the overexpression of P450, and monitoring of field populations suggests the same gene may be involved in both imidacloprid and thiamethoxam resistance.

- Zhang *et al.* (2021e) looked at the effect that different concentrations of imidacloprid and thiamethoxam had on the development and reproduction of the soybean aphid *Aphis glycines*. They suggested that resistance can develop owing to exposure to low-lethal or sublethal concentrations that increase the reproduction rate.

Recent reviews of alternatives to the use of neonicotinoids

- Frank and Tooker (2020) argued that current use patterns may actually be creating more risks than benefits and concluded that neonicotinoids should only be used when they will improve economic returns for farmers rather than corporations, and when risks can be minimised. (This is in line with an earlier paper by Tooker *et al.* (2017) pointing to the blanket application of neonicotinoids through seed treatment as being contrary to IPM, increasing environmental loadings and resistance while delivering negligible benefits to farmers.)

- Furlan *et al.* (2021) provided a comprehensive review of the literature on the use of systemic insecticides in pest management, effects on crop yields and the development of pest resistance. A diverse range of pest management tactics is already available, all of which can achieve efficient pest control below the economic injury level while maintaining the productivity of the crops. The authors included examples of frameworks for a truly sustainable agriculture that relies mainly on natural ecosystem services instead of chemicals.

- Jactel *et al.* (2019) reviewed alternatives for each pest targeted by neonicotinoids (120 crops and 279 pest insects). An effective alternative to neonicotinoid use was available in 96% of the 2968 case studies analysed. In 78% of cases, at least one non-chemical alternative method could replace neonicotinoids, although further field studies were required for many non-chemical methods before they could be routinely used by farmers. The study identified the need to promote such methods through regulation and funding.

- McGrane and Noakes (2021) also highlighted the impact that over-reliance on a small group of insecticides is having on developing resistance of grain pests. They noted that large, mechanised grain farms, and zero tolerance of invertebrates in exports, has meant pest outbreaks are controlled on farms by the use of 'insurance sprays' owing to difficulties in predicting pest outbreaks.

- Novel methods of neonicotinoid applications are also being investigated. For example, Meng *et al.* (2021) reported the use of a (magnetic metal-organic framework) nano-composite as a delivery vehicle for imidacloprid. This method of delivery was found to increase the insecticidal activity of imidacloprid. In the case of green peach aphid, they note that neonicotinoids, sulfoximine, carbamates, organophosphates and synthetic pyrethroids are applied prophylactically which has created strong selection pressures and contributed to resistance. The use of phenotypic and genetic screening is used to identify resistant populations and for planning purposes. They concluded that IPM that reduces chemical use alongside resistant management strategies is essential for maintaining effectiveness of existing insecticides.

- An IPM strategy to control fall armyworm in Africa has been shown to be effective: Midega *et al.* (2018) showed high reductions (>80%) in larval abundance and damage, and higher yields (×2.7), in maize plots using a push–pull system of an inter-crop that repelled the moths and a border crop that attracted them.

- Overton *et al.* (2021) conducted a literature review of the effects of prophylactic chemical control (insecticides and miticides) on natural enemies of pests in the Australian grain industry and identified many gaps in knowledge about toxicity effects on key natural enemies of potential importance for IPM strategies. Neonicotinoids (imidacloprid, thiamethoxam, clothianidin) continue to be commonly applied as seed treatments but little research has looked at which natural enemies are affected from exposure to seed treatments. For Bt cotton in Australia, IPM has been shown – when used in conjunction with selective chemical control options- to result in higher gross margins than famers using conventional broad-spectrum insecticides and miticides.

Independence of advice

It has been pointed out (e.g. Tooker *et al.* 2017) that educational materials guiding the use of pesticides are often sponsored or co-created by pesticide manufacturers, raising potential conflicts of interest. They pointed to the failure to consider negative ecosystem impacts of neonicotinoids at two sponsored webinars from the American Society of Agronomy.

In summary, the latest scientific literature reinforces the messages conveyed in the EASAC (2015) and NASAC (2019) reports and adds to the evidence that the uses of neonicotinoids need to be reduced and pesticide use placed within the framework of IPM. Of particular note are the ecosystem effects well-documented by Yamamuro *et al.* (2019) and the demonstration by Straub *et al.* (2019) of the mechanisms through which neonicotinoids increase susceptibility to the *Varroa* mite (often referred to by pesticide-producing companies as the main cause of honeybee losses). The extent of environmental contamination into aquatic systems and in human food and water intakes has also become much clearer.

Annex 3 Developing alternatives to the original neonicotinoids

Since the first synthetic commercially available neonicotinoid, imidacloprid, was introduced to the market in 1991, the widespread use of neonicotinoids has led to the development of pest resistance (Brown *et al.* 2016; Veres *et al.* 2020; Furlan *et al.* 2021) while concerns about their environmental impacts have led to regulatory restriction. Such trends reinforce efforts to develop alternatives, and there are many potential candidates ready or in development, with 2076 neonicotinoid substances registered in China alone (Zhao *et al.* 2020).

In the European Union (EU), two such formulations (sulfoxaflor and flupyradifurone) are already registered and in use. However, evidence is emerging that these may be so called 'regrettable substitutions' where new products introduced to replace old environmentally damaging products turn out to be as harmful as the originals (Di Bartolomeis *et al.* 2019). In such cases, shortcomings in pesticide design, testing, risk assessment and registration processes (Maertens *et al.* 2021) mean that non-target and sublethal impacts are identified only after licensing (Siviter and Muth 2020). Currently available open-source literature on some of these 'new' neonicotinoids is summarised in this annex.

1 Identifying neonicotinoid analogues (IRAC Mode of Action classification system)

As a starting point for identifying neonicotinoid analogues, the Insecticide Resistance Action Committee (IRAC) pesticide Mode of Action classification system (IRAC 2021) was used. This system classifies pesticide agents with structural similarities – and therefore common modes of action – into groups *for the purposes of reducing insecticide resistance*. It includes 32 groups of insecticides, acaricides and biologics (Sparks *et al.* 2020). The neonicotinoids fall into group 4: the nicotinic acetylcholine receptor (nAChR) (competitive modulator) Mode of Action group.

Within this group IRAC have identified six sub-groups: (4A) neonicotinoids, (4B) nicotine, (4C) sulfoximines, (4D) butenolides, 4(E) mesoionics and (4F) pyridylidenes (IRAC 2021). Although they share the same method of toxicity, these active substances are different enough in structure, or mode of interaction with the target protein, that the chance of selection for cross-resistance is reduced (Sparks *et al.* 2020; IRAC 2021).

The neonicotinoids (4A) sub-group includes acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid and thiamethoxam. Of these, only dinotefuran and acetamiprid remain authorised for use in the EU. Regulatory approval for the use of dinotefuran as a biocidal product (type 18) was due to expire in May 2022 but has been extended until 2024 pending the outcome of the scientific review process.[27] Regulatory approval for acetamiprid has been renewed until 2033.[28] The French (and later Dutch) Governments requested EFSA to review recently published papers on human health and environmental impacts. EFSA have since stated that the evidence presented did not demonstrate a higher hazard to human health or the environment, but they did recommend an assessment of its endocrine disrupting properties, and the updating of the risk assessment to include consideration of the impacts of long-term exposure on bird reproduction, the sensitivity of worms and interspecies sensitivity of bees.[29]

The last four sub-groups (the sulfoximines, butenolides, mesoionics and pyridylidenes) have fluorine atoms in their design (Jeschke 2022). The active substances sulfoxaflor and flupyradifurone are included in the sulfoximine (4C) and (4D) butenolide sub-groups respectively. Both have been identified as candidates for replacing the restricted neonicotinoids, or in areas with high levels of pest resistance (Siviter and Muth 2020). Truflumezopyrim and flupyrimin fall within the mesoionic (4E) and pyridylidene (4F) sub-groups respectively.

Other recent neonicotinoids referenced in the literature are not yet listed by IRAC. These are sometimes referred to as 'fourth generation' neonicotinoids and include cycloxaprid, guadipyr, imidalothiz and paichongding (Thompson *et al.* 2020).

A brief overview is provided below of the substances listed by IRAC in the subclasses 4C, 4D, 4E and the newer 'fourth generation' neonicotinoid substances. The naturally occurring (*S*)-nicotine subclass (4B) has not been included within this review.

1.1 Sub-group 4C: sulfoximines

Sulfoxaflor is the only compound registered within the sulfoximine insecticide class (Babcock *et al.* 2010; Sparks *et al.* 2013). Launched in 2012 (Crossthwaite *et al.* 2017), it was the first of the fluorinated nAChR competitive modulators to be commercially available (Jeschke 2020). In 2020, it was registered in 81 countries around the world (Siviter *et al.* 2020) including the EU,[30] for use in major crops including cotton, leafy and fruiting vegetables, apples, soybeans and rice, citrus, cereals and grapes.[31] It is used as a seed treatment and foliar spray (Siviter *et al.* 2019b).

Like the neonicotinoids, sulfoxaflor is systemic in nature and acts on insect nicotinic receptors, although it is chemically

---

[27] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32021D1286&rid=14.

[28] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0113&from=FR.

[29] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2022.7031.

[30] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32015R1295&from=EN.

[31] https://www.corteva.com/content/dam/dpagco/corteva/global/corporate/general/files/active-ingredients/DF_Isoclast-Active-TechBulletin_LO7_2019.pdf.

distinct with a unique set of structure–activity relationships (Zhu *et al.* 2011; Sparks *et al.* 2013; Watson *et al.* 2021). These chemical differences mean that sulfoxaflor is effective against a wide range of sap-feeding insect pests, including aphids, leafhoppers, mealybugs, whiteflies, etc., that are resistant to other classes of insecticides including the original neonicotinoids (Babcock *et al.* 2010; Zhu *et al.* 2011; Longhurst *et al.* 2012; Sparks *et al.* 2013; Jeschke 2020), although reports of low levels of pest resistance are now beginning to emerge in the literature (Liao *et al.* 2017; Li *et al.* 2021e). Thanks to its high potency and low cross-resistance with other insecticides, sulfoxaflor is considered to be an alternative to, and even better than, some neonicotinoids (Li *et al.* 2021f). However, because of its similar mode of action, concerns have been raised that it may also have the same suite of environmental impacts, and its potential application over vast geographical areas led to sulfoxaflor (and the sulfoximine group) being ranked as one of the top emerging threats to pollinators (Brown *et al.* 2016). A range of non-target impacts have been observed (reviewed by Siviter and Muth 2020) across a broad range of insect groups.

Because sulfoxaflor is absorbed and systematically distributed throughout the plant, it can be present in plant pollen or nectar and so is available to foraging bees and other pollinating species. Although found in one study to be less toxic to *Apis mellifera, Bombus terrestris* and *Osmia bicornis* than imidacloprid, thiamethoxam and clothianidin (but much more toxic than acetamiprid and thiacloprid) (Azpiazu *et al.* 2021), the evidence available so far suggests that sulfoxaflor is toxic to bees at high concentrations, and at lower doses mortality may depend on interactions with other environmental variables (Siviter and Muth 2020). Linguadoca *et al.* (2021), for example, found in a laboratory study that field realistic, worst-case sulfoxaflor exposure increased bumblebee mortality and at sublethal concentrations negatively affected bee fecundity (but not survival).

Chronic exposure to sulfoxaflor, at dosages consistent with potential post-spray field exposure, has severe sublethal effects on bumblebee colonies, and may have comparable negative impacts on reproductive output as the neonicotinoids (Siviter *et al.* 2018, 2019b, 2020). The severity of impact seems to be species-specific, with *Osmia* bee species observed to be more sensitive than *Bombus terrestris* and *Apis mellifera* (Azpiazu *et al.* 2021). Although exposure does not seem to impair bee behaviour (Siviter *et al.* 2019b; Parkinson *et al.* 2020), the data on this are very limited.

Synergistic effects have also been recorded; even low doses of sulfoxaflor had negative effects when bees were simultaneously exposed to the fungicide (fluxapyroxad) (Azpiazu *et al.* 2021). Under semi-field conditions, Tambourini *et al.* (2021) found that sulfoxaflor reduced *Bombus terrestris* colony growth and size, and when applied in combination with the fungicide azoxystrobin reduced individual foraging performance.

There is much less research into the effects of sulfoxaflor in aquatic systems than terrestrial environments. According to Damasceno *et al.* (2021), the time required to degrade in sediment/aquatic systems can range between 37 and 88 days. Exposure of the green crab (*Carcinus maenas*) to sulfoxaflor led to decreases in detoxification capacity and increases in oxidative damage, and reductions in energy metabolism and feeding (Damasceno *et al.* 2021). Liu *et al.* (2021b) also found that exposure of *Chironomus kiinensis* to sulfoxaflor caused mitochondrial dysfunction and impaired energy metabolism, and inhibited growth and emergence.

Although approved for use in the EU in 2015, subsequent assessment by EFSA concluded there is a high (acute) risk to honeybees and bumblebees from sulfoxaflor in field and non-permanent structures/greenhouses (for treated crops except after flowering, weeds and field margins), and insufficient data available to finalise the assessment of the chronic risks for bumblebees, or the acute and chronic risk to solitary bees (EFSA 2020). As a result, the European Commission has restricted the outside use of sulfoxaflor (chapter 2.4).

1.2 Sub-group 4D: butenolides

Flupyradifurone is the only insecticide listed in the IRAC butenolide sub-group. It is based on the molecular structure of the compound stemofoline from the plant *Stemona japonica* (Bell *et al.* 2019). Although it has the same mode of action as the neonicotinoids, and a chemical structure partly overlapping with imidacloprid, nitenpyram, acetamiprid and thiacloprid, it has structural differences involving the pharmacophore (Nauen *et al.* 2014).

Flupyradifurone is another of the fluorinated nAChR competitive modulators (Jeschke 2020), and was introduced to the market as a tool for IPM (Nauen *et al.* 2014; Haas *et al.* 2021). First registered in 2014 in Guatemala and Honduras (Nauen *et al.* 2014), then in the USA and EU in 2015, it is now available globally and is used as a spray, drip irrigation, soil treatment and seed treatment (Tosi *et al.* 2021). As a relatively new insecticide, few pest species have developed resistance and so it is used to manage a variety of pests including aphids, psyllids, scales, leafhoppers, mealy bugs and whiteflies which are vectors of viruses such as the tomato yellow leaf curl virus and cucurbit yellow stunting disorder virus (Haas *et al.* 2021). It is used on a wide diversity of crops including vegetables, potatoes, pome fruits, grapes, citrus, cotton, soybean, coffee, hops and ornamentals (Tosi *et al.* 2021).

Flupyradifurone is relatively persistent in the environment, lasting in soil for several months (Siviter and Muth 2020). It has been labelled 'bee-safe' (Haas *et al.* 2021), as differences in structural chemistry to the neonicotinoids have led to the suggestion that it may be around 700-fold less toxic than the *N*-nitroguinidine neonicotinoids because bees are more efficient at its detoxification, thereby reducing its bioaccumulation (Haas *et al.* 2021; Tosi *et al.* 2021).

In a recent review, Siviter and Muth (2020) found exposure to flupyradifurone had a significant negative effect on the mortality, fitness and behaviour of beneficial insects (pollinators and predatory insects) although the severity of impact seems to be species-specific and seasonally and age-dependent (Tosi and Nieh 2019).

Most of the literature available looks at impacts on honeybees. Exposure has been shown to reduce honeybee survival, flight success, thermoregulation and food consumption (Tong *et al.* 2019). Acute exposure at high doses impairs bee taste, cognition and motor abilities, and reduces foraging onset and bee survival (Hesselbach and Scheiner 2019; Hesselbach *et al.* 2020). Long-term exposure to (chronic) low, field realistic levels can lead to reduced bee survival and food consumption over longer periods, as well as abnormal behaviours such as reduced olfactory learning, motion coordination deficits, hyperactivity and apathy over the short term (Naggar and Baer 2019). Tosi *et al.* (2021) also found that, under laboratory conditions, exposure to sublethal doses significantly reduced survival of honeybees (larvae and adult bees) and altered the expression of several immune and detoxification genes. Evidence of synergistic effects has also been observed. Tosi and Nieh (2019), for example, found toxicity was amplified when flupyradifurone was used in combination with the fungicide propiconoazole.

Fluropyradifurone is persistent in soil, with dissipation from surface soils often exceeding 1 year in field studies. It also has the potential to reach the aquatic environment through runoff, erosion and leaching to groundwater (Giorio *et al.* 2021). These attributes have led to calls in the EU for its authorisation to be reviewed (chapter 2.4).

1.3 Sub-group 4E: mesoionics

Triflumezopyrim[32] is the first member of a new class of insecticides (the mesoionics). It has a similar mode of action to the other fluorinated neonicotinoids in targeting insect nAChRs but acts instead to inhibit the orthosteric binding site of the nAChR (Cordova *et al.* 2016; Onazaki *et al.* 2017; Jeshcke 2020, 2022; Lu *et al.* 2022), making the insects lethargic and poisoned (Zhang *et al.* 2020). It is not currently registered for use in the USA or EU.

Triflumezopyrim is also a systemic insecticide. According to the manufacturer (Corteva) it is applied as a foliar spray and has a 'favourable environmental profile with low toxicity to birds, fish, aquatic invertebrates, earthworms and bees … and so is an excellent fit in IPM of rice ecosystems' (Corteva 2019). It is not recommended that it is used in conjunction with imidacloprid and thiacloprid as they share similar nAChR targets (Lu *et al.* 2022).

It has been used to control leafhopper and planthopper populations in rice in Malaysia, India, China, Philippines and Korea (Li *et al.* 2019) and, although little information is available in the published literature, has been reported to have minimal side effects on beneficial insects (Zhu *et al.* 2020). Wang *et al.* (2020d), however, observed 100% mortality when *Solenopsis invicta* ants were given 10 μg/ml in sugar water for 2 weeks, leading the authors to conclude that triflumezopyrim could be a potentially useful bait treatment for *S. invicta* control.

Much less information is available in the open literature about this substance, although the FAO (2017) reported a half-life in various soils ranging from 53 to 133 days, and in (dark) water a half-life of 23–41 days.

1.4 Sub-group 4E: pyridylidenes

Flupyrimin is the most recent of the fluorinated neonicotinoid substances to have been developed (Jeschke 2022), and is the only active substance listed in the sub-group pyridylidenes. Very little information is available about this substance. Flupyrimin acts on insect nAChRs as an antagonist in a different way to the (other) neonicotinoids (Onazaki *et al.* 2017), and is more potent to rice pests (such as brown planthopper and rice stem borer) than imidacloprid and other standard insecticides, including those that have developed resistance to existing insecticides. It is claimed to be harmless to pollinators (*Apis, Bombus* and *Osmia* species) and to be safe for mammals (Onazaki *et al.* 2017). A new compound, so far flupyrimin has been licensed for control of rice pests in Southeast Asia, Japan, South Korea, Taiwan, India and China.

2 Other neonicotinoid analogues from the open literature

Four other substances were also referenced in the open literature (cycloxaprid, paichongding, imidaclothiz and guidapyr), although much less information is available about their chemistry and/or non-target impacts. For reasons that are unclear, they are not included within the IRAC classification scheme although all are registered for use in China.

2.1 Cycloxaprid

Cycloxaprid is a novel synthesised neonicotinoid product developed in 2008. First named in China in 2011 (Zhang *et al.* 2018c) it was registered in China in 2015 (Singh and Leppanen 2020) and is different to the other neonicotinoids because it has an NO_2 group in the *cis*-configuration, while the other commercially available neonicotinoids have NO_2 groups in a *trans*-configuration (Pan *et al.* 2014). It serves as a slow-release reservoir for (nitromethylene)imidazole with selective activity for insect nAChRs (Pan *et al.* 2014).

Although its precise mode of action remains unclear, cycloxaprid was designed to control a wide range of imidacloprid- (and other neonic-)resistant sap-feeding and biting insect pests (Ciu *et al.* 2018; Zhang *et al.* 2018c; Qi *et al.* 2020). It is especially effective against imidacloprid-resistant pests, showing a 50-fold higher activity against the brown planthopper than imidacloprid (Ciu *et al.* 2016).

A systematic review of the published literature on the target and non-target effects of cycloxaprid found very few studies looking at non-target effects, with data only available for five non-target species (*Apis mellifera*, *Chrysoperia sinica*, *Harmonia axyridis*, *Daphnia magna* and *Eisenia fetida*) (Singh and Leppanen 2020). Zhang *et al.* (2022) found surface treatment of cycloxaprid caused high mortality of *Solenopsis invicta* workers. Sublethal effects such as gene expression, enzyme activity, reproduction and development, and behaviour or morphology were also identified (Singh and Leppanen 2020).

---

[32] Detailed information can be found at http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report2017/5.38_TRIFLUMEZOPYRIM__303_.pdf

2.2 Paichongding

Paichongding is a novel *cis*-nitromethylene neonicotinoid insecticide (Cai *et al.* 2016). It was developed in China in 2008 and, although not fully registered until 2017, in 2009 1000 tonnes had reportedly been sprayed over 3.3 million hectares (Zhou *et al.* 2018). It is applied to a large variety of crops including fruit trees, wheat, soybean, vegetables, paddy rice and corn (Qin *et al.* 2013), and has been promoted as having low mammalian toxicity, high insecticidal activities and broad-spectrum action against insect pest species (Qin *et al.* 2013). The half-life of paichongding in anoxic, flooded soils from China was estimated to be between 0.18 and 3.15 days, and in the laboratory in anaerobic flooded soils to be short (<1 to 3.7 days) (Giorio *et al.* 2021). A risk assessment was completed in 2018 in China and concluded that risks to bees were acceptable (Tan *et al.* 2019) (although the risk assessment itself has not been published).

2.3 Imidclothiz

Imidclothiz is a nitroguinadine thiazole neonicotinoid pesticide registered for use in China (Thompson *et al.* 2020; Ma *et al.* 2021) for control of sucking and biting insects including aphids, whiteflies, planthoppers, leafhoppers, beetles and Lepidoptera in wheat, rice, fruit, vegetables and tea plant (Wu *et al.* 2010; Ma *et al.* 2021). Degradation in soil is dependent on soil type and oxygen conditions. In greenhouses and the open field it has a half-life in soil of 2.7–3.7 days (Tang *et al.* 2021b), while in sterilised soils it had a half-life of 173.3 days (Ma *et al.* 2021), leading to the conclusion that imidaclothiz does not degrade easily in water and soil environments under natural conditions. In chemical structure it is similar to imidacloprid, thiamethoxam and clothianidin. There is little information available in the open-access literature about its toxicity; however, Ma *et al.* (2021) report that imidaclothiz has low toxicity to *Daphnia magna* and *Danio rerio* but high acute toxicity to *Apis mellifera*, but that two of its metabolites were much more toxic. 'M149', for example, had an acute toxicity to *D. magna* 79 times higher than the parent compound and a chronic toxicity of 48 times. In fish it was 95 times higher and 77 times respectively; and in green algae 38 and 26 times higher (Ma *et al.* 2021).

2.4 Guadipyr

Guadipyr was developed in 2008 and registered in China in 2017. It was designed by combining the pharmacophores of neonicotinoids and semicarbazone (Yang *et al.* 2018). Like the other neonicotinoids, it targets the nAChR but has a negative carbon alkyl chain containing an imine substituent (Yang *et al.* 2018). It is effective against aphids and other sap-feeding insects that are resistant to imidacloprid and is reportedly effective against cotton bollworms and beet armyworms.[33] In a laboratory study looking at the effects on *Daphnia magna*, low acute toxicity was observed but development and reproductive success were found to be affected at sublethal concentrations (Qi *et al.* 2013). Giorio *et al.* (2021) reported a half-life in paddy water of 0.22–0.37 days.

---

[33] https://news.agropages.com/News/NewsDetail—21294.htm.

References

AASSA (2022). Risk Assessment of Neonicotinoids in the Asia-Pacific Region. Seoul, Korea: Association of Academies and Societies of Science in Asia. http://www.aassa.asia.

Abafe, O.A. and Chokwe, T. (2021). Determination and dietary risk assessment of neonicotinoid and insect growth regulators in honey. *Journal of Environmental Exposure Assessment* **1** (1), 3.

Abdollahdokht, D. *et al.* (2022). Conventional agrochemicals towards nano-biopesticides: an overview on recent advances. *Chemical and Biological Technologies in Agriculture* **9**, 13.

Al-Awar, M.S.A. *et al.* (2021). Effect of imidacloprid on the testicular activity and endocrine disruptive and its impact on fertility in male rats. *Indian Journal of Forensic Medicine & Toxicology* **15** (3), 4695.

Alsafran, M. *et al.* (2022). Neonicotinoid insecticides in the environment: a critical review of their distribution, transport, fate, and toxic effects. *Journal of Environmental Chemical Engineering* **10** (5), 108485.

Alvarez, R. (2022). Comparing productivity of organic and conventional farming systems: a quantitative review. *Archives of Agronomy and Soil Science* **68** (14), 1947–1958.

Anai, A. and Hisada, A. (2021). Urinary neonicotinoids level among pregnant women in Japan. *International Journal of Hygiene and Environmental Health* **236**, 113797.

Anjos, C.S. *et al.* (2021). An overview of neonicotinoids: biotransformation and biodegradation by microbiological processes. *Environmental Science and Pollution Research* **28**, 37082–37109.

Annoscia, D. *et al.* (2020). Neonicotinoid clothianidin reduces honey bee immune response and contributes to *Varroa* mite proliferation. *Nature Communications* **11**, 5887.

Anstett, M.C., Leon de Treveret, M. and Louapre, P. (2019). La pollinisation du cassis: Etat des lieux dans un contexte de changements Anthropiques. *Revue scientific que Bourgogne-Franche-Comte Nature* **29**, 194–205.

Aricam, Y.E. *et al.* (2019). The sub-chronic effects of acetamiprid on the global DNA methylation levels in Sprague-Dawley rat brain and liver. *Istanbul Journal of Pharmacy* **49** (3), 167–172.

Assad, Y.O.H. *et al.* (2017). Determination of insecticide residues in okra fruit wash using mosquito larvae (*Anopheles arabiensis* Patton) as a bioindicator. *Agricultural Research Journal* **54** (3), 373–379.

Azpiazu, C. *et al.* (2021). Toxicity of the insecticide sulfoxaflor alone and in combination with the fungicide fluxapyroxad in three bee species. *Scientific Reports* **11**, 682.

Babcock, J. *et al.* (2010). Biological characterisation of sulfoxaflor, a novel insecticide. *Pest Management Science* **67** (3), 328–334.

Baloda, A. *et al.* (2021). Efficacy of insecticides as standing treatment against white grubs in groundnut crop. *Journal of Entomology and Zoology Studies* **9** (2), 973–975.

Barman, M. *et al.* (2021). Effect of neonicotinoids on bacterial symbionts and insecticide-resistant gene in whitefly, *Bemisia tabaci*. *Insects* **12** (8), 742.

Barmentlo, S.H. *et al.* (2019). Environmental levels of neonicotinoids reduce prey consumption, mobility and emergence of the damselfly *Ischnura elegans*. *Journal of Applied Ecology* **56**, 2034–2044.

Barzman, M. *et al.* (2015). Eight principles of integrated pest management. *Agronomy for Sustainable Development* **35** (4), 1199–1215.

Bass, C. *et al.* (2015). The global status of insect resistance to neonicotinoid insecticides. *Pesticide Biochemistry and Physiology* **121**, 78–87.

Becker, J.M. *et al.* (2020). Pesticide pollution in freshwater paves the way for schistosomiasis transmission. *Scientific Reports* **10**, 3650.

Bell, H. *et al.* (2019). The novel butenolide pesticide flupyradifuone does not alter responsiveness to sucrose at either acute or chronic short-term field-realistic doses in the honey bee, *Apis mellifera*. *Pest Management Science* **76** (1), 111–117.

Berheim, E.L. *et al.* (2019). Effects of neonicotinoid insecticides on physiology and reproductive characteristics of captive female and fawn white-tailed deer. *Scientific Reports* **9**, 4534.

Bernardes, R.C. *et al.* (2017). Azadirachtin-induced antifeeding in Neotropical stingless bees. *Apidologie* **48**, 275–285.

Bijleved van Lexmond, M. *et al.* (2015). Worldwide integrated assessment on systemic pesticides; global collapse of the entomofauna exploring the role of systemic insecticides. *Environment Science Pollution Research* **22**, 1–4.

Blanton, A.G. and Peterson, B.F. (2020). Symbiont-mediated insecticide detoxification as an emerging problem in insect pests. *Frontiers in Microbiology* **11**, 547108.

Bonmatin, J.-M. *et al.* (2015). Environmental fate and exposure; neonicotinoids and fipronil. *Environmental Science and Pollution Research* **22**, 35–67.

Bonmatin, J.-M. *et al.* (2019). A survey and risk assessment of neonicotinoids in water, soil and sediments of Belize. *Environmental Pollution* **249**, 949–958.

Borsuah, J.F. *et al.* (2020). Literature review: global neonicotinoid insecticide occurrence in aquatic environments. *Water* **12** (12), 3388.

Bowler, D. *et al.* (2019). Long-term declines of European insectivorous bird populations and potential causes. *Conservation Biology* **33** (5), 1120–1130.

Breitenmoser, S. *et al.* (2022). Intercropping winter oilseed rape (*Brassica napus* L.) has the potential to lessen the impact of the insect pest complex. *Agronomy* **12**, 723.

Brewer, M.J. and Goodell, P.B. (2012). Approaches and incentives to implement integrated pest management that addresses regional and environmental issues. *Annual Review of Entomology* **57**, 41–59.

Brown, M. *et al.* (2016). A horizon scan of future threats and opportunities for pollinators and pollination. *PeerJ.* **4**, e2249.

Brühl, C.A. and Zaller, J.G. (2019). Biodiversity decline as a consequence of an inappropriate environmental risk assessment of pesticides. *Frontiers in Environmental Science* **7**, 177.

Buckwell, A. *et al.* (2020). Crop Protection & the EU Food System. Where are they going? Brussels: RISE Foundation.

Bueno, A.F. *et al.* (2001). Effects of integrated pest management, biological control and prophylactic use of insecticides on the management and sustainability of soybean. *Crop Protection* **30**, 937e945.

Burke, A.P. (2016). *A Neurodevelopmental Study of Mice following In Utero and Early Postnatal Exposure to Imidacloprid a Neonicotinoid Pesticide*. Toronto, Canada: Department of Pharmaceutical Sciences, University of Toronto.

Burtscher-Schaden, H. (2022). HRI 1: A Risk Indicator to Promote Toxic Pesticides? GLOBAL 2000. http://www.global2000.at.

Busse, M. *et al.* (2021). How farmers think about insects: perceptions of biodiversity, biodiversity loss and attitudes towards insect-friendly farming practices. *Biodiversity and Conservation* **30** (11), 3045–3066.

Cai, Z. *et al.* (2016). Effects of the novel cis-nitromethylene neonicotinoid insecticide Paichongding on enzyme activities and micro-organisms in yellow loam and Huangshi soils. *Environmental Science and Pollution Research* **23** (8), 7786–7793.

Calvo-Agudo, M. *et al.* (2019). Neonicotinoids in excretion product of phloem-feeding insects kill beneficial insects. *Proceedings of the National Academy of Sciences of the USA* **116** (34), 16817–16822.

Calvo-Agudo, M. *et al.* (2021). Neonicotinoids from coated seeds toxic for honeydew-feeding biological control agents. *Environmental Pollution* **289**, 117813.

Castellanos, N.L. *et al.* (2019). Imidacloprid resistance in the neotropical brown stink bug *Euschistus heros*: selection and fitness costs. *Journal of Pest Science* **2** (92), 847–860.

Cavallaro, M.C. *et al.* (2019). Neonicotinoids and other agricultural stressors collectively modify aquatic insect communities. *Chemosphere* **226**, 945–955.

Cech, R., Leisch, F. and Zaller, J.G. (2022). Pesticide use and associated greenhouse gas emissions in sugar beet, apples, and viticulture in Austria from 2000 to 2019. *Agriculture* **12**, 879.

Cech, R. *et al.* (2023). Pesticide drift mitigation measures appear to reduce contamination of non-agricultural areas, but hazards to humans and the environment remain. *Science of the Total Environment* **854**, 158814.

Chakrabarti, P. *et al.* (2020). Field rates of Sivanto™ (flupyradifurone) and Transform® (sulfoxaflor) increase oxidative stress and induce apoptosis in honey bees (*Apis mellifera* L.). *PLoS ONE* **15** (5), e0233033.

Chen, Y. *et al.* (2019). Ecological risk assessment of the increasing use of the neonicotinoid insecticides along the east coast of China. *Environment International* **127**, 550–557.

Chen, D. *et al.* (2020a). Dietary exposure to neonicotinoid insecticides and health risks in the Chinese general population through two consecutive total diet studies. *Environment International* **135**, 105399.

Chen, D. *et al.* (2020b). Nationwide biomonitoring of neonicotinoid insecticides in breast milk and health risk assessment to nursing infants in the Chinese population. *Journal of Agriculture Food Chemistry* **68**, 13906–13915.

Chen, Y. *et al.* (2022). High spatial resolved cropland coverage and cultivation category determine neonicotinoid distribution in agricultural soil at the provincial scale. *Journal of Hazardous Materials* **430**, 128476.

Cheng, Y. *et al.* (2018). A semi-field study to evaluate effects of sulfoxaflor on honey bee (*Apis mellifera*). *Bulletin of Insectology* **71** (2), 225–233.

Chow, R. *et al.* (2022). Seasonal drivers and risks of aquatic pesticide pollution in drought and post-drought conditions in three Mediterranean watersheds. *Science of the Total Environment* **858** (2), 159784.

Cimino, A.M. *et al.* (2017). Effects of neonicotinoid pesticide exposure on human health: a systematic review. *Environmental Health Perspectives* **125**, 155–162.

Ciu, L. *et al.* (2016). Cycloxaprid: a novel *cis*-nitrimethylene neonicotinoid insecticide to control imidacloprid-resistant cotton aphid (*Aphis gossypii*). *Pesticide Biochemistry and Physiology* **132**, 96–101.

Ciu, L. *et al.* (2018). Sublethal effects of the novel cis-nitromethylene neonicotinoids cycloxaprid on the cotton aphid (*Aphis gossypii*) Glover (Hemiptera: Aphididae). *Nature Scientific Reports* **8**, 8915.

Colin, T. *et al.* (2020). The miticide thymol in combination with trace levels of the neonicotinoid imidacloprid reduces visual learning performance in honey bees (*Apis mellifera*). *Apidologie* **51**, 499–509.

CORDIS (2016). Final Report Summary - C-IPM (Coordinated Integrated Pest Management in Europe). https://cordis.europa.eu/project/id/618110/reporting.

Cordova, D. *et al.* (2016). Mode of action of triflumezopyrim: a novel mesoionic insecticide which inhibits the nicotinic acetylocholine receptor. *Insect Biochemistry and Molecular Biology* **74**, 32–41.

Corteva (2019). *Pyraxalt active Technical Bulletin*. Corteva Agriscience.

Costas-Ferreira, C. and Faro, L.R.F. (2021). Neurotoxic effects of neonicotinoids on mammals: what is there beyond the activation of nicotinic acetylcholine receptors? A systematic review. *International Journal of Molecular Science* **22** (16), 8413.

Crossthwaite, A. *et al.* (2017). The invertebrate pharmacology of insecticides acting at nicotinic acetylcholine receptors. *Journal of Pesticide Science* **42** (3), 67–83.

Craddock, H.A. *et al.* (2019). Trends in neonicotinoid pesticide residues in food and water in the United States, 1999–2015. *Environmental Health* **18** (1), 7.

Crall, J.D. *et al.* (2018). Neonicotinoid exposure disrupts bumblebee nest behavior, social networks, and thermoregulation. *Science* **362** (6415), 683–686.

Curchod, L. *et al.* (2020). Temporal variation of pesticide mixtures in rivers of three agricultural watersheds during a major drought in the Western Cape, South Africa. *Water Research X*, **6**, 100039. https://www.sciencedirect.com/science/article/pii/S2589914719300751.

Dainese, M. *et al.* (2019). A global synthesis reveals biodiversity-mediated benefits for crop production. *Science Advances* **5**, eaax0121.

Damasceno, J.M. *et al.* (2021). Exposure to the insecticide sulfoxaflor affects behaviour and biomarkers of responses of *Carcinus maenas* (Crustacea: Decapoda). *Biology* **10** (12), 1234.

Dara, S. (2019). The new integrated pest management paradigm for the modern age. *Journal of Integrated Pest Management* **10** (1), 12.

Datta, J. *et al.* (2021). Current resistance status of the brown planthopper *Nilaparvata lugens* (Stål) to commonly used insecticides in China and Bangladesh. *Crop Protection* **150**, 105789.

Decio, P. *et al.* (2021). Thiamethoxam exposure deregulates short *ORF* gene expression in the honey bee and compromises immune response to bacteria. *Scientific Reports* **11**, 1489.

Deguine J.-P. *et al.* (2021). Integrated pest management: good intentions, hard realities. A review. *Agronomy for Sustainable Development* **41**, 38.

De Lima, C.S. *et al.* (2017). Comparative toxicity of imidacloprid and thiacloprid to different species of soil invertebrates. *Ecotoxicology* **26**, 555–564.

De Lima, C.S. *et al.* (2018). Assessing the toxicity of thiamethoxam, in natural LUFA 2.2 soil, through three generations of *Folsomia candida*. *Ecotoxicology* **27**, 764–771.

De Lima, C.S. *et al.* (2020). Toxicity in neonicotinoids to *Folsima candida* and *Eisenia andrei*. *Environmental Toxicology and Chemistry* **39**, 548–555.

De Lima, C.S. *et al.* (2021). Bringing ecology into toxicology: life-cycle toxicity of two neonicotinoids to four different species of springtails in LUFA 2.2 natural soil. *Chemosphere* **263**, 128245.

Deutsch, C.A. *et al.* (2018). Increase in crop losses to insect pests in a warming climate. *Science* **361** (6405), 916–919.

Devi, S., Diksha, D. and Singh, S.J. (2021). Pesticides use in plant protection with respect to honeybees: a review. *Pharma Innovation* **10** (7), 156–166.

Di Bartolomeis, M. *et al.* (2019). An assessment of acute insecticide toxicity loading (AITL) of chemical pesticides used on agricultural land in the United States. *PLoS ONE* **14** (8), e0220029.

Dicks, L. *et al.* (2021). A global assessment of drivers and risks associated with pollinator decline. *Nature Ecology & Evolution* **5**, 1453–1461.

Duchet-Annez, M., Denis, C. and Anstett, M.C. (2022). Projet Cassis: Approche pluridisciplinaire pour des mesures agro-ecologiques. *Revue scientifique Bourgogne-Franche-Comte Nature* **35**, 268–276.

EASAC (2015). Ecosystem services, agriculture and neonicotinoids. Halle (Saale), Germany: The German National Academy of Sciences Leopoldina. https://easac.eu/publications/details/ecosystem-services-agriculture-and-neonicotinoids/

EASAC (2022). Regenerative agriculture in Europe. Halle (Saale), Germany: The German National Academy of Sciences Leopoldina. https://easac.eu/publications/details/regenerative-agriculture-in-europe/.

EC (2009). Sustainable Use of Pesticides Directive (2009/128/EC).

EC (2016). REFIT - Evaluation of the EU legislation on plant protection products and pesticides residues. https://food.ec.europa.eu/plants/pesticides/refit_en.

EC (2017). Member State National Action Plans and on progress in the implementation of Directive 2009/128/EC on the sustainable use of pesticides. COM(2017) 587 final.

EC (2018a). Implementing Regulations 2018/784, 2018/785, and 2018/786 on the conditions of approval of the active substances imidacloprid, clothianidin and thiamethoxam respectively.

EC (2018b). Commission notice concerning a list of potentially low-risk active substances approved for use in plant protection (2018/C 265/02).

EC (2019). Document 32019R1381.Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain.

EC (2020). A Farm to Fork Strategy for a fair, healthy and environmentally-friendly food system. COM (2020) 381.

EC (2021). Proposal for a Regulation on statistics on agricultural input and output and repealing Regulations (EC) No 1165/2008, (EC) No 543/2009, (EC) No 1185/2009 and Council Directive 96/16/EC.

EC (2022a). Proposal on the sustainable use of plant protection products and repealing Directive 2009/128/EC. https://corporateeurope.org/sites/default/files/2022–03/202201%20Draft%20SUP%20ISC%20draft.pdf

EC (2022b). European Commission, Directorate General for Health and Food Safety, Feijao, C. *et al*. Development of future scenarios for sustainable pesticide use and achievement of pesticide-use and risk-reduction targets announced in the Farm to Fork and Biodiversity Strategies by 2030, final report, 2022.

EC (2022c). Supporting farmers to reduce the use of chemical pesticides with the CAP. Factsheet.

ECA (2020). Sustainable use of plant protection products: limited progress in measuring and reducing risks. European Court of Auditors.

EFSA (2016). Conclusion on the peer review of the pesticide risk assessment of the active substance flupyradifurone. *EFSA Journal* **13** (2), 4020.

EFSA (2017). Draft Scientific Opinion addressing the state of the science on risk assessment of plant protection products for in-soil organisms. *EFSA Supporting Publication*: EN-1164.

EFSA (2020). Peer review of the pesticide risk assessment for the active substance sulfoxaflor in light of confirmatory data submitted. *EFSA Journal* **18** (3).

EFSA (2022a). Statement on the active substance flupyradifurone. *EFSA Journal* **20** (1), 7030.

EFSA (2022b), Development of a roadmap for action on new approach methodologies in risk assessment. *EFSA Journal* **19** (6), EN-7341.

EFSA (2022c). The 2020 European Union report on pesticide residues in food. *EFSA Journal* **20** (1), 7215.

EFSA (2022d). Theme (concept) paper – building a European partnership for next generation, systems-based environmental risk assessment (PERA). *EFSA Journal* **19** (5), e200503.

EFSA Scientific Committee (2016). Recovery in environmental risk assessments at EFSA. *EFSA Journal* **14** (2), 4313–4385.

Emery, S.E. *et al.* (2021). The potential of intercropping for multifunctional crop protection in oilseed rape (*Brassica napus* L.). *Frontiers in Agronomy* **3**, 782686.

Eng, M.L., Stutchbury, J.M. and Morrissey, C.A. (2019). A neonicotinoid insecticide reduces fueling and delays migration in songbirds. *Science* **365** (6458), 1177–1180.

Epstein, Y. (2021). EU Court to rule on banned pesticide use. *Science* **373** (6552), 290.

Epstein, Y. *et al.* (2022). What is an emergency? Neonicotinoids and emergency situations in plant protection in the EU. *Ambio* **51**, 1764–1771.

Erdogan, C. *et al.* (2021). Detection of resistance to pyrethroid and neonicotinoid insecticides in the greenhouse whitefly. *Crop Protection* **146**, 105661.

Ewere, E.E. *et al.* (2021). Impacts of neonicotinoids on molluscs: what we know and what we need to know. *Toxics* **9** (2), 21.

FAO (2017). Pesticide Residues in Food 2017. Plant Production and Protection Paper 233. Rome: FAO.

Farkas, A. *et al.* (2022). Physiological and metabolic alterations induced by commercial neonicotinoid formulations in *Daphnia magna*. *Ecotoxicology* **31**, 415–424.

Filho, F.H. *et al.* (2020). Drones: innovative technology for use in precision pest management. *Journal of Economic Entomology* **113**, 1–25.

Flores, J.M. *et al.* (2021). A three-year large-scale study on the risk of honey bee colony exposure to blooming sunflowers grown from seeds treated with thiamethoxam and clothianidin neonicotinoids. *Chemosphere* **262**, 127735.

Frank, S.D. and Tooker, J.F. (2020). Neonicotinoids pose undocumented threats to food webs. *Proceedings of the National Academy Of Sciences of the USA* **117** (37), 22609–22613.

Fujii, T. *et al.* (2019). Long-term field insecticide susceptibility data and laboratory experiments reveal evidence for cross resistance to other neonicotinoids in the imidacloprid-resistant brown planthopper *Nilaparvata lugens*. *Pest Management Science* **76** (2), 480–486.

Furlan, L. and Kreutzweiser, D. (2015). Alternatives to neonicotinoid insecticides for pest control: case studies in agriculture and forestry. *Environmental Science Pollution Research* **22**, 135–147.

Furlan, L. *et al.* (2021). An update of the Worldwide Integrated Assessment (WIA) on systemic insecticides. Part 3: alternatives to systemic insecticides. *Environmental Science and Pollution Research* **28**, 11798–11820.

Gao, J. *et al.* (2020). Physiological analysis and transcriptome analysis of Asian honey bee (*Apis cerana cerana*) in response to sublethal neonicotinoid imidacloprid. *Insects* **11** (11), 753.

Gardarin, A. *et al.* (2018). Understanding plant–arthropod interactions in multitrophic communities to improve conservation biological control: useful traits and metrics. *Journal of Pest Science* **91** (3), 943–955.

Garthwaite, D. *et al.* (2015). Collection of pesticide application data in view of performing Environmental Risk Assessments for pesticides. *EFSA Supporting Publications* **12** (7), 846E.

Gateuille, D. and Naffrechoux, E. (2022). Transport of persistent organic pollutants: another effect of microplastic pollution? *WIREs Water* e1600.

Ge, J. *et al.* (2018). Sub-lethal effects of six neonicotinoids on avoidance behavior and reproduction of earthworms (*Eisenia fetida*). *Ecotoxicology and Environmental Safety* **162**, 423–429.

Ghayyar, S. *et al.* (2020). A comparative study on the effects of selected pesticides on hemato-biochemistry and tissue histology of freshwater fish *Cirrhinus mrigala*. *Saudi Journal of Biological Sciences* **28** (1), 603–611.

Gill, P. *et al.* (2021). Assessment of neonicotinoid insecticide imidacloprid LC50 and their toxicity parameters against earthworm (*Eisenia fetida*). *Research Square*. Preprint available at https://doi.org/10.21203/rs.3.rs-587464/v1.

Giorio, C. *et al.* (2021). An update of the Worldwide Integrated Assessment (WIA) on systemic insecticides. Part 1: new molecules, metabolism, fate and transport. *Environmental Science Pollution Research* **28**, 11716–11748.

Girolami, V. *et al.* (2022). Effect of repeated intakes of a neonicotinoid insecticide on the foraging behaviours of *Apis mellifera* in field trials. *Environmental Science and Pollution Research* https://doi.org/10.1007/s11356-022-22977-y.

Giunti, G. *et al.* (2022). Non-target effects of essential oil-based biopesticides for crop protection: impact on natural enemies, pollinators, and soil invertebrates. *Biological Control* https://www.sciencedirect.com/science/article/abs/pii/S1049964422002365?via%3Dihub.

Gong, P. *et al.* (2021). The sensitivity of field populations of *Metopolophium dirhodum* (Walker) (Hemiptera: Aphididae) to seven insecticides in northern China. *Agronomy* **11**, 1156.

Gossner, M.M. *et al.* (2016). Land-use intensification causes multitrophic homogenization of grassland communities. *Nature* **540**, 266–269.

Goulson, D. (2013). An overview of the environmental risks posed by neonicotinoid insecticides. *Journal of Applied Ecology* **50**, 977–987.

Goulson, D. (2015). Neonicotinoids impact bumblebee colony fitness in the field; a reanalysis of the UK's Food & Environment Research Agency 2012 experiment. *PeerJ* **3**, e854.

Goulson, D. (2020). Pesticides, corporate irresponsibility, and the fate of our planet. *One Earth* **2**, 302–305.

Goulson, D. *et al.* (2018), Rapid rise in toxic load for bees revealed by analysis of pesticide use in Great Britain. *PeerJ* **6**, e5255.

Gul, H. *et al.* (2021). Sublethal concentrations of clothianidin affect fecundity and key demographic parameters of the chive maggot, *Bradysia odoriphaga*. *Ecotoxicology* **30**, 1150–1160.

Gunstone, T. *et al.* (2021). Pesticides and soil invertebrates: a hazard assessment. *Frontiers in Environmental Sciences* **9**, 643847.

Gupta, A. and Nair, S. (2020). Dynamics of insect-microbiome interaction influence host and microbial symbiont. *Frontiers in Microbiology* **11**, 1357.

Gurr, G.M. *et al.* (2017). Habitat management to suppress pest populations: progress and prospects. *Annual Review of Entomology* **62**, 91–109.

Haas, J. *et al.* (2021). A toxicogenomics approach reveals characteristics supporting the honey bee (*Apis mellifera* L.) safety profile of the butenolide insecticide flupyradifurone. *Ecotoxicology and Environmental Safety* **217**, 112247.

Hallmann, C. *et al.* (2014). Declines in insectivorous birds are associated with high neonicotinoid concentrations. *Nature* **511**, 341–343.

Hallmann, C. *et al.* (2017). More than 75 percent decline over 27 years in total flying insect biomass in protected areas. *PLoS ONE* **12** (10), e0185809.

Han M.-H. *et al.* (2021). Pollution, human exposure and harmful effects of neonicotinoid pesticides. *Shanghai Journal of Preventive Medicine* **12**, 534–543.

Han, M. *et al.* (2022). Neonicotinoids residues in the honey circulating in Chinese market and health risk on honey bees and humans. *Environmental Pollution* **313**, 120146.

Hano, T. *et al.* (2019). Occurrence of neonicotinoids and fipronil in estuaries and their potential risks to aquatic invertebrates. *Environmental Pollution A* **252**, 205–215.

Harada, K.H. *et al.* (2016). Biological monitoring of human exposure to neonicotinoids using urine samples, and neonicotinoid excretion kinetics. *PLoS ONE* **11**, e0146335.

Hartman C. *et al.* (2021). Epigenetic effects promoted by neonicotinoid thiacloprid exposure. *Frontiers in Cell Developmental Biology* **9**, 691060.

Harwood, G.P. and Dolezal, A.G. (2020). Pesticide–virus interactions in honey bees: challenges and opportunities for understanding drivers of bee declines. *Viruses* **12**, 566.

Hasan, M. *et al.* (2021). Histopathological alterations in the gills of banded gourami (*Trichogaster fasciata*) exposed to thiamethoxam. *Bangladesh Journal of Fisheries* **33** (1), 49–56.

Hassell, M.P. (2000). *Insect Parasitoid Population Dynamics*. Oxford: Oxford University Press.

Hatfield, R.G. *et al.* (2021). Neonicotinoid pesticides cause mass fatalities of native bumble bees: a case study from Wilsonville, Oregon, United States. *Environmental Entomology* **50** (5), 1095–1104.

Hauer, M. *et al.* (2017). Neonicotinoids in sugar beet cultivation in Central and Northern Europe: efficacy and environmental impact of neonicotinoid seed treatments and alternative measures. *Crop Protection* **93**, 132–142.

Heimpel, G.E. and Mills, N.J. (2017). *Biological Control*. Cambridge University Press

Heimpel, G.E. *et al.* (2013). Environmental consequences of invasive species: greenhouse gas emissions of insecticide use and the role of biological control in reducing emissions. *PLoS ONE* **8** (8), e72293.

Helepciuc F.-E. *et al.* (2021). Evaluating the effectiveness of the EU's approach to the sustainable use of pesticides. *PLoS ONE* **16** (9), e0256719.

Herbertsson, L. *et al.* (2021). Scientific note: imidacloprid found in wild plants downstream permanent greenhouses in Sweden. *Apidologie* **52**, 946–949.

Hesselbach, H. and Scheiner, R. (2019). The novel pesticide flupyradifurone (Sivanto) affects honeybee motor abilities. *Ecotoxicology* **28** (3), 354–366.

Hesselbach, H. *et al.* (2020). Chronic exposure to the pesticide Flupyradifurone can lead to premature onset of foraging in honeybees *Apis mellifera*. *Journal of Applied Ecology* **57**, 609–618.

Hladik, M.L. *et al.* (2018a). Year-round presence of neonicotinoid insecticides in tributaries to the Great Lakes, USA. *Environmental Pollution* **235**, 1022–1029.

Hladik, M., Main, A. and Goulson, D. (2018b). Environmental risks and challenges associated with Neonicotinoid Insecticides. *Environmental Science and Technology* **52** (6), 3329–3335.

Hornok, L. (2022). The European Green Deal rashly restricts chemical plant protection. *Journal of Hungarian Science* https://mersz.hu/hivatkozas/matud202210_f80651/#matud202210_f80651.

Hoshi, N. (2021). Adverse effects of pesticides on regional biodiversity and their mechanisms. In: Matsuda, T. *et al.* (eds) *Risks and Regulation of New Technologies* (chapter 1). *Kobe University Monograph Series in Social Science Research*. Singapore: Springer.

Hotchkiss, M.Z., Poulain, A.J. and Forrest, J.R.K. (2022). Pesticide-induced disturbances of bee gut microbiotas. *FEMS Microbiology Reviews* **46** (2), fuab056.

Hough, R.L. (2021). A world view of pesticides. *National Geosciences* **14**, 183–184.

Huang, Y. *et al.* (2021). Imidacloprid induces locomotion impairment of the freshwater crayfish, *Procambarus clarkii* via neurotoxicity and oxidative stress in digestive system. *Aquatic Toxicology* **238**, 105913.

Humman-Guilleminot, S. *et al.* (2019). A large-scale survey of house sparrow feathers reveals ubiquitous presence off neonicotinoids in farmlands. *Science of the Total Environment* **660**, 1091–1097.

Hutchison, W.D. and Naranjo, S.E. (2014). Sustainable management of insect-resistant crops. In: *Plant Biotechnology: Experience and Future Prospects* (chapter 14). http://dx.doi.org/10.1007/978-3-319-06892-3_10. Matsuda, T., Wolff, J. and Yanagawa, T. (eds) *Risks and Regulation of New Technologies. Kobe University Monograph Series in Social Science Research*. Singapore: Springer.

Ichikawa, G. *et al.* (2019). LC-ESI/MS/MS analysis of neonicotinoids in urine of very low birth weight infants at birth. *PLoS ONE* **14** (7), e0219208.

Ihara, M. and Matsuda, K. (2018). Neonicotinoids: molecular mechanisms of action, insights into resistance and impact on pollinators. *Current Opinion in Insect Science* **30**, 86–92.

Ikenaka, Y. *et al.* (2019). Exposures of children to neonicotinoids in pine wilt disease control areas. *Environmental Toxicology and Chemistry* **38** (1), 71–79.

IRAC (2021). IRAC Mode of Action Classification Scheme. IRAC. https://irac-online.org.

Ivaskovic, P. *et al.* (2021). Sensing of airborne infochemicals for green pest management: what is the challenge? *ACS Sensors* **6**, 3824–3840.

Jacquet, F. *et al.* (2022). Pesticide-free agriculture as a new paradigm for research. *Agronomy for Sustainable Development* **42**, 8.

Jactel, H. *et al.* (2019). Alternatives to neonicotinoids. *Environment International* **129**, 423–429.

Jactel, H. *et al.* (2021). Insect decline: immediate action is needed. *Comptes Rendus Biologies* https://doi.org/10.5802/crbiol.37.

Janssen, A. and van Rijn, P.C.J. (2021). Pesticides do not significantly reduce arthropod pest densities in the presence of natural enemies. *Ecology Letters* **24** (9), 2010–2024.

Jensen, E. (2015). Banning neonicotinoids: ban first, ask questions later. *Seattle Journal of Environmental Law* **5** (1), 3.

Jeschke, P. (2020). Status and outlook for acaricide and insecticide discovery. *Pest Management Science* **77**, 64–76.

Jeschke, P. (2022). Manufacturing approaches of new halogenated agrochemicals. *European Journal of Organic Chemistry* **12**, e202101513.

Kandie, F.J. *et al.* (2020a). Occurrence and risk assessment of organic micropollutants in freshwater systems within the Lake Victoria South Basin, Kenya. *Science of the Total Environment* **714**, 136748.

Kandie, F.J. *et al.* (2020b). Multi-compartment chemical characterization and risk assessment of chemicals of emerging concern in freshwater systems of western Kenya. *Environmental Science Europe* **32**, 115.

Karedla, A.K. *et al.* (2021). Effect of thiamethoxam on the survival of brood in *Apis mellifera* L. colonies placed in mustard fields. *Journal of Agricultural Research* https://www.tandfonline.com/doi/full/10.1080/00218839.2021.1958565.

Kaur, J. and Kumar, V. (2020). Residual effect of neonicotinoids on the whitefly *Bemisia tabaci* (Gennadius) in Bt cotton. *Indian Journal of Entomology* **82** (4), 745–749.

Kavanagh, S. *et al.* (2021). Neonicotinoid residues in honey from urban and rural environments. *Environment Science Pollution Research* **28**, 28179–28190.

Khan, Z.R. *et al.* (2014). Achieving food security for one million sub-Saharan African poor through push–pull innovation by 2020. *Philosophical Transactions of the Royal Society B* **369**, 20120284.

Khovarnagh, N. and Seyedalipour, B. (2021). Antioxidant, histopathological and biochemical outcomes of short-term exposure to acetamiprid in liver and brain of rat: the protective role of *N*-acetylcysteine and *S*-methylcysteine. *Saudi Pharmaceutical Journal* **29** (3), 280–289.

Klarich Wong, K. *et al.* (2019). Chlorinated byproducts of neonicotinoids and their metabolites: an unrecognized human exposure potential? *Environmental Science and Technology Letters* **6** (2), 98–105.

Kniss, A.R. *et al.* (2016). Commercial crop yields reveal strengths and weaknesses for organic agriculture in the United States. *PLoS ONE* **11** (11), e0165851.

Korenko, S. *et al.* (2019). Prey contaminated with neonicotinoids induces feeding deterrent behavior of a common farmland spider. *Scientific Reports* **9**, 15895.

Krishna, M.S. and Reddy, Y.R. (2020). Comparative efficacy of novel insecticide molecules against sucking pests in cotton. *Journal of Entomology and Zoology Studies* **8** (5), 2288–2292.

Kruse-Plaß, M. *et al.* (2021). Pesticides and pesticide-related products in ambient air in Germany. *Environmental Science Europe* **33**, 114.

Kumar, J. *et al.* (2021). An overview of some biopesticides and their importance in plant protection for commercial acceptance. *Plants* **10** (6), 1185.

Kumar, R. and Mall, P. (2021). Effect of thiamethoxam 25 WG spray at pre-bloom on the foraging activity of *Apis mellifera* in mustard crop under open field condition. *Journal of Entomology and Zoology Studies* **9** (1), 2047–2052.

Kumari, D.A. *et al.* (2020). Efficacy of insecticides against leaf hoppers and whitefly in Okra. *Agricultural Research Journal* **57** (6), 943–946.

Labrie, G. *et al.* (2020). Impacts of neonicotinoid seed treatments on soil-dwelling pest populations and agronomic parameters in corn and soybean in Quebec (Canada). *PLoS ONE* **15** (2), e0229136.

Laubscher, B. *et al.* (2022). Multiple neonicotinoids in children's cerebro-spinal fluid, plasma, and urine. *Environmental Health*, **21** (1), 10.

Lavik, M.S. *et al.* (2020). Comparison of conventional and IPM cropping systems: a risk efficiency analysis. *Journal of Agricultural and Applied Economics* **52**, 385–397.

Leach, A. *et al.* (2022). Does IPPM bear fruit? Evaluating reduced-risk insecticide programs on pests, pollinators, and marketable yield. *Journal of Applied Biology* http://dx.doi.org/10.1111/1365-2664.14294.

Leather, S.R. and Pope, T.W. (2019). Botanical biopesticides – where to now? *Outlooks on Pest Management* **30**, 75–77.

Lechenet, M. *et al.* (2017). Reducing pesticide use while preserving crop productivity and profitability on arable farms. *Nature Plants* **3**, 17008.

Lefebre *et al.* (2015). Incentives and policies for integrated pest management in Europe. A review. *Agronomy for Sustainable Development* **35** (1), 27–45.

Lennon, R.J. *et al.* (2019). Using long-term datasets to assess the impacts of dietary exposure to neonicotinoids on farmland bird populations in England. *PLoS ONE* **14** (10), e0223093.

Lewis, K.A. *et al.* (2016). An international database for pesticide risk assessments and management. *Human and Ecological Risk Assessment* **22** (4), 1050–1064.

Li, Q. *et al.* (2019). Effects of maximum residue limit of triflumezopyrim exposure on fitness of the red imported fire ant (*Solenopsis invicta*). *PeerJ.* e8241.

Li, Y., Miao, R. and Khanna, M. (2020). Neonicotinoids and decline in bird biodiversity in the United States. *Nature Sustainability* **3**, 1027–1035.

Li J.-Y. *et al.* (2021a). Spatio-temporal distribution patterns of *Plutella xylostella* (Lepidoptera: Plutellidae) in a fine-scale agricultural landscape based on geostatistical analysis. *Scientific Reports* **11**, 13622.

Li, H. *et al.* (2021b). Juvenile hormone and transcriptional changes in honey bee worker larvae when exposed to sublethal concentrations of thiamethoxam. *Ecotoxicology and Environmental Safety* **225**, 112744.

Li, S. *et al.* (2021c). Neonicotinoid insecticides triggers mitochondrial bioenergetic dysfunction via manipulating ROS-calcium influx pathway in the liver. *Ecotoxicology and Environmental Safety* **224**, 112690.

Li, F. *et al.* (2021d). Imbalance of intestinal microbial homeostasis caused by acetamiprid is detrimental to resistance to pathogenic bacteria in *Bombyx mori*. *Environmental Pollution* **289**, 117866.

Li, X. *et al.* (2021e). Field-evolved sulfoxaflor resistance of three wheat aphid species in China. *Agronomy* **11** (11), 2325.

Li, J. *et al.* (2021f). Sub-lethal effects of Isoclast™ Active (50% sulfoxalfor water dispersible granules) on larval and adult worker honey bees (*Apis mellifera*). *Ecotoxicoloty and Environmental Safety* **220**, 112379.

Liao, X. *et al.* (2017). Temporal variability and resistance correlation of sulfoxaflor susceptibility among Chinese populations of the brown planthooper *Nilaparvata lugens* (Stahl). *Crop Protection* **102**, 141–146.

Liao, J.-R. *et al.* (2020). Semi-automated identification of biological control agent using artificial intelligence. *Scientific Reports* **10**, 14632.

Liess, M., Henz, S. and Shahid, N. (2020). Modelling the synergistic effects of toxicant mixtures. *Environment Science Europe* **32**, 119.

Liess, M. *et al.* (2021). Pesticides are the dominant stressors for vulnerable insects in lowland streams. *Water Research* **201**, 117 262.

Lin, Q. *et al.* (2021). *Myzus persicae* management through combined use of beneficial insects and thiacloprid in pepper seedlings. *Insects* **12** (9), 791.

Linguadoca, A. *et al.* (2021). Sulfoxaflor and nutritional deficiency synergistically reduce survival and fecundity in bumblebees. *Science of the Total Environment* **795**, 148680.

Linhart, C. *et al.* (2019). Pesticide contamination and associated risk factors at public playgrounds near intensively managed apple and wine orchards. *Environmental Sciences Europe* **31**, 28.

Linhart, C. *et al.* (2021). Year-round pesticide contamination of public sites near intensively managed agricultural areas in South Tyrol. *Environmental Sciences Europe* **33**, 1.

Liu, Y. *et al.* (2021a). Thiamethoxam exposure induces endoplasmic reticulum stress and affects ovarian function and oocyte development in mice. *Agriculture Food Chemistry* **69** (6), 1942–1952.

Liu, P. *et al.* (2021b). The neonicotinoid alternative sulfoxaflor causes chronic toxicity and impairs mitochondrial energy production in *Chironomus kiinensis*. *Aquatic Toxicology* **235**, 105822.

Liu, T. *et al.* (2021c). Clothianidin loaded TA/Fe (III) controlled-release granules: improve pesticide bioavailability and alleviate oxidative stress. *Journal of Hazardous Materials* **415**, 125861.

Longhurst, C. *et al.* (2012). Cross-resistance relationships of the sulfoximine insecticide sulfoxaflor with neonicotinoids and other insecticides in the whiteflies *Bemisia tabaci* and *Trialeurodes vaporariorum*. *Pest Management Science* **69** (7), 809–813.

Lu, C. *et al.* (2018). Neonicotinoid residues in fruits and vegetables: an integrated dietary exposure assessment approach. *Environmental Science and Technology.* **52**, 3175–3184.

Lu, W. *et al.* (2022). Nicotonic acetylcholine receptor modulator insecticides act on diverse receptor subtypes with distinct subunit compositions. *PLoS Genetics* **18** (1), e1009920.

Lundin, O. (2019). No-till protects spring oilseed rape (*Brassica napus* L.) against crop damage by flea beetles (*Phyllotreta* spp.). *Agriculture, Ecosystems & Environment* **278**, 1–5.

Lundin, O. (2021). Consequences of the neonicotinoid seed treatment ban on oilseed rape production – what can be learnt from the Swedish experience? *Pest Management Science* **77**, 3815–3819.

Lundin, O. *et al.* (2020). Pest management and yield in spring oilseed rape without neonicotinoid seed treatments. *Crop Protection* **137**, 105261.

Lundin, O. *et al.* (2021). Integrated pest and pollinator management – expanding the concept. *Frontiers in Ecology and Environment* **19** (5), 283–291.

Ma, C. *et al.* (2021). Kinetics, mechanisms and toxicity of the degradation of imidaclothiz in soil and water. *Journal of Hazardous Materials* **403**, 124033.

Macaulay, S.J. *et al.* (2019). Imidacloprid dominates the combined toxicities of neonicotinoid mixtures to stream mayfly nymphs. *Science of the Total Environment* **761**, 143263.

Maeda, M. *et al.* (2021). Fetal and lactational exposure of the no-observed-adverse-effect level (NOAEL) dose of the neonicotinoid pesticide clothianidin inhibits neurogenesis and induces different behavioral abnormalities at the developmental stages in male mice. *Journal of Veterinary Medical Science* **83** (3), 542–548.

Maertens, A., Golden, E. and Hartung, T. (2021). Avoiding regrettable substitutions; green toxicology for sustainable chemistry. *ACS Sustainable Chemistry Engineering* **9**, 7749–7758.

Mahai, G. *et al.* (2021). A nationwide study of occurrence and exposure assessment of neonicotinoid insecticides and their metabolites in drinking water of China. *Water Research* **189**, 11663.

Mahmoudi-Dehpauni, B. *et al.* (2021). Exposure route affects the toxicity class of thiamethoxam for the predatory bug, *Orius albidipennis* (Hemiptera: Anthocoridae) by changing its fitness. *Journal of Economic Entomology* **114** (2), 684–693.

Makoni, M. (2020). Malaria fighters' latest chemical weapon may not last long. *Science* **369** (6508), 1153–1155.

Marfo, J.T. *et al.* (2015). Relationship between urinary *N*-desmethyl-acetamiprid and typical symptoms including neurological findings: a prevalence case-control study. *PLoS One* **10**, e0142172.

Matsuda, K. *et al.* (2020). Neonicotinoid insecticides: molecular targets, resistance, and toxicity. *Annual Review of Pharmacology and Toxicology* **60**, 241–255.

McGrane, L. and Noakes, F. (2021). Pesticide resistance in Australian grain regions – lessons to be learnt. GRDC Update paper. https://grdc.com.au/resources-and-publications/grdc-update-papers/tab-content/grdc-update-papers/2021/02/pesticide-resistance-in-australian-grain-regions-lessons-to-be-learnt

McNamara, L. *et al.* (2020). Management of yellow dwarf disease in Europe in a post-neonicotinoid agriculture. *Pest Management Science* **76**, 2276–2285.

Meng, W. *et al.* (2021). Fe_3O_4 magnetic cores coated with metal-organic framework shells as collectable composite nanoparticle vehicles for sustained release of the pesticide imidacloprid. *ACS Applied Nano Materials* **4** (6), 5864–5870.

Merga, L.B. and Ven den Brink, P.J. (2021). Ecological effects of imidacloprid on a tropical freshwater ecosystem and subsequent recovery dynamics. *Science of the Total Environment* **784**, 147167.

Mesnage, R. *et al.* (2021). Improving pesticide-use data for the EU. *Nature Ecology & Evolution* **5**, 1560.

Midega, C.A.O. *et al.* (2018). A climate adapted push-pull system effectively controls fall armyworm, *Spodoptera frugiperda* (J E Smith) in maize in East Africa. *Crop Protection* **105**, 10–15.

Mie, A. and Rudén, C. (2022). What you don't know can still hurt you - underreporting in EU pesticide regulation. *Environmental Health* **21**, 79.

Milner, A.M. and Boyd, I.L. (2017). Towards pesticidovigilance. *Science* **357** (6357), 1232–1234.

Mineau, P. (2019). An Assessment of Neonicotinoid Insecticides with Emphasis on New York: Use, Contamination, Impacts on Aquatic Systems and Agronomic Aspects. https://www.nrdc.org/sites/default/files/assessment-neonicotinoid-insecticides-emphasis-new-york.pdf.

Mineau, P. (2020). Neonicotinoids in California. Their Use and Threats to the State's Aquatic Ecosystems and Pollinators, with a Focus on Neonic-Treated Seeds. https://www.researchgate.net/profile/Pierre_Mineau/contributions?ev=prf_act.

Miotelo, L. *et al.* (2022). Transcriptomic analysis of Malpighian tubules from the stingless bee *Melipona scutellaris* reveals thiamethoxam-induced damages. *Science of the Total Environment* **850**, 158086.

Mitchell, E. *et al.* (2017). A worldwide survey of neonicotinoids in honey. *Science* **358**, 109–111.

More, S.J. *et al.* (2019). Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA Journal* **17** (3), e05634.

More, S. *et al.* (2021). A systems-based approach to the environmental risk assessment of multiple stressors in honey bees. *EFSA Journal* **19** (5), e06607.

Morley, C.G. *et al.* (2017). The potential of using unmanned aerial vehicles (UAVs) for precision pest control of possums (*Trichosurus vulpecula*). *Rethinking Ecology* **2**, 27–39.

Mörtl, M. *et al.* (2016). Study on soil mobility of two neonicotinoid insecticides. *Journal of Chemistry* **2016**, 4546584.

Mörtl, M. *et al.* (2017). Occurrence of neonicotinoids in guttation liquid of maize – soil mobility and cross-contamination. *International Journal of Environmental Analytical Chemistry* **97** (9), 868–884.

Mörtl, M. *et al.* (2019a) Aquatic toxicity and loss of linear alkylbenzenesulfonates alone and in a neonicotinoid insecticide formulation in surface water. *Science of the Total Environment* **652**, 780–787.

Mörtl, M. *et al.* (2019b) Contamination of the guttation liquid of two common weeds with neonicotinoids from coated maize seeds planted in close proximity. *Science of the Total Environment* **649**, 1137–1143.

Mörtl, M. *et al.* (2020a) Neonicotinoids: spreading, translocation and aquatic toxicity. *International Journal of Environmental Research and Public Health* **17** (6), 2006.

Mörtl, M. *et al.* (2020b) Appearance of thiacloprid in the guttation liquid of coated maize seeds. *International Journal of Environmental Research and Public Health* **17** (6), 3290.

Mourtzinis, S. *et al.* (2019). Neonicotinoid seed treatments of soybean provide negligible benefits to US farmers. *Scientific Reports* **9**, 11207.

Munkhbayar, O. *et al.* (2021). First report of voltage-gated sodium channel M918V and molecular diagnostics of nicotinic acetylcholine receptor R81T in the cotton aphid. *Journal of Applied Entomology* **145** (3), 261–269.

Naggar, Y. and Baer, B. (2019). Consequences of a short time exposure to a sublethal dose of Flupyradifurone (Sivanto) pesticide early in life on survival and immunity in the honeybee (*Apis mellifera*). *Scientific Reports* **9**, 19753.

Nakrani, B.R. and Sevak, K.K. (2021). Evaluation of bio-efficacy and phytotoxicity of Gaucho 600 FS (imidacloprid 600 FS) as seed treatment against termite in groundnut crop. *Plant Archives* **21** (1), 736–742.

NASAC (2019). Neonicotinoid Insecticides: Use and Effects in African Agriculture. https://www.interacademies.org/publication/neonicotinoid-insecticides-use-and-effects-african-agriculture-review-and

Nauen, R. *et al.* (2014). Flupyradifurone: a brief profile of a new butenolide insecticide. *Pest Management Science* **71** (6), 850–62.

Negi, R. *et al.* (2021). Lethal and sublethal effects of thiamethoxam, a neonicotinoid molecule, on colony performance of *A. mellifera*. *Environmental Science Pollution Research* **29**, 10826–10837.

Noleppa, S. (2017). *Banning neonicotinoids in the European Union. An ex-post assessment of economic and environmental costs*. HFFA research GmbH.

Onazaki, Y. *et al.* (2017). Flupyrimin: a novel insecticide acting at the nicotinic acetylcholine receptors. *Journal of Agricultural and Food Chemistry* **65** (36), 7865–7869.

O'Neal, S.T., Anderson, T.D. and Wu-Smart, J.Y. (2018). Interactions between pesticides and pathogen susceptibility in honey bees. *Current Opinion in Insect Science* **26**, 57–62.

Ortega-Ramos, P.A. *et al.* (2022). Integrated pest management strategies for cabbage stem flea beetle (*Psylliodes chrysocephala*) in oilseed rape. *GCB Bioenergy* **14**, 267–286.

Osaka, A. *et al.* (2016). Exposure characterization of three major insecticide lines in urine of young children in Japan—neonicotinoids, organophosphates, and pyrethroids. *Environmental Research* **146**, 89–96.

Ospina, M. *et al.* (2019). Exposure to neonicotinoid insecticides in the U.S. general population: data from the 2015–2016 National Health and Nutrition Examination Survey. *Environmental Research* **176**, 108555.

Oumaima, F. *et al.* (2020). Overview of pesticide use in Moroccan apple orchards and its effects on the environment. *Current Opinion in Environmental Science & Health* **19**, 100223.

Overton, K. *et al.* (2021). Toxicity of insecticides and miticides to natural enemies in Australian grains. a review. *Insects* **12** (2), 187.

Paleolog, J. *et al.* (2020). Imidacloprid markedly affects hemolymph proteolysis, biomarkers, DNA global methylation, and the cuticle proteolytic layer in western honeybees. *Apidologie* **51**, 620–630.

PAN Europe (2017). Bee emergency call. How some Member States are threatening bees by allowing the use of prohibited pesticides and how the Commission does nothing to stop them.

PAN Europe (2020). REFIT of the Pesticide (EC 1107/2009) and Maximum Residue Limits in food (EC 396/2005) Regulations.

PAN Europe (2021). Position paper on the revision of the Sustainable Use of Pesticides Directive.

Pan, H. *et al.* (2014). Lethal and sublethal effects of cycloxaprid, a novel cis-nitromethylene neonicotinoid insecticide, on the mirid bug *Apolygus lucorum*. *Journal of Pest Science* **87** (4), 731–738.

Pang, S. *et al.* (2020). Insights into the microbial degradation and biochemical mechanisms of neonicotinoids. *Frontiers in Microbiology* **11**, 868.

Parkinson, R., Zhang, S. and Gray, J. (2020). Neonicotinoid and sulfoximine pesticides differentially impair insect escape behaviour and motion detection. *Proceedings of the National Academy of Sciences of the USA* **117** (10), 5510–5515.

Parsa, S. *et al.* (2014). Obstacles to integrated pest management adoption in developing countries. *Proceedings of the National Academy of Sciences of the USA* **111** (10), 3889–3894.

Pecenka, J.R. *et al.* (2021). IPM reduces insecticide applications by 95% while maintaining or enhancing crop yields through wild pollinator conservation. *Proceedings of the National Academy of Sciences of the USA* **118** (44), e2108429118.

Pedersen, J.E., Bergqvist, C.A. and Larhammar, D. (2019). Evolution of vertebrate nicotinic acetylcholine receptors. *BMC Evolutionary Biology* **19** (1), 38.

Pelosi, C. *et al.* (2021). Residues of currently used pesticides in soils and earthworms: a silent threat? *Agriculture, Ecosystems and Environment* **305**, 07167.

Perananthan, V. *et al.* (2020). The clinical toxicity of imidacloprid self-poisoning following the introduction of newer formulations, *Clinical Toxicology* **59** (4), 347–350.

Perkins, R. *et al.* (2020). Potential role of veterinary flea products in widespread contaminations of English rivers. *Science of the Total Environment* **755** (1), 143560.

Persson, L. *et al.* (2022). Outside the safe operating space of the planetary boundary for novel entities. *Environmental Science and Technology* **56**, 1510–1521.

Pimentel, D. and Peshin, R. (2014). Integrated pest management: pesticide problems. Springer Science & Business Media.

Pisa, L. *et al.* (2021). An update of the World Integrated Assessment (WIA) on systemic insecticides. Part 2, impacts on organisms and ecosystems. *Environmental Science Pollution Research* **28**, 11749–11797.

Plaza, J. *et al.* (2022). Classification of airborne multispectral imagery to quantify common vole impacts on an agricultural field. *Pest Management Science* http://dx.doi.org/10.1002/ps.6857.

Popp, J. *et al.* (2012). Pesticide productivity and food security. A review. *Agronomy for Sustainable Development* **33** (1), 243–255.

Potts, J. *et al.* (2022). Acetamiprid fate in a sandy loam with contrasting soil organic matter contents: a comparison of the degradation, sorption and leaching of commercial neonicotinoid formulations. *Science of the Total Environment* **842**, 156711.

Priyadharshini, E. *et al.* (2020). Baseline toxicity study of sulfoxaflor against rice brown planthopper, *Nilaparvata lugens* (Stål) populations of Tamil Nadu. *Journal of Entomology and Zoology Studies* **8** (5), 2176–2180.

Qi, S. *et al.* (2013). Toxicity assessments with *Daphnia magna* of guadipyr, a new neonicotinoid insecticide and studies of its effect on acetylcholinesterase (AChE), glutathione *S*-transferase (GST), catalase (CAT) and chitobiase activities. *Ecotoxicoloty and Environmental Safety* **98**, 339–344.

Qi, H. *et al.* (2020). Molecular insights into the insensitivity of lepidopteran pests to cycloxaprid. *Journal of Agricultural and Food chemistry* **68** (4), 982–988.

Qin, X. *et al.* (2013). Sublethal effects of paichongding on *Nilaparvata lugens* (Homoptera: Delphacidae). *Journal of Economic Entomology* **106** (1), 10–15.

Redhead, J. *et al.* (2022). The effect of a decade of agri-environment intervention in a lowland farm landscape on population trends of birds and butterflies. *Journal of Applied Ecology* **9**, 2486–2496.

Renaud, M. *et al.* (2018). Effects of the neonicotinoids acetamiprid and thiacloprid in their commercial formulations on soil fauna. *Chemosphere* **194**, 85–93.

Řezáč, M., Řezáčová, V. and Heneberg, P. (2019). Contact application of neonicotinoids suppresses the predation rate in different densities of prey and induces paralysis of common farmland spiders. *Scientific Reports* **9**, 5724.

Řezáč, M. *et al.* (2022). Contact exposure to neonicotinoid insecticides temporarily suppresses the locomotor activity of *Pardosa lugubris* agrobiont wolf spiders. *Scientific Reports* **12**, 14745.

Riedo, J. *et al.* (2021). Widespread occurrence of pesticides in organically managed agricultural soils—the ghost of a conventional agricultural past? *Environmental Science & Technology* http://dx.doi.org/10.1021/acs.est.0c06405.

Ritchie, E.E. *et al.* (2019). Lethal and sublethal toxicity of thiamethoxam and clothianidin commercial formulations to soil invertebrates in a natural soil. *Environ Toxicol Chem* **38**, 2111–2120.

Rundlöf, M. *et al.* (2022). Flower plantings support wild bee reproduction and may also mitigate pesticide exposure effects. *Journal of Applied Ecology* https://besjournals.onlinelibrary.wiley.com/doi/10.1111/1365-2664.14223.

Saeed, R. *et al.* (2018). Field evolved resistance to pyrethroids, neonicotinoids and biopesticides in *Dysdercus koenigii* (Hemiptera: Pyrrhocoridae) from Punjab, Pakistan. *Chemosphere* **213**, 149–155.

Sajjad, M. *et al.* (2022). Microplastics in the soil environment: a critical review. *Environmental Technology & Innovation* **27**, 102408.

SAM (2018). Scientific opinion on plant protection products.

Sánchez-Bayo, F. and Tennekes, H.A. (2020). Time-cumulative toxicity of neonicotinoids: experimental evidence and implications for environmental risk assessments. *International Journal of Environmental Research and Public Health* **17**, 1629.

Sánchez-Bayo, F. and Wyckhuys, K. (2019). Worldwide decline of the entomofauna: a review of its drivers. *Biological Conservation* **232**, 8–27.

SAPEA (2018). Science Advice for Policy by European Academies. Improving authorisation processes for plant protection products in Europe: a scientific perspective on the potential risks to human health. Berlin: SAPEA.

Schäfer, R.B. *et al.* (2019). Future pesticide risk assessment: narrowing the gap between intention and reality. *Environmental Sciences Europe* **31**, 21.

Seufert, V. and Ramankutty, N. (2017). Many shades of gray - the context-dependent performance of organic agriculture. *Science Advances* **10** (3), e1602638.

Sgolastra, F. *et al.* (2020). Bees and pesticide regulation: lessons from the neonicotinoid experience. *Biological Conservation* **241**, 108356.

Shah, R. (2020). Pesticides and human health. *Intech Open* http://dx.doi.org/10.5772/intechopen.93806.

Silva, V. *et al.* (2019). Pesticide residues in European agricultural soils—a hidden reality unfolded. *Science of the Total Environment* **653**, 1532–1545.

Silva, V. *et al.* (2022). Environmental and human health at risk – scenarios to achieve the Farm to Fork 50% pesticide reduction goals. *Environment International* **165**, 107296.

Silvanima, J. *et al.* (2022). Regional extent, environmental relevance, and spatiotemporal variability of neonicotinoid insecticides detected in Florida's ambient flowing waters. *Environmental Monitoring and Assessment* **194**, 416.

Singh, A. and Leppanen, C. (2020). Known target and nontarget effects of the novel neonicotinoid cycloxaprid to arthropods: a systematic review. *Integrated Environmental Assessment and Management* **16** (6), 831–840.

Singh, A. *et al.* (2020). Advances in controlled release pesticide formulations: prospects to safer integrated pest management and sustainable agriculture. *Journal of Hazardous Materials* **385**, 121525.

Siviter, H. and Muth, F. (2020). Do novel insecticides pose a threat to beneficial insects? *Proceedings of the Royal Society B* **287**, 20201265.

Siviter, H., Brown, M.J.F. and Leadbetter, E. (2018). Sulfoxaflor exposure reduces bumblebee reproductive success. *Nature* **561** (7721), 109–112.

Siviter, H. *et al.* (2019a). No evidence for negative impacts of acute sulfoxaflor exposure on bee olfactory conditioning or working memory. *PeerJ* **7**, e7208.

Siviter, H. *et al.* (2019b). Sulfoxaflor exposure reduces egg laying in bumblebees *Bombus terrestris*. *Journal of Applied Ecology* **57** (1), 160–169.

Siviter, H. *et al.* (2020). Individual and combined impacts of sulfoxaflor and *Nosema bombi* on bumblebee (*Bombus terrestris*) larval growth. *Proceedings of the Royal Society B* **287**, 20200935.

Söftje, M. *et al.* (2020). Novel nicotinoid structures for covalent modification of wood: an environmentally friendly way for its protection against insects. *RSC Advances* **10**, 15726–15733.

Sollen-Norrlin, M. *et al.* (2020). Agroforestry benefits and challenges for adoption in Europe and beyond. *Sustainability* **12**, 7001.

Song, Y. *et al.* (2021). Comparative ecotoxicity of insecticides with different modes of action to *Osmia excavata* (Hymenoptera: Megachilidae). *Ecotoxicology and Environmental Safety* **212**, 112015.

Sparks, T. *et al.* (2013). Sulfoxaflor and the the sulfoximine insecticides: chemistry, mode of action, and basis for efficacy on resistant insects. *Pesticide Biochemistry and Physiology* **107** (1), 1–7.

Sparks, T. *et al.* (2020). Insecticides, biologics and nematicides: updates to IRAC's mode of action classification - a tool for resistance management. *Pesticide Biochemistry and Physiology.* **167**, 104597.

Sriapha, C. *et al.* (2020). Acute imidacloprid poisoning in Thailand. *Therapeutics and Clinical Risk Management* **16**, 1081–1088.

Straub, L. *et al.* (2019). Neonicotinoids and ectoparasitic mites synergistically impact honeybees. *Scientific reports* **9**, 8159.

Stuligross, C. and Williams, N.W. (2021). Past insecticide exposure reduces bee reproduction and population growth rate. *Proceedings of the National Academy of Sciences of the USA* **118** (48), e2109909118.

Sunamura, E. *et al.* (2021). Efficacy of two neonicotinoid insecticides against invasive wood borer *Aromia bungii* larvae in dietary toxicity test. *Insects* **12** (7), 592.

Šunta, U. *et al.* (2020). Adsorption of acetamiprid, chlorantraniliprole and flubendiamide on different type of microplastics present in alluvial soil. *Chemosphere* **261**, 12776219.

Takács, E. *et al.* (2017). Effects of neonicotinoid insecticide formulations and their components on *Daphnia magna* – the role of active ingredients and co-formulants. *International Journal of Environmental Analytical Chemistry* **97** (9), 885–900.

Taira, T. *et al.* (2011). Detection of chrolopyridinyl neonicotinoid insecticide metabolite 6-chloronicotinic acid in the urine: six cases with subacute nicotinic symptoms. *Japan Journal of Clinical Toxicology* **24**, 222–230.

Tambourini, G. *et al.* (2021). Fungicide and insecticide exposure adversely impacts bumblebees and pollination services under semi-field conditions. *Environment International* **157**, 106853.

Tan, L. *et al.* (2019). Registration status review and primary risk assessment to bees of neonicotinoid pesticides. *Asian Journal of Ecotoxicology* **6**, 292–303.

Tang, F.H.M. *et al.* (2021a). Risk of pesticide pollution at the global scale. *National Geosciences* **14**, 206–210.

Tang, H. *et al.* (2021b). Residue behaviour and dietary risk assessment of six pesticides in pak choi using QuEChERS method coupled with UPLC-MS/MS. *Exotoxicology and Environmental Safety* **213**, 11022.

Tao, Y. *et al.* (2019a). Urinary monitoring of neonicotinoid imidacloprid exposure to pesticide applicators. *Science of the Total Environment* **669**, 721–728.

Tao, Y. *et al.* (2019b). Characteristics of neonicotinoid imidacloprid in urine following exposure of humans to orchards in China. *Environment International* **132**, 105079.

Tasman, K., Rands, S. and Hodge, J. (2020). The neonicotinoid insecticide Imidacloprid disrupts bumblebee foraging rhythms and sleep. *iScience* **23** (12), 101827.

Thompson, D.A. *et al.* (2020). A critical review on the potential impacts of neonicotinoid insecticide use: current knowledge of environmental fate, toxicity, and implications for human health. *Environmental Science: Processes & Impacts* **22** (6), 1315–1346. https://pubs.rsc.org/en/content/articlelanding/2020/em/c9em00586b.

Tong, L., Nieh, J.C. and Tosi, S. (2019). Combined nutritional stress and a new systemic pesticide (flupyradifurone, Sivanto) reduce bee survival, food consumption flight success, and thermoregulation. *Chemosphere* **237**, 124408.

Tooker, J.F., Douglas, M.R. and Krupke, C.H. (2017). Neonicotinoid seed treatments: limitations and compatibility with integrated pest management. *Agricultural and Environment Letters* **2**, 170026.

Topping, C.J. *et al.* (2014). Recovery based on plot experiments is a poor predictor of landscape-level population impacts of agricultural pesticides. *Environmental Toxicology and Chemistry* **33** (7), 1499–1507.

Topping, C.J., Aldrich, A. and Berny, P. (2020). Overhaul environmental risk assessment for pesticides. *Science* **367** (6476), 360–363.

Tosi, S. and Nieh, J. (2019). Lethal and sublethal synergistic effects of a new systemic pesticide, Flupyradifurone (Sivanto) on honeybees. *Proceedings of the Royal Society B* **286**, 20190433.

Tosi, S. *et al.* (2021). Long-term field-realistic exposure to a next-generation pesticide, flupyradifurone, impairs honey bee behaviour and survival. *Community Biology* **4**, 805.

Tscharntke, T. *et al.* (2021). Beyond organic farming – harnessing biodiversity-friendly landscapes. *Trends in Ecology & Evolution* **36** (10), 919–930.

Ullah, F. *et al.* (2019). Impact of low lethal concentrations of buprofezin on biological traits and expression profile of chitin synthase 1 gene (*CHS1*) in melon aphid, *Aphis gossypii*. *Science Reports* 9, 12291.

Vanderpoint, A.K. *et al.* (2022). Fate of thiamethoxam from treated seeds in mesocosms and response of aquatic invertebrate communities. *Ecotoxicology* **31**, 341–356.

van Dijk, J. *et al.* (2021). Towards 'one substance - one assessment': an analysis of EU chemical registration and aquatic risk assessment frameworks. *Journal of Environmental Management* **280**, 111692.

van Gestel, C.A.M. *et al.* (2017). Multigeneration toxicity of imidacloprid and thiacloprid to *Folsomia candida*. *Ecotoxicology* **26**,320–328.

van Hoesel, W. *et al.* (2017). Single and combined effects of pesticide seed dressings and herbicides on earthworms, soil microorganisms, and litter decomposition. *Frontiers in Plant Science* **8**, 215.

Varah, A. *et al.* (2020). Temperate agroforestry systems provide greater pollination service than monoculture. *Agricultural Ecosystems and Environment* **301**, 107031.

Vehovszky, Á. *et al.* (2015). Neonicotinoid insecticides inhibit cholinergic neurotransmission in a molluscan (*Lymnaea stagnalis*) nervous system. *Aquatic Toxicology* **167**, 172–179.

Vehovszky, Á. *et al.* (2018). Neonicotinoid insecticides are potential substrates of the multixenobiotic resistance (MXR) mechanism in the non-target invertebrate, *Dreissena* sp. *Aquatic Toxicology* **205**, 148–155.

Veres, A. *et al.* (2020). An update of the Worldwide Integrated Assessment (WIA) on systemic pesticide. Part 4, alternatives in major cropping systems. *Environmental Science and Pollution* **27**, 29867–29899.

Vieira, J.L. *et al.* (2022). Area-wide survey of thiamethoxam resistance and control failure likelihood in the rice stink bugs *Oebalus poecilus* and *O. ypsilongriseus*. *Journal of Pest Science* **95**, 1151–1161.

Voice, D.G. *et al.* (2022). The eradication of pea weevil *Bruchus pisorum* (L.) (Coleoptera: Chrysomelidae) from New Zealand. *CABI Agriculture and Bioscience* **3**, 31.

Waddington, H. and White, H. (2014). Farmer field schools: from agricultural extension to adult education. Syst Rev Sum 1. https://researchonline.lshtm.ac.uk/id/eprint/4647439.

Wade, A. *et al.* (2019). Combined toxicity of insecticides and fungicides applied to California almond orchards to honey bee larvae and adults. *Insects* **10** (1), 20.

Wagner, D. *et al.* (2022). Insect decline in the Anthropocene: death by a thousand cuts. *Proceedings of the National Academy of Sciences of the USA* **118** (2), e2023989118.

Wan, Y. *et al.* (2019). Neonicotinoids in raw, finished, and tap water from Wuhan, Central China: assessment of human exposure potential. *Science of the Total Environment* **675**, 519–523.

Wang, Z. *et al.* (2019), Comparative mammalian hazards of neonicotinoid insecticides among exposure durations. *Environment International* **125**, 9–24.

Wang, X. *et al.* (2020a). Occurrence of neonicotinoids in Chinese apiculture and a corresponding risk exposure assessment. *Environmental Science & Technology* **54** (8), 5021–5030.

Wang, Y. *et al.* (2020b). Synergistic toxicity and physiological impact of thiamethoxam alone or in binary mixtures with three commonly used insecticides on honeybee. *Apidologie* **51**, 395–405.

Wang, H. *et al.* (2020c). Predictors, sources, and health risk of exposure to neonicotinoids in Chinese school children: a biomonitoring-based study. *Environment International* **143**, 105918.

Wang, L. *et al.* (2020d). Toxicity and sublethal effect of triflymezopyrim against red imported fire ant (Hymenoptera: Formicidae). *Ecology and Behaviour* **113** (4), 1753–1760.

Wang, Z.J. *et al.* (2021). Insecticide resistance and resistance mechanisms in the melon aphid, *Aphis gossypii*, in Shandong, China. *Pesticide Biochemistry and Physiology* **172**, 104768.

Ward, L.T. *et al.* (2022). Pesticide exposure of wild bees and honey bees foraging from field border flowers in intensively managed agriculture areas. *Science of the Total Environment* **831**, 154697.

Warne, M.S. *et al.* (2022). Temporal variation of imidacloprid concentration and risk in waterways discharging to the Great Barrier Reef and potential causes. *Science of the Total Environment* **823**, 153556.

Watson, G.B. *et al.* (2021). Sulfoxaflor - a sulfoximine insecticide: review and analysis of mode of action, resistance and cross-resistance. *Pesticide Biochemistry and Physiology* **178**, 104924.

Wei, F. *et al.* (2021). Joint toxicity of imidacloprid and azoxystrobin to Chironomus dilutus at organism, cell, and gene levels. *Aquatic Toxicology* **233**, 105783.

Weisner, O. *et al.* (2021). Risk from pesticide mixtures – the gap between risk assessment and reality. *Science of the Total Environment* **796**, 149017.

Willow, J. *et al.* (2019). Acute effect of low-dose thiacloprid exposure synergised by tebuconazole in a parasitoid wasp. *PLoS ONE* **14** (2), e0212456.

Wong, K.L. *et al.* (2019). Chlorinated by-products of neonicotinoids and their metabolites: an unrecognized human exposure potential? *Environmental Science and Technology Letters* **6** (2), 98–105.

Wood, T.J. and Goulson, D. (2017), The environmental risks of neonicotinoid pesticides: a review of the evidence post 2013. *Environmental Science Pollution Research* **24**, 17285–17325.

Woodcock, B. *et al.* (2016). Impacts of neonicotinoid use on long-term population changes in wild bees in England. *Nature Communications* **7**, 12459.

Woodcock, B. *et al.* (2017). Country-specific effects of neonicotinoid pesticides on honey bees and wild bees. *Science* **356** (6345), 1393–1395.

Wu, N. *et al.* (2010). Study of Imidaclothiz residues in cabbage and soil by HPLC with UV detection. *Environmental Contamination Toxicology* **84**, 289–293.

Wu, C. *et al.* (2020). Effects of imidacloprid, a neonicotinoid insecticide, on the echolocation system of insectivorous bats. *Pesticide Biochemistry and Physiology* **163**, 94–101.

Wyckhuys, K.A.G. *et al.* (2019). Ecological illiteracy can deepen farmers' pesticide dependency. *Environmental Research Letters* **14**, 093004.

Wyckhuys, K.A.G. *et al.* (2020). Resolving the twin human and environmental health hazards of a plant-based diet. *Environment International* **144**, 106081.

Wyckhuys, K.A.G. *et al.* (2022). Carbon benefits of enlisting nature for crop protection. *Nature Food* **3**, 299–301.

Yamamuro, M. *et al.* (2019). Neonicotinoids disrupt aquatic food webs and decrease fishery yields. *Science* **366** (6465), 620–623.

Yang, D. *et al.* (2018). Design, synthesis and insecticidal activity of novel 1-alkoxy-2-nitroguanidines. *RSC Advances* **8**, 1838.

Yang, X. *et al.* (2021). Epitranscriptomic regulation of insecticide resistance. *Science Advances* **7** (19), eabe5903.

Yu, Z. *et al.* (2021a). The human and ecological risks of neonicotinoid insecticides in soils of an agricultural zone within the Pearl River Delta, south China. *Environmental Pollution* **284**, 117358.

Yuan, X. *et al.* (2019). Gut microbiota: an underestimated and unintended recipient for pesticide-induced toxicity. *Chemosphere* **227**, 425–434.

Zaller, J.G. *et al.* (2016). Pesticide seed dressings can affect the activity of various soil organisms and reduce decomposition of plant material. *BMC Ecology* **16**, 37.

Zaller, J.G. *et al.* (2022). Pesticides in ambient air, influenced by surrounding land use and weather, pose a potential threat to biodiversity and humans. *Science of the Total Environment* **838** (2), 156012.

Zhang, D. and Lu, S. (2022). Human exposure to neonicotinoids and the associated health risks: a review. *Environment International* **163**, 107201.

Zhang, Q. *et al.* (2018a). Potential human exposures to neonicotinoid insecticides: a review. *Environmental Pollution* **236**, 71–81.

Zhang, P. *et al.* (2018b). Sorption, desorption and degradation of neonicotinoids in four agricultural soils and their effects on soil microorganisms. *Science of the Total Environment* **615**, 59–69.

Zhang, Y. *et al.* (2018c). Resistance to cycloxaprid in *Laodelphax striatellus* is associated with altered expression of nicotinic acetylocholine receptor subunits. *Pest Management Science* **74** (4), 837–843.

Zhang, C. *et al.* (2019a). Occurrence, distribution and seasonal variation of five neonicotinoid insecticides in surface water and sediment of the Pearl Rivers, South China. *Chemosphere* **217**, 437–446.

Zhang, Q. *et al.* (2019b). Dietary risk of neonicotinoid insecticides through fruit and vegetable consumption in school-age children. *Environment International* **126**, 672–681.

Zhang, T. *et al.* (2019c). A nationwide survey of urinary concentrations of neonicotinoid insecticides in China. *International* **192**, 105114.

Zhang, S. *et al.* (2020). Sublethal effects of Triflumezopyrim on Biological traints and detoxification enzyme activities in the Small Brown Planthopper Laodelphax striatellus (Hemiptera Delpacidae). *Frontiers in Physiology* **11**, 261.

Zhang, Y. *et al.* (2021a). The transcriptomic landscape of molecular effects after sublethal exposure to dinotefuran on *Apis mellifera*. *Insects* **12** (10), 898.

Zhang, C. *et al.* (2021b). Contamination of drinking water by neonicotinoid insecticides in China: human exposure potential through drinking water consumption and percutaneous penetration. *Environment International* **156**, 106650.

Zhang, H. *et al.* (2021c). Profiles of neonicotinoid insecticides and their metabolites in paired saliva and periodontal blood samples in human from South China: association with oxidative stress markers. *Ecotoxicology and Environmental Safety* **212**, 112001.

Zhang, J. *et al.* (2021d). Circadian regulation of night feeding and daytime detoxification in a formidable Asian pest *Spodoptera litura*. *Communications Biology* **4**, 286.

Zhang, A. *et al.* (2021e). Effects of imidacloprid and thiamethoxam on the development and reproduction of the soybean aphid *Aphis glycines*. *PLoS ONE* **16** (9), e0250311.

Zhang, L. *et al.* (2022). Toxicity, horizontal transfer, physiological and behavioural effects of cycloxaprid against *Solenopsis invicta* (Hymenoptera: Formicidae). *Pest Management Science* **78** (6), 2228–2239.

Zhao, Y. *et al.* (2020). Exposure level of neonicotinoid insecticides in the food chain and the evaluation of their human health impact and environmental risk: an overview. *Sustainability* **12**, 7523.

Zhou, X. *et al.* (2018). Eukaryal composition and diversity in anaerobic soils influenced by the novel chiral insecticide Paichongding. *AMB Express* **8**, 62.

Zhou, Y. *et al.* (2021). Comparison of neonicotinoid residues in soils of different land use types. *Science of the Total Environment* **782**, 146803.

Zhu, Y. *et al.* (2011). Discovery and characterisation of sulfoxaflor, a novel insecticide targeting sap-feeding pests. *Journal of Agricultural Food Chemistry* **59** (7), 2950–2957.

Zhu, J. *et al.* (2020). Effects of a novel mesoionic insecticide, triflumezopyrim on the feeding behaviour of rice planthoppers *Nilaparvata lugens* and *Sogatella furcifera* (Hemiptera: Delphacidae). *Journal of Integrative Agriculture* **19** (10), 2488–2499.

EASAC, the European Academies' Science Advisory Council, consists of representatives of the following European national academies and academic bodies who have issued this report:

The Austrian Academy of Sciences
The Royal Academies for Science and the Arts of Belgium
The Bulgarian Academy of Sciences
The Croatian Academy of Sciences and Arts
The Cyprus Academy of Sciences, Letters and Arts
The Czech Academy of Sciences
The Royal Danish Academy of Sciences and Letters
The Estonian Academy of Sciences
The Council of Finnish Academies
The Académie des sciences (France)
The German National Academy of Sciences Leopoldina
The Academy of Athens
The Hungarian Academy of Sciences
The Royal Irish Academy
The Accademia Nazionale dei Lincei (Italy)
The Latvian Academy of Sciences
The Lithuanian Academy of Sciences
The Royal Netherlands Academy of Arts and Sciences
The Norwegian Academy of Science and Letters
The Polish Academy of Sciences
The Academy of Sciences of Lisbon
The Romanian Academy
The Slovak Academy of Sciences
The Slovenian Academy of Sciences and Arts
The Spanish Royal Academy of Sciences
The Swiss Academies of Arts and Sciences
The Royal Swedish Academy of Sciences
The Royal Society (United Kingdom)

Academia Europaea
ALLEA

For further information:

EASAC Publications Office
Bulgarian Academy of Sciences
1 '15 Noemvri' Street
BG-1040
Sofia
Bulgaria

tel: +359 2979 5241; +359 2979 5236
publications@easac.eu

EASAC Brussels Office
Royal Academies for Science and the
Arts of Belgium (RASAB)
Hertogsstraat 1 Rue Ducale
1000 Brussels
Belgium

tel +32 (2) 550 23 32
brusselsoffice@easac.eu

The affiliated network for Europe of

iap SCIENCE HEALTH POLICY
the interacademy partnership

EASAC contributes to the implementation of the

SUSTAINABLE DEVELOPMENT GOALS

Printed by Schaefer Druck und Verlag GmbH, Teutschenthal, Germany