Neonicotinoids:

The Science and Regulatory Complexity

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Contents

Introduction

Growth in the agrochemical industry has been driven by the need to produce enough food to feed a rapidly growing global population. During the last century, global food production has doubled, driven initially by the introduction of mineral phosphate fertilizers in the early 20th century and then, in the 1940s, by the introduction of synthetic crop protection products (CPPs).[1]

However, despite the increased crop yields resulting from synthetic pesticide use, concerns over toxicity have also been highlighted, so the development of pesticides has proceeded with the aim of creating more effective and safer active ingredients to overcome the problems of the past.

The e-book provides an overview; introducing neonicotinoids, explaining the science behind their use, the reasons for safety concerns and reviewing their regulatory status across the globe.

It is, therefore, slightly ironic that neonicotinoids, which were trumpeted as safer and more effective alternatives to chlorinated hydrocarbons, organophosphates, carbamates and pyrethroids, are now regarded as toxic to bees and other pollinators, as well as a wider group of species – with some neonicotinoids now banned in the European Union (EU).

The agricultural and environmental consequences of neonicotinoid use, and the recent EU regulatory restriction, has made this topic one of the most controversial involving science and policy.[2]

The History and Rationale of Neonicotinoid Use

Neonicotinoids, also known as neonics or NNIs, are a class of active substances used in CPPs. Neonicotinoid essentially means new 'nicotine-like insecticide' and, as the name suggests, they are chemically similar to nicotine.[3]

Neonicotinoids in Context of Insecticide Development

Neonicotinoids offered advantages over existing insecticides, such as, better selective toxicity to arthropods over vertebrates; high persistence; a systemic activity; versatility in application, which could reduce the exposure risks to operators; and high water solubility, leading to the assumption of lower bioaccumulation and thus less impact on fish and other vertebrates.[4] However, the panacea that they appeared to offer, like previous generations of insecticides, gave way to concerns over pollinator safety; leading to restrictions in their use and bans in some jurisdictions because of their impact on bees.

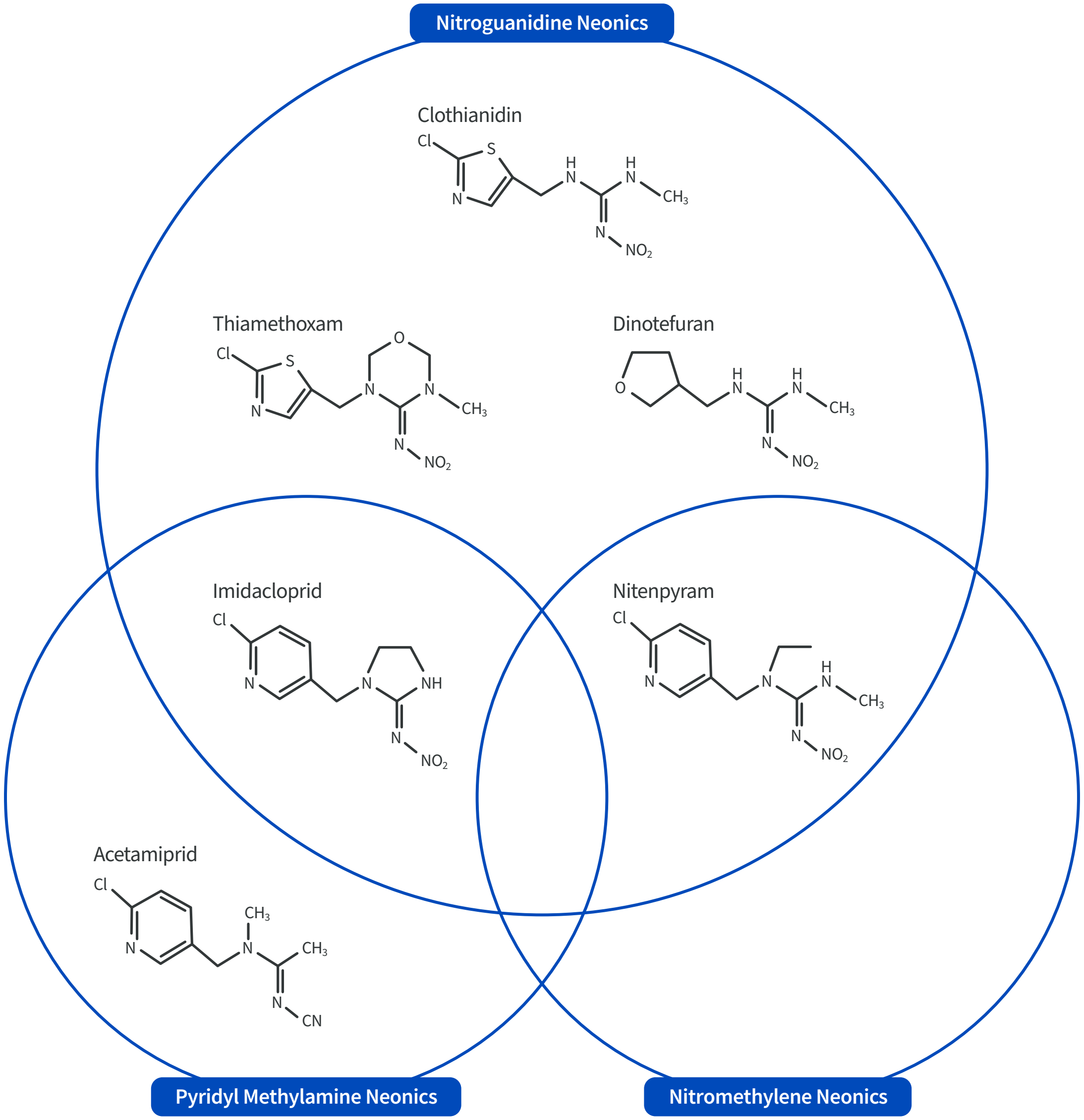
Types of Neonicotinoids

The first neonicotinoid to be developed was imidacloprid which, appeared on the market in 1991.[4] Further neonicotinoids followed on the heels of imidacloprid (Figure 1) and, as a class, neonics soon became the insecticide of choice, dominating the global market in the 1990s and 2000s.[5]

Neonicotinoids are systemic insecticides

that are taken up by the roots, or via the leaves, and then translocated to other parts of the plant, making the plants toxic to herbivorous insects. This provides direct protection from herbivorous pests, which are mainly sap-sucking insects, and indirect protection from plant viruses that are transmitted by insects.[4]

Figure 1. Sub-groups and Molecular Structures of the Most Widely Used Neonicotinoids[4,6]



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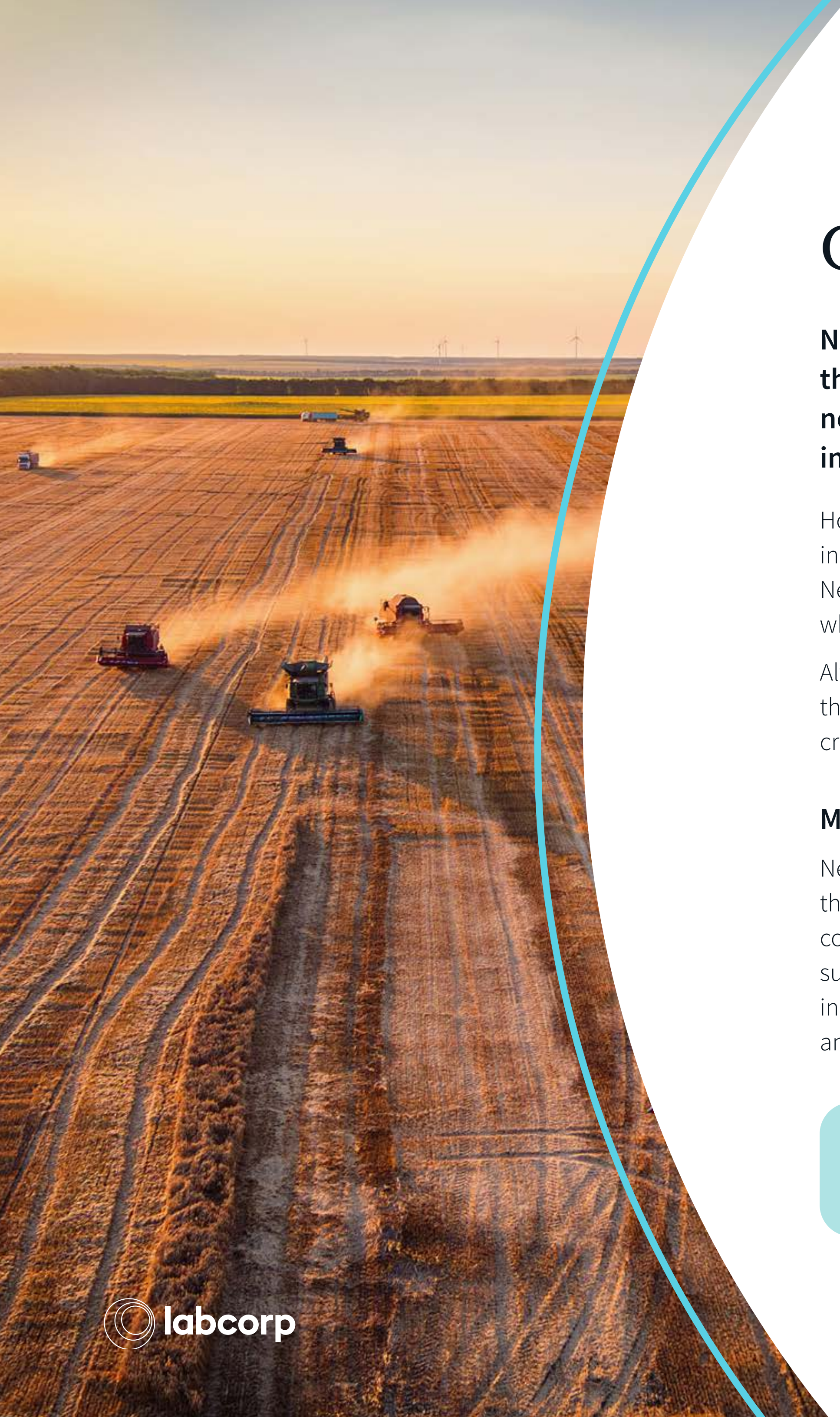


Chemistry of Neonicotinoids

Neonics are water soluble and this enables their translocation throughout the plant into stems, leaves, flowers, fruit, pollen, nectar and guttation fluid (sap exuded through the tips of leaves in some plants).

However, it is estimated that given this water solubility, only 5% of the active neonic ingredient is taken up by crops, with most dispersing into the wider environment.[5] Neonicotinoids are persistent, with half-lives in soil measured in months or years, which means that they offer the potential for long-term crop protection.[4]

Although these characteristics are attractive for efficient pest control, they also mean that neonics can spread beyond the target crop and they have been found in nearby crops, wild plants, waterways and honey.[7]

Mode of Action

Neonics act by binding to nicotinic acetylcholine receptors (nAChRs) on nerve cells in the central nervous system (CNS) of insects. Neonics act as agonists to nAChRs, activating continuous nerve activity which eventually leads to a block of nerve transmission and subsequent paralysis (Figure 2).[8] In insects, nAChRs are confined to the CNS, whereas in mammals they can be found throughout the central and peripheral nervous system and in skeletal muscle.[8]

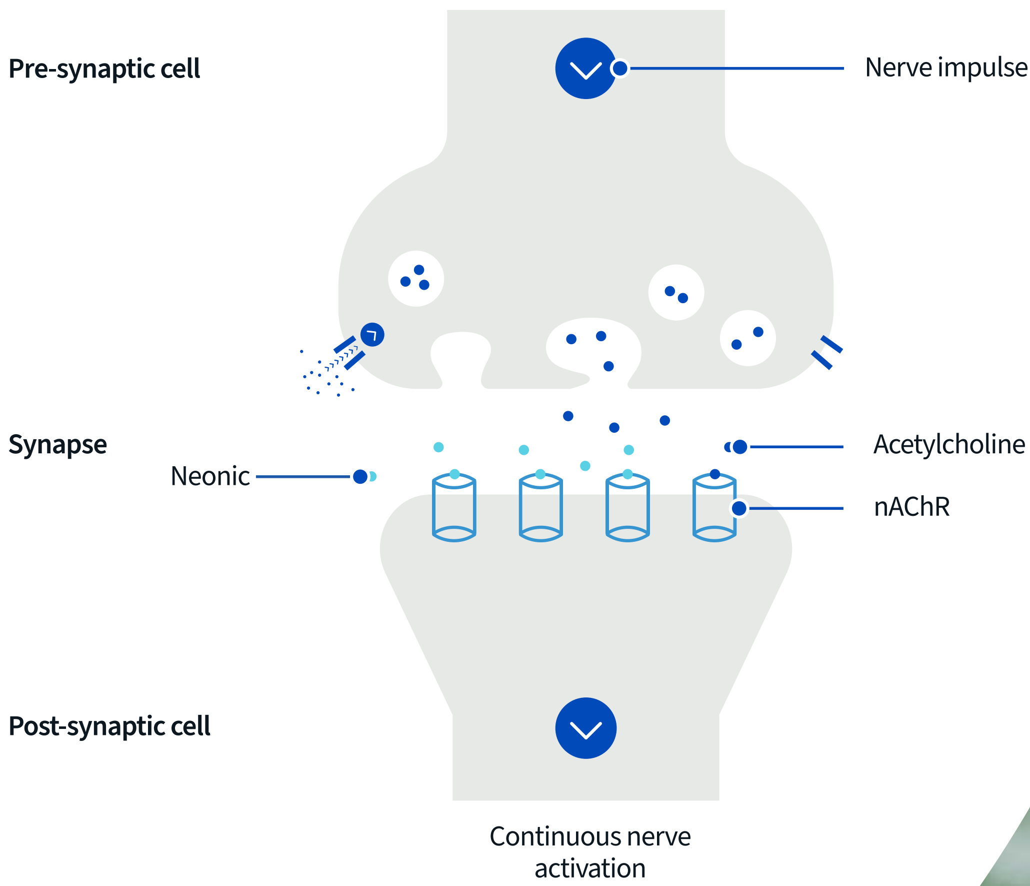
There are multiple subtypes of nAChRs, each with a varying sensitivity to different neonics.[4] Differences in sub-unit structure between nAChRs in insects and mammals predicts higher neonic selectivity for arthropods over vertebrates.[4]

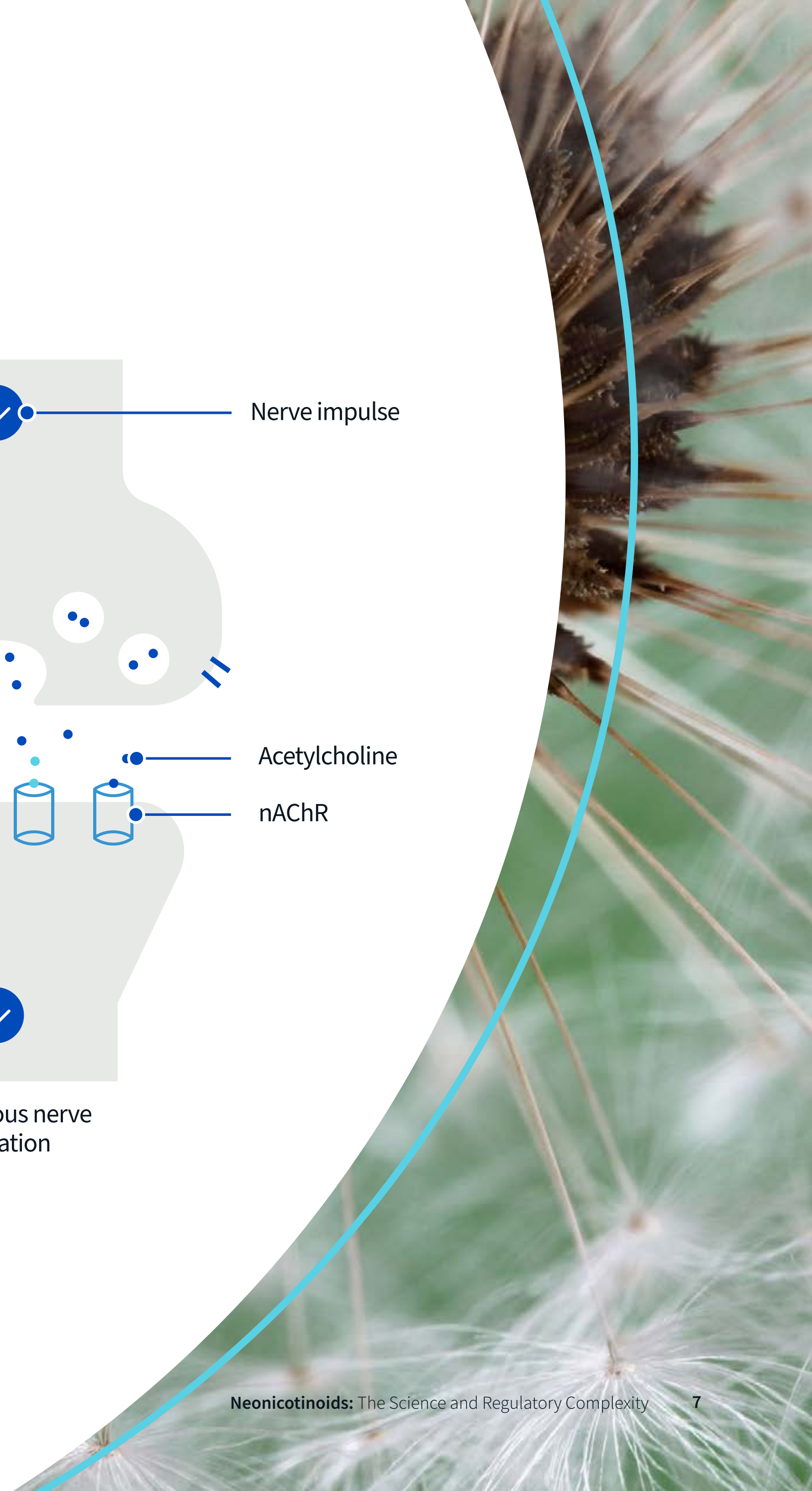
Figure 2. Mode of Action of Neonicotinoids

01 Acetylchlorine is released from the pre-synaptic cell in response to a nerve impulse.

02 Acetylchlorine is broken down by the enzyme acetylcholinesterase and transported back into the pre-synaptic cell. Neonics are not broken down in this way and remain in the synapse.

03 Binding of neonics to nAChRs on the post-synaptic cell produces continuous nerve activation.





As well as being used in agriculture, horticulture, tree nursery and forestry settings, neonicotinoids are also used for pest control in urban areas (e.g., to combat cockroaches), for veterinary applications (e.g., flea treatments) and in fish farming.[4]

Agricultural Uses of Neonicotinoids

From an agricultural standpoint, two characteristics of neonics that make them attractive is their effect on a broad-spectrum of pests that target economically important crops and their mode of application (Table 1).[4]

By far the most common application method used for neonics is seed dressing, where it is applied prophylactically to the seeds and then translocated through the plant as it grows.[4] Neonicotinoid seed treatment can provide protection to seedlings for up to ten weeks and can also reduce the need for subsequent multiple pesticide sprays to the growing crop.[7]

In developed countries, seed application has often been routine and used regardless of the presence or absence of pests.[4] In fact, in North America, untreated maize seeds are difficult to obtain, as insurers will not pay out on claims for crop losses unless farmers can demonstrate they have followed usual agricultural practice such as sowing treated seeds.[4] Interestingly, in Italy in 2012, insurance systems were in place to reduce the use of neonics where pest levels were low. In this scenario because the risk of crop damage was small, no control was needed and compensation was available if the crop failed.[9]

Table 1. Examples of Pests Targeted, and Crops Protected, by Neonicotinoids[4,10]

Pests Targeted	Crops Protected	Methods of Application
Hemipteran sap-feeding insects: • Aphididae (aphids) • Aleyrodidae (whitefly) • Cicadellidae (leafhoppers) • Fulgoroidea (planthoppers) • Pseudococcidae (mealybugs) **Foliar feeding insects:** • Leptinotarsa (Colorado potato beetle) • Lepidoptera Plutellidae (diamondback moth) • Phytophagous mites (various species) **Soil pests:** • Chrysomelidae (western corn rootworm, among others) • Elateridae (wireworms) • Coleoptera: Scarabaeidae (white grubs)	• Cereals including maize • Oilseed rape • Rice • Potato • Sugar beet • Sunflower • Fruit, like citrus and apple • Vegetables • Soy • Ornamental plants • Cotton	• Foliar spraying • Seed dressing • Seed pilling • Soil treatment • Granular application • Dipping of seedlings • Chemigation • Soil drenching • Furrow application • Trunk injections in trees • Mixing with irrigation water • Drenching of flower bulbs • Brush application to stems of fruit trees

Concerns over Neonicotinoid Safety

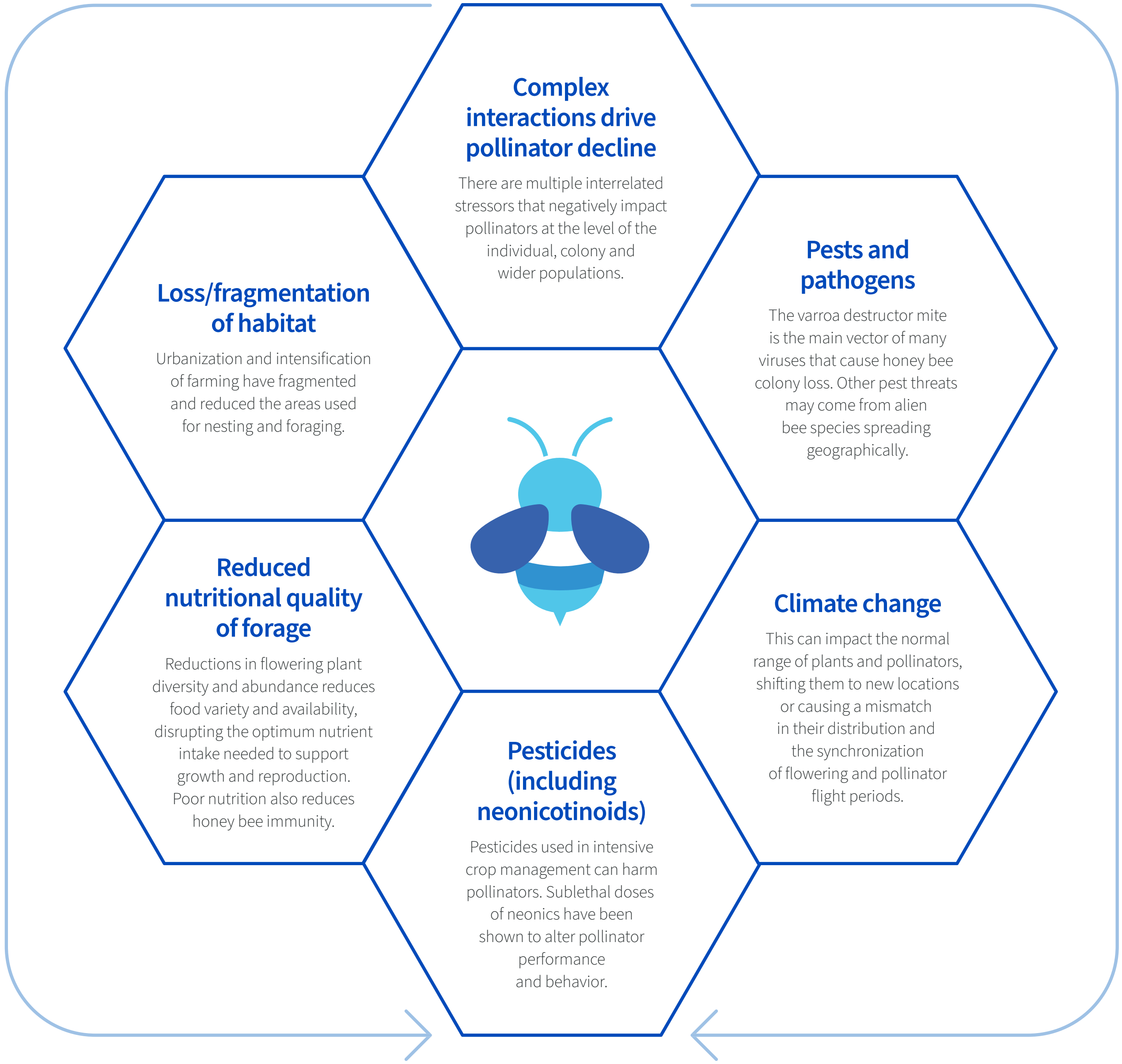
One of the benefits of neonics – their broad-spectrum of activity against multiple pests – is also a drawback, as non-target arthropod species are also affected.

Initial concerns over neonic safety related to their impact on bees and other pollinators; however, wider concern has grown regarding their effect on terrestrial and aquatic invertebrates and vertebrates, including humans.[11] The primary concern of regulators has been the impact of neonics on bees, given their importance on ecosystems and their commercial value to crop yields. Pollinators are estimated to provide or stabilize yields of approximately 75% of global crop species.[12] The main crop pollinators in Europe and North America are the honeybee (Apis mellifera) and bumble bees (Bombus).[13]

Bee and Pollinator Health

Figure 3. Multiple Pressures Impact Pollinator Health[12]

The health of bee and pollinator populations is threatened by multiple factors, not just neonics (Figure 3).



Observed Effects of Neonicotinoids on Bees

Neonics, at sublethal doses, have been shown to impact bee behavior and performance; however, the risk of exposure is dependent on neonic application rate, application type and crop type.[5]

The impact of neonics on pollinators has been most extensively studied in individual honey bees and bumble bees.[2,14] Neonics have been observed to alter a number of bee behaviors including:[5,13]

- Memory
- Foraging efficiency
- Flight ability
- Initial flower preference
- Navigation
- Survival
- Colony development
- Queen production

Regulatory Review of Neonicotinoids

European Regulation

Regulators across the globe have been concerned about the impact of neonicotinoids on bee health, as a reduction in bee numbers was observed at about the same time neonics were introduced in some countries, although this pattern is not consistent worldwide.

In 2012, the European Commission (EC) commissioned the European Food Safety Authority (EFSA) to produce a risk assessment on the impact of three neonicotinoids – imidacloprid, clothianidin and thiamethoxam – as seed dressing or granules on honey bees, bumble bees and solitary bees. This kicked off a six-year review process involving the EC, EFSA, member states (MSs), producers and non-governmental organizations (NGOs) – see Figure 4.

Figure 4. EU Review Process for Imidacloprid, Clothianidin and Thiamethoxam[6]

2012

EC commissions EFSA to produce a risk assessment on the impact of imidacloprid, clothianidin and thiamethoxam, as seed dressings or granules, on pollinators.

2013

EFSA publishes report.

EC and MSs adopt regulation 485/2013 which limits the use of the three neonics.

Additional data requested from producers to provide additional information to address uncertainties identified in the risk assessment.

Review in 2 years requested.

2015

EFSA publishes risk assessment for the three neonics on application types other than as seed dressings or granules.

Previous limitations upheld.

2016

Based on additional data supplied by producers and the MS review, EFSA publishes conclusions for:

Imidacloprid

Clothianidin

Insufficient information provided for thiamethoxam

2018

EFSA publishes a new set of conclusions from the 2-year review, including evaluation of data supplied by MSs, producers and NGOs as part of the data-call in. This leads to strengthening of the conditions for approval and EC adopting regulations:

2018/783 (imidacloprid)

2018/784 (clothianidin)

2018/785 (thiamethoxam)

Summary of Limitations

Regulation 485/2013 prescribes:

- Use by private individuals is banned
- Seed treatment is restricted

MSs had to adapt their national authorizations by September 30, 2013.
More information was requested from producers on areas of uncertainty.
Review of scientific information relevant for the risk assessment reviewed in 2 years.

Strengthened Limitations

- PPPs containing ≥1 of the three neonicos may only be applied to crops which, during their entire life cycle, remain in a permanent greenhouse, or on seeds that are exclusively intended for use in permanent greenhouses (the plant obtained remains in this greenhouse throughout its life cycle)
- MSs needed to adjust authorizations by September 19, 2018 to reflect this
- Farmers needed to comply with restrictions by December 19, 2018

EFSA's decision, and the subsequent EC legislation **restricting/banning the use of these three neonics**, was widely criticized by producers and farmers and it was out of step with other regulators globally. Some of the key aspects driving the EC/EFSA decision making and the views of opponents are captured below.

EFSA Viewpoint on Risk Assessments	Opponent Viewpoint on Risk Assessments
EFSA used the Guidance Document on the risk assessment of plant protection products on bees otherwise known as the Bee Risk Guidance Document (BRGD) as the basis for their risk assessment.[15] This risk assessment was designed to overcome concerns regarding the appropriateness of existing risk assessments and to provide a consistent and level playing field for assessment and interpretation of bee data.	The BRGD is a draft guidance document; however, the EC recommended its use by EFSA in the risk assessment for neonicotinoids, despite many MSs being opposed to it. The MSs felt it set the bar for risk at an unrealistic level that could result in substances that are not of concern to bees being wrongly identified as posing a risk to them.[6]
The BRGD allowed for a tiered testing approach and considered data from three bee species, in eight different exposure scenarios, for 17 different crops, taking into account application approach and timing of harvesting; making it a wide ranging and comprehensive review of likely sources of risk that could occur under normal agricultural conditions. **Assessment was carried out at three different levels or tiers:** • Tier I: screening assessments • Tier II: partly field-based and partly caged studies • Tier III: full field studies	The assessment was hugely complex with multiple variables and, of over 1,700 assessments considered, only a small fraction reflected higher tier studies (Tiers II and III). However, for most of EFSA's assessments, Tier II or Tier III data was absent, especially for treated crop scenarios where neonicotinoid-treated seeds are used. Therefore, the evidence basis EFSA used to interpret risk may have been scientifically inappropriate.
EFSA rated the risk to each bee type (honey, bumble and solitary) separately for specific exposure scenarios for different crops. EFSA took the overall risk across all the species. For example, for imidacloprid use on oilseed rape (winter and spring), although the exposure risk for honey bees was low from residues in nectar and pollen, the risk for bumble bees was high. Furthermore, the exposure risk was high for honey bees for exposure via dust drift in the same crop. Therefore the overall risk assessment was high.[17]	Opponents disagreed with the interpretation of overall risk, stating that 'high risk was reached for only 5% of more than 500 scenarios and that in 70% of the cases where a final risk conclusion could be reached, EFSA concluded a low risk; in 25% of cases a conclusion of uncertain risk was reached.'[18] Therefore interpretation of overall risk were overly conservative.

There are two other neonicotinoids currently approved in the EU – acetamiprid and thiacloprid. Acetamiprid was assessed as being of low risk and thiacloprid is a candidate for substitution because of its endocrine disrupting properties (Table 2).

What's Been Happening on a Member State (MS) Level?

A number of MSs have been using emergency authorizations, which are valid for 120 days, in situations where it is deemed that there is no other reasonable protection against a pest other than neonics.[6]

In 2017, Bulgaria, Estonia, Finland, Hungary, Latvia, Lithuania and Romania applied such emergency authorizations.[19] EFSA, at the request of the EC, have now developed a methodology for evaluating the data supporting the use of emergency authorizations.[20]

An Example of the Rationale for Emergency Authorizations[21]

Belgium have also approved the use of an emergency 120-day authorization of thiametoxam and clothianidin seed treatment for sugar beets, carrots and lettuce grown in the open for the 2019 growing season. Belgium's rationale was that use of low quantities of these neonics, applied to seeds, avoids later foliar application of broad-spectrum pyrethroids, which are more hazardous to all beneficial arthropods. Risk to bees is minimized because the seed treatment does not cause dust drift and the crops do not flower or show guttation, so exposure is limited.

To add further protection, the authorization includes a restriction of the full crop rotation to the planting of non-flowering or non-bee-attractive successive crops.

Summary of Regulatory Status in Other Jurisdictions

The EU view on the risk posed to bees by neonicotinoid-treated seed is out of step with many other regulators globally; with the US Environmental Protection Agency (EPA), U.S. Department of Agriculture and agencies in Canada and Australia all stating that neonics, as seed treatment, are not a major health threat to honey bees.[16]

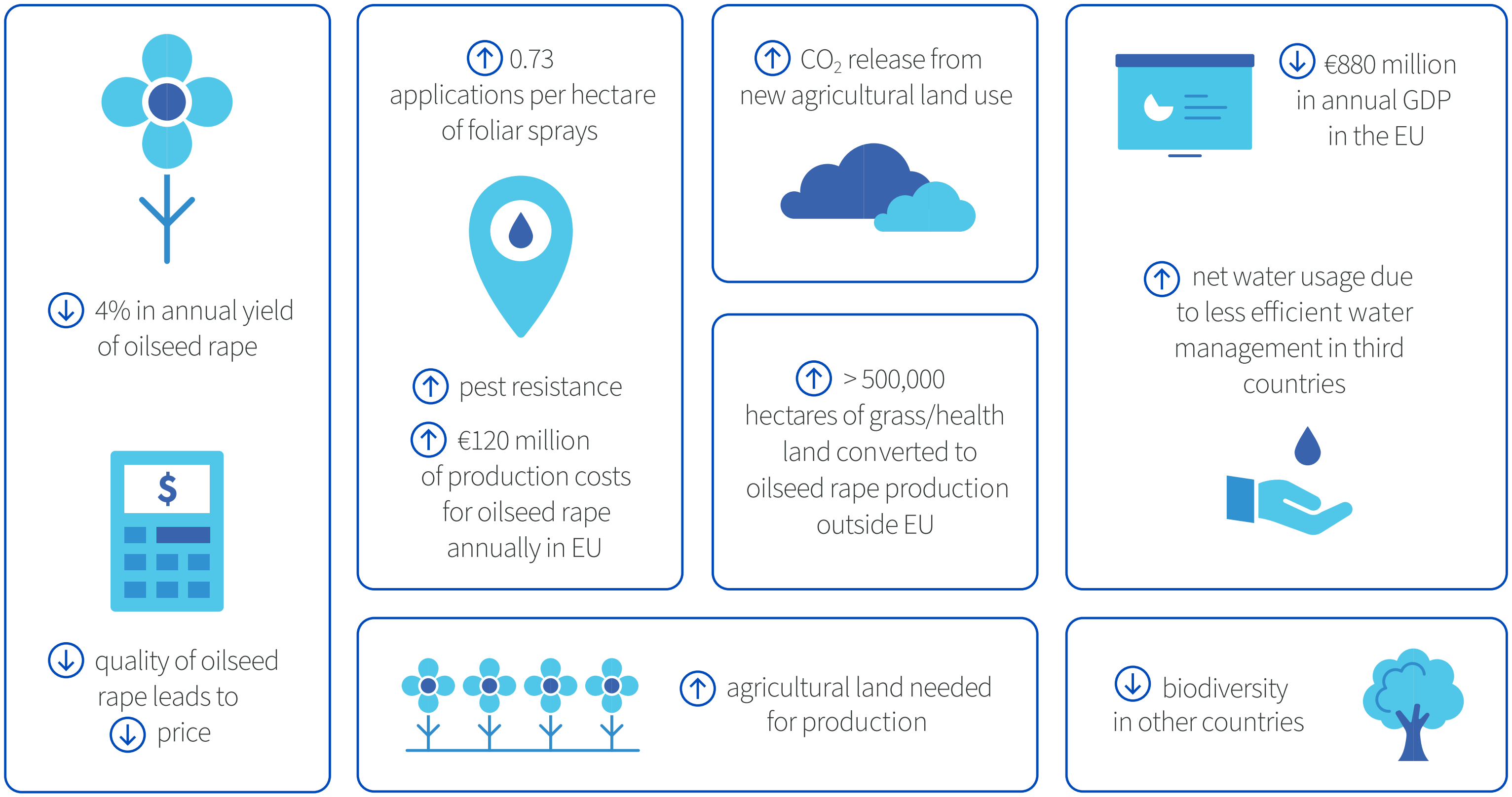
Table 2. Regulatory Status of the Main Neonicotinoid Active Substances Used in Cpps in Europe and America

Active Substance	Regulatory Status	
	EPA[22]	EFSA[3]
Imidacloprid	Updated pollinator risk assessment and a proposed interim decision will be issued for public comment in spring 2019.	The use in bee-attractive crops (including maize, oilseed rape and sunflower) is prohibited, with the exception of uses: • in greenhouses • of treatment of some crops after flowering • of winter cereals. Applicants are obliged to provide 'confirmatory information' in order to confirm the safety of the uses still allowed.
Clothianidin		
Thiamethoxam		
Acetamiprid	A proposed interim decision decision was issued for public comment in spring 2019.	EFSA established a low risk to bees so there is no ban or further restrictions. Acetamiprid has been renewed until 2033.
Thiacloprid	Registration review voluntarily cancelled by registrant. Case closure issued Nov 2014.	Is a candidate for substitution because of its endocrine disrupting properties. National authorities need to carry out comparative assessment to establish if more favorable alternative plant protection processes exist. The current approval expired on April 30, 2019 but a renewal application is ongoing.
Dinotefuran	Updated pollinator risk assessment and a proposed interim decision will be issued for public comment in spring 2019.	Not licensed in the EU.

Other jurisdictions do asses risks to bees – for example in 2014, the U.S. and Canadian governments published their 'Guidance for Assessing Pesticide Risks to Bees'.[23]

The EPA has also issued a bee advisory box on labels to highlight its strengthened pollinator protection. However, no other jurisdiction round the globe has yet followed Europe's ban on neonics.

Consequence of the Restriction/Bans on Neonicotinoid Use in the EU



The consequences of the neonic ban, although designed to reduce one of the multiple stressors which bees are exposed to, may lead to other negative ecological and economic effects. Figure 5 shows one assessment of the ecological and economic impact, estimated from data for the 2013 neonic ban, looking specifically at the impact related to oilseed rape.[24]

Summary

It is clear from the scientific research that neonicotinoids produce sublethal toxic effects in bees. It is also clear that the risk is related to the way neonics are used.

However, the consequences of a blanket ban on their use may, inadvertently, lead to other negative ecological effects through the frequent application of less potent, but more toxic, insecticides. The reality is that bees are under multiple stressors in addition to neonicotinoids and it is only by addressing those multiple factors that bee health, at a colony and population level, will be improved. This multifactorial challenge needs multifactorial solutions which requires the collaboration of a wide range of different stakeholders including farmers, bee keepers, regulators, ecologists, scientists and producers.

However, the debate on neonicotinoids in Europe has been polarized, which has made balanced, reasoned debate difficult. It has also made it difficult to generate solutions that focus on working out what insecticide options are safest to use in a given scenario and how best to support the responsible use of those insecticides. For such solutions to be achieved, it is important that all stakeholders are 'mindful of the nuances at the intersection [of] science, economics, and society.'[25]

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