THE SCIENCE OF BEE TESTING AND PESTICIDE RISK ASSESSMENT

Crop protection products (pesticides) undergo years of safety testing before they can be approved for use on the market. Advances in bee risk assessment are taking the science to a new level of rigor and requirement.

SCHNUFFEL

Crop protection products are among the most heavily regulated goods in any industry. They are as strictly regulated as pharmaceutical products and also require extensive environmental safety testing to ensure that they will not pose any unreasonable risks to wildlife, plants and the environment. Each new crop protection product requires many years of testing to meet the highest standards of safety at a cost of hundreds of millions of euros, before it can be used. Perhaps the fastest-growing area of regulatory research involves bee risk assessment, mainly driven by an increased public awareness of the importance of bees which made policy makers even more cautious when it comes to pesticide regulation. In fact, the focus on bee safety can continue throughout the entire life cycle of a pesticide product, as needed.

Crop protection products are as strictly regulated as pharmaceutical products, requiring even more extensive environmental safety testing.

Bees and other pollinating insects have an important role to play when it comes to crop pollination, so that protecting crops and ensuring bee safety is not an “either-or” option, they need to go hand-in-hand. Although scientists have identified more than 20,000 species of bees, a large part of the most economically relevant crops are pollinated by only a relatively small number of species (Kleijn et al. 2015). Of these, no other individual species is more important to agriculture than the honey bee (*Apis mellifera*), even in regions where it is not a native insect.

Therefore, and because they are relatively easy to handle and to rear, the bulk of today’s regulatory research on pollinator safety has focused on increasing our understanding of the interaction of crop protection products and honey bees to derive measures and agronomic practices that make both compatible: crop protection and pollination.

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Protecting a superorganism: the honey bee colony

The regulatory protection goal for honey bees is focused on the colony level and not on the individual bee. To better understand the background for this, it is helpful to know more about the social structure of a honey bee colony in its evolutionary and ecological context.

For so-called eusocial hymenopteran insects like honey bees, there is a distinct caste system and division of reproduction and labor between one female queen, a limited number of reproductive males (called drones, in the case of the honey bee) and many non-reproductive female workers. Honey bee evolution has produced a society in which most individuals have given up the role of reproduction and, instead, devote themselves to the care and well-being of their collective family. Solitary organisms, including humans, have an evolutionary imperative to support their own offspring, who act as the carriers of their genes to the next generation. In the case of eusocial insects such as honey bees, a female worker invests her energy in supporting her fellow bee "sisters", such as providing brood care for their mother's offspring.

In this context, honey bee workers have evolved to be disposable and quickly replaceable. Unlike the queen, who can live for two to over four years, a worker's natural lifespan during the summer is only three to six weeks. The death of any worker bee is easily compensated by the queen, which lays up to 2,000 eggs per day. Since a colony may hold up to 60,000 bees, a single worker has little individual "value" from an evolutionary perspective (she cannot reproduce and is designed by nature for quick replacement). Instead, as part of a "superorganism" – the colony – she acts solely as a tool to ensure its survival.

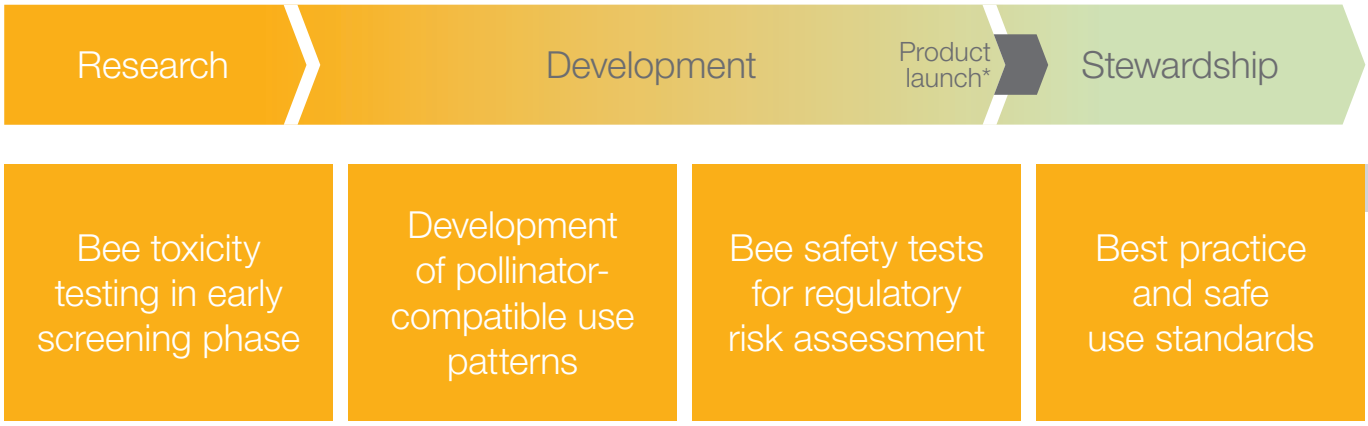
There is no reason for a guardian worker bee to flee when her hive is attacked – she cannot pass on her genes – so she is genetically hard-wired to sacrifice her life in defense of the colony to preserve its collective gene pool.

During honey bee evolution most individuals have given up the role of reproduction and, instead, devote themselves to the care and survival of their colony.

The honey bee colony perseveres through an endless cycle of worker attrition and replacement. Even in the absence of a major catastrophic event, such as a violent thunderstorm, which can kill thousands of foraging workers, it is not unusual for hives to lose hundreds of workers every day. And the same compensation mechanism is activated whenever a colony is exposed to other stressors.

Therefore, when it comes to honey bee risk assessment, it is all about the colony, which is defined as the protection goal of the risk assessment (e.g. EU, 2009). Due to their short life span and high rate of replacement, the value of honey bee workers must be seen as a continuum, operating within the whole and not as individual set pieces. Evolution has honed the colony to function as a collective and within this entity – the superorganism – honey bees demonstrate that they are truly more than the sum of their parts.

Focus on bee safety along the entire product lifecycle of a crop protection product



* On average, only one out of every 160,000 compounds evaluated successfully reaches the market.

Figure 1

Safety before sales

How confident can we be that a new crop protection product won't harm bees? To answer this question, one must first understand that the process of developing and registering a new pesticide is extremely rigorous.

On average, the development of each new crop protection product costs 250 million EUR and requires 11 to 14 years of testing (Phillips McDougall, 2016) to ensure it meets the highest standards of safety before it can be sold. Satisfying the performance and safety requirements needed to bring a new product to market is analogous to finding the proverbial "needle in a haystack". For every 160,000 compounds screened, only one will typically survive this testing process to reach full commercialization (Phillips McDougall, 2016).

Ensuring a product's safety to pollinators starts early in its development and continues throughout the registration process – and may even continue years after it enters the market *(figure 1)*. Early screening tests indicate an inherent hazard to bees, which can range from essentially non-toxic to highly toxic, depending on the active ingredient.

As the development process continues and a pesticide's use patterns are fully identified, additional studies help to assess its potential risk to bees when used as intended. These can be effectively mitigated by adopting appropriate label use restrictions, which stipulate how and when a pesticide may be used to avoid harm to pollinators. Only after the bee safety of a product related to the intended uses can be clearly demonstrated will it be registered.

Additionally, in some countries, namely in North America and Europe, pesticides are routinely subject to periodic re-evaluation to ensure that registered products continuously meet the highest standards of safety to protect human health and the environment, according the most recent scientific knowledge, including the protection of pollinators. In essence, the testing never really ends.

Due to the importance of bees to agriculture, intensive product stewardship, based on best management practices in the field, are complementary means to safeguard that potential product exposures are minimized to levels which are not harmful to bees during and after treatment of the crop. These efforts include training on safe handling and use of pesticides, user certification, implementation of new technologies to reduce potential risks, as well as monitoring and investigation of incidents of bee intoxication.

Intensive product stewardship involves measures to minimize the exposure of bees to pesticides. Like, for instance, technical improvements of sowing machineries that minimize the emission of dust from pesticide-coated seeds. Shown in the picture is a SweepAir, a novel tool for the reduction of dust emission.

Risk is defined as hazard (or toxicity) x exposure.

A lion, for example, represents a potentially high hazard to humans – but when safely confined in a cage, it represents a realistically low risk. However, if one were to step into the lion's cage, then it most certainly would become a high risk situation, as the exposure to the hazard has increased significantly.

Multiple tiers of testing

The science of evaluating the impact of crop protection products on bees can range from the relatively simple to the extraordinarily complex, following a stepwise, hierarchical approach (EPPO, 2010; US EPA & Health Canada, 2014). All pesticides must undergo basic laboratory toxicity tests (also known as tier 1 studies) on honey bees. In these highly standardized tests (OECD 1998a, b; OECD 2013), honey bees (both adults and larval stages) are exposed to various dose levels to determine a product's innate toxicity or potential hazard. If the dose or amount which kills 50 percent of the animals tested (the LD_{50} value) is below an established threshold level (set by the regulating agency) and the product will be used where there is the potential for exposure to bees, then higher-tiered testing or risk assessment approaches to better determine exposure and potential effects in the field will be required (*figure 2*).

It is important to understand the LD_{50} value in itself is not a trigger to conclude the risk assessment, nor does it mean that it is acceptable for a product to kill 50 percent of exposed bees. When evaluating pesticide risks to bees, regulators use a term known as the **Hazard Quotient (HQ)** to help determine if higher-tier testing is warranted. The HQ value of a pesticide is based on its application rate (exposure) and its inherent toxicity to bees. This calculation includes a substantial safety factor, so that if a product's HQ is found to be less than or equal to a certain trigger value defined by the regulatory authorities, it is generally considered to pose little risk to bees and higher-tier testing is not required (Aldridge & Hart, 1993; EPPO, 2010).

Test marathon: Each new crop protection product requires many years of testing to ensure it meets the highest standards of safety at a cost of hundreds of millions of euros, before it can be used.

Many insecticides have honey bee LD_{50} levels that do not meet the accepted thresholds for first-tier assessment, which is not surprising since insecticides are purposely designed to kill insects. However, it is important to recognize that hazard alone does not determine actual risk. **Risk is defined as hazard (or toxicity) x exposure**. For example, a lion represents a potentially high hazard to humans – but when safely confined in a cage, it represents a realistically low risk. However, if one were to step into the lion's cage, then it most certainly would become a high risk situation, as the exposure to the hazard has increased significantly.

When evaluating honey bees, higher-tiered testing is designed to more accurately assess a product's true risk potential by increasing both the complexity of the study and the realism of the results. Thus, the different tiers of testing have different purposes, or endpoints, which work together to refine the risk assessment process. Figure 2 includes an example of the different types of studies associated with the testing tiers, according to the U.S. Environmental Protection Agency (US EPA & Health Canada, 2014).

Different tiers of honey bee testing

TIER 1 TESTING

LABORATORY STUDIES

Highly standardized tests conducted under controlled conditions in the laboratory to determine acute or chronic laboratory toxicity of pesticides to individual bees (adults and larvae).

Example tests:
- acute oral adult toxicity
- acute contact adult toxicity
- acute larval toxicity
- 10-day adult chronic toxicity
- 21-day larval chronic toxicity
- toxicity of residues on foliage

Endpoints:
- LD50 or no observed effect concentration (NOEC)
- duration of residual toxicity

TIER 2 TESTING

SEMI-FIELD AND COLONY EXPOSURE TRIALS

Semi-field studies incorporating caged bee colonies ("bee tunnels") and colony feeding studies, designed to more closely reflect real-world exposure to pesticides and effects on the colony. Complemented by specific crop residue studies to determine potential exposure of bee colonies via nectar and pollen.

Example tests:
- semi-field (tunnel) testing for honey bees
- colony feeding study (artificial feeding in the field)
- determination of residues in pollen and nectar

Endpoints:
- mortality, flight activity, brood development, food storage, colony health, foraging activity, colony strength, behavior
- potential exposure of bees in treated crops

TIER 3 TESTING

FIELD TRIALS

Most complex and realistic of all bee studies, with colonies placed in experimental fields and exposed to crops that are treated with pesticides under typical agricultural conditions.

Example tests:
- field testing study (free-foraging bees)

Endpoints:
- mortality, flight activity, brood development, food storage, colony health, foraging activity, colony strength, behavior, overwintering survival

Study complexity and relevance

Source: US Environmental Protection Agency EPA & Health Canada Pest Management Regulatory Agency, 2014

Figure 2

Semi-field tests ("tunnel tests")

Bee colonies are exposed to pesticide treatment according to agricultural practice in so-called "tunnels" made of insect-proof gauze.

The surrogate crops typically used under these confined exposure conditions are highly attractive to bees.

If laboratory studies on individual bees and product use patterns warrant it, semi-field testing (*tier 2*) and/or full-field testing (*tier 3*), in which entire bee colonies are tested, are required to more realistically assess the potential risk to bees. Semi-field studies are conducted under relatively controlled near-natural, but "worst case" conditions (for example using bee enclosures, also known as "tunnels") to ensure the bees are confined to the treatment area. A caged tunnel study usually involves a period of pesticide exposure on a treated crop (the duration depending on the flowering period of the tested crop, but typically around 1–2 weeks) in the tunnel, followed by a more extended observation period where bees are allowed to forage freely. Observations of the colony can be made during and after the exposure period to evaluate potential acute or chronic effects. Tier 2 studies can evaluate a wide range of experimental endpoints, depending on the research objectives (*figure 2*). Results from colony feeding studies, which examine effects on colonies following exposures to known concentrations of a pesticide in a food source fed to the colony, can be compared to pesticide residues found in pollen and nectar of treated crops to help fully quantify the risk potential.

Full-field (*tier 3*) tests (EPPO, 2010; US EPA & Health Canada, 2014) are the most representative of real-world conditions and exposures, yet they are still controlled to ensure proper hive placement and consistency of environmental conditions between non-treated ("control") and treated fields with exposed bee colonies.

Tier 3 tests are also the most complex in size and scope, requiring intricate planning and a little luck to minimize the influence of naturally occurring variables (e.g. weather). These studies are custom-designed to address specific uncertainties that were identified in the lower-tier studies. To better account for these uncertainties, the study protocol is not completely standardized and ideally should be shaped by scientific consultation between the regulatory authority and industry experts to ensure the study design is practical and the endpoints obtained are meaningful. Since honey bees forage over long distances, the field study area can be quite large and care must be taken to adequately separate the different treatment and control test groups, as well as to isolate hives from any bee-attractive crops or other flowering vegetation (*figure 3*).

Higher-tiered testing may be complemented by other studies, including those that evaluate the amount of pesticide residues found in the nectar or pollen of treated crops and correspondingly, in the pollen, wax or honey samples collected directly from honey bee hives.

Additional studies may be made to assess the level of chemical residues found in flowering weeds adjacent to crops, and, in the case of soil or seed-applied systemic products, in succeeding crops (i.e. those planted in the same field after the treated crop is harvested) to determine potential exposure of foraging bees.

When assessing the potential risk to bees, the total number of tests conducted can be massive. For example, in recent years Bayer has conducted between 150 and 200 bee studies annually, approximately one quarter of which is higher-tier.

Example: large-scale field study

Neonicotinoid seed treatment in Northern Germany

Bayer commissioned* one of the largest and most comprehensive landscape assessments ever conducted for bees in Germany. The goal was to evaluate the potential effects of a neonicotinoid seed treatment on different bee pollinators under realistic use conditions in the field.

KEY FINDINGS

1. Insecticide residues found in pollen and nectar were on average 10 times below the established levels that are deemed safe to honey bee colonies by regulators.
2. Consistent with other large-scale field studies, no adverse effects were found on honey bee colony development, bumble bee populations or the reproduction of solitary bees.

* The study was performed by a contract research organization in cooperation with renowned experts, e.g. from the Oberursel Bee Research Institute and Cologne University. The results were published by Heimbach et al. 2016, Peters et al. 2016, Rolke et al. 2016 and Sterk et al. 2016.

65 KM²

Area of the study's control and treatment site, which is roughly 30 times larger than Monaco.

3

Number of pollinator species studied, including the honey bee, a bumble bee and a solitary bee.

600–800

Number of hectares in each observation area grown with oilseed rape, incorporating 17 to 18 large oilseed rape fields.

Figure 3

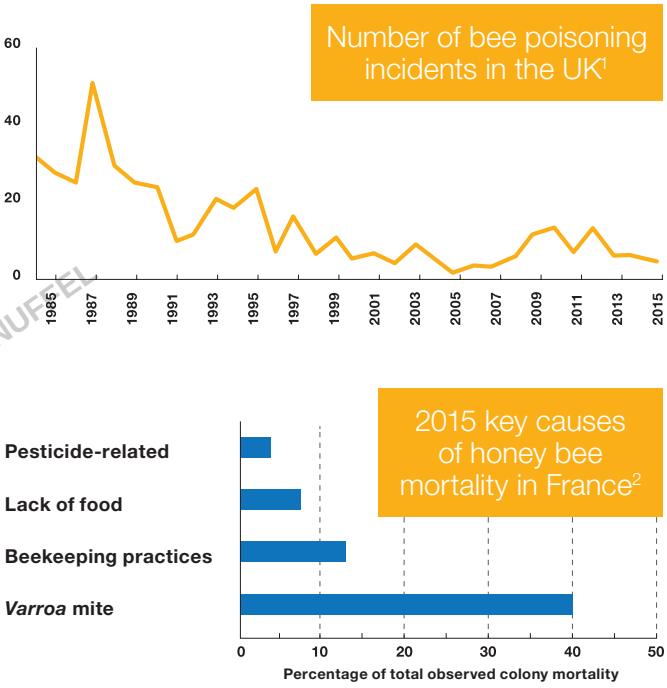
Putting testing into practice

A step-wise, sequential testing procedure is followed until an unequivocal evaluation can be made regarding pollinator safety. When a product is of low intrinsic toxicity to bees, lower-tier tests (*tier 1*) may be sufficient to conclude that a product is safe (even under worst-case exposure conditions) and that higher-tier testing is not required. In all other cases, tier 1 tests provide only an indication of a product's hazard potential, as they are insufficient to accurately evaluate its true risk potential. Taken in isolation, decisions based on such lower-tier tests could unnecessarily eliminate useful crop protection products from the market, without bringing any real benefit in terms of improved safety to bees. Higher-tiered studies incorporate a more realistic design in which honey bees are evaluated within the context of their colony and the results are far more meaningful for establishing risk assessments. Using the totality of information obtained from lower-tier tests and higher-tiered studies enables regulators and manufacturers to take reasonable precautionary steps to ensure critically-needed crop protection products can be safely used without harming bees.

Based on the data obtained from the combination of lower- and higher-tiered studies, the tested products contain explicit use directions, which are specified on the product label, to avoid harmful exposures and minimize potential risks to bees. The product label includes sufficient guidance for a safe use to farmers who are considering a pesticide treatment, also providing mandatory use instructions to reduce unwanted exposures to bees.

Additionally, the farmers' adoption of best management practices, with emphasis on product stewardship and good communication between beekeeper and farmer, further enhance pollinator protection. The relatively low number of harmful bee incidences, as reported in incident monitoring programs established for instance in Canada, Germany, the UK and the USA, is a testament to the success of these important mitigation practices (*figure 4*).

Agriculture: working to keep bees safe



- Labels of crop protection products contain specific instructions to minimize potentially harmful exposures to bees.
- The adoption of best management practices (BMPs) is helping farmers and beekeepers work together to avoid accidental honey bee colony losses.
- Some countries use monitoring systems to track reported pesticide incidents with bees and those show a decreasing trend over time.
- Country surveys have shown that non-pesticide factors play a substantially greater role in honey bee mortality than pesticides.

[1]Source: Jones, A. (2016).
[2]Source: Direction générale de l'alimentation DGAL (2016).

Figure 4

GLP: ensuring study integrity

Good Laboratory Practice (GLP) deals with the organization, process and conditions under which regulatory studies are planned, performed, monitored, recorded, archived and reported. While that is extremely important for regulatory compliance, the true purpose of GLP in pesticide testing is to make sure the products used to protect crops will not harm people, wildlife or our environment. Ultimately, the use of GLP ensures the data underpinning a product's registration are reliable indicators of its safety.

The desire to ensure the integrity and reliability of scientific safety testing prompted regulators to develop a system of management controls to govern the work of research laboratories and organizations worldwide. In 1992, the Organization for Economic Co-operation and Development (OECD) established the Principles of GLP (OECD, 1998), which have been adopted by nearly all industrialized countries as the basis for modern pesticide regulation.

Under GLP, virtually every aspect of research, including the test facility, personnel, responsibilities, study plan, quality assurance, operating process, inspection, equipment, data management, record-keeping and reporting must conform to a detailed, pre-approved checklist. This meticulous process was established to prevent fraud or data falsification and to reassure the public that regulatory testing follows a strictly enforced system to ensure the safety of products to humans and the environment.

The use of GLPs provides quality assurance officers and other regulatory authorities the means to oversee and enforce safety testing, which includes regular inspection of testing facilities and review of study documentation. It also enables them to determine if the study in question was conducted properly and transparently, even years after it was completed. This ensures data integrity and test reproducibility by making each study available for re-evaluation by regulatory authorities, as needed.

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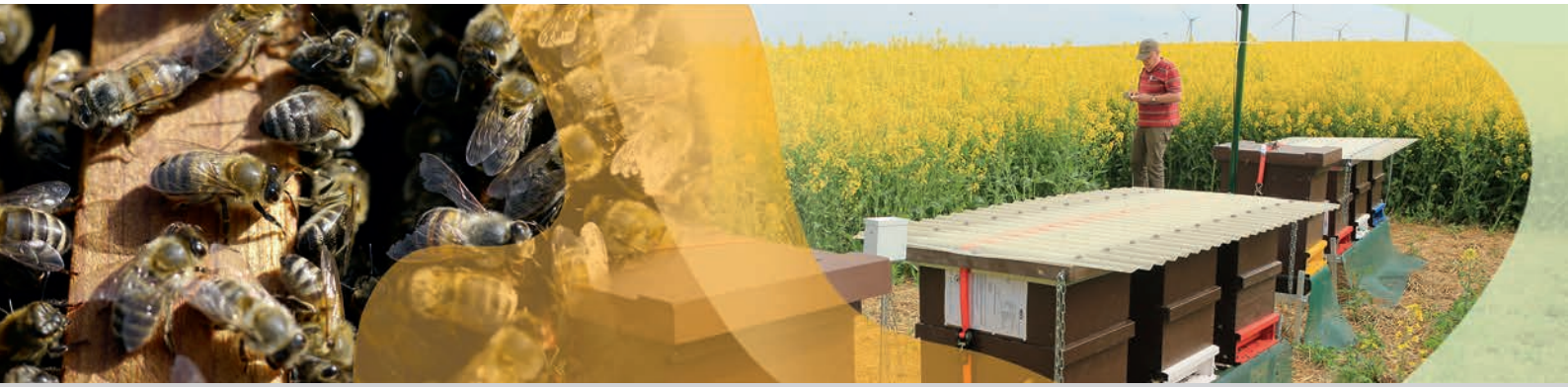
When comparing the peer-review process, where independent researchers assess a study before it is published in a scientific publication as a critical check on research integrity, with the GLP process, the latter can be far more rigorous. This clearly applies to studies in the areas of public health or environmental safety. In fact, while it is possible for a scientist to publish a peer-reviewed paper of a study that is not conducted according to GLP, it is not possible for a non-GLP study to be accepted by authorities as key evidence for the purpose of regulatory approval.

Regulators have adopted GLP to safeguard the integrity of the research upon which a pesticide's registration is based. This provides consumers with the confidence of knowing that the products used to protect crops will not harm their families or the environment.



Evolution of bee health research and risk assessment

Thirty years ago, the focus of pollinator testing was to understand whether or not spray applications killed bees. While this is still essential information, today's research has extended the focus to alternative application types (e.g. seed treatment) and explores many more parameters, such as a product's potential impact on bee behavior, reproduction and colony strength. Laboratory studies cannot duplicate the complexity of field situations or measure the colony's behavioral dynamics in responding to multiple environmental influences. A field colony's response to external stressors, such as parasites, diseases, pesticides, food availability or adverse weather, can effectively mitigate potential harm through a variety of mechanisms that are unavailable to an individual bee.

Due to the dynamic nature of factors affecting a colony, regulators are increasingly requesting that researchers also identify the mechanistic aspects of a risk assessment – to explain why a product does not harm bees, instead of merely showing that it does not cause harm. Deriving a predictable mechanism to explain the interaction between a honey bee colony and a pesticide is not easy, as our understanding is still developing and we know that certain mechanisms that we can study in the laboratory may not lead to the same effects outside of a tightly controlled laboratory environment. When developing a meaningful registration data package involving this level of complexity, scientific dialog and collaboration among regulators and industry scientists is essential to validate testing protocols and ensure transparency, consistency and reproducibility of data.

Validation of testing methods, especially highly-standardized, lower-tier testing methodologies, is important to exclude as many extrinsic variables, that may influence the results of a test, as possible. While it is not easy to develop a new testing design for bees, it is critically important (and a substantially greater challenge) that the experimental method used will ensure all other testing facilities conducting similar work will generate consistent, reproducible results.

Laboratory studies cannot duplicate the complexity of field situations or measure the colony's behavioral dynamics in responding to multiple environmental influences.

Certain crop protection products may be of low intrinsic toxicity for adult bees but potentially more harmful for their larvae. Therefore, products are also tested on bee brood.

This validation usually follows a quality assurance process (known as ring testing), in which a number of laboratories – operating in parallel – further develop the testing protocols and, by this iterative process, arrive at a globally acceptable methodology. Only after completing this procedure can a method be approved as an official testing guideline, and only these officially validated methods should be used for regulatory purposes.

Clearly, the science of the interaction between crop protection products and bee health is not static. As we learn more about bees and other pollinators, the research has grown increasingly more complex and sophisticated. For several years, regulatory agencies across the globe have been reviewing and revising testing protocols to better assess risks to bees.

It is essential that regulators come to a consensus on how best to conduct meaningful risk assessments that will allow for the protection of crops and at the same time protect the health of bees.

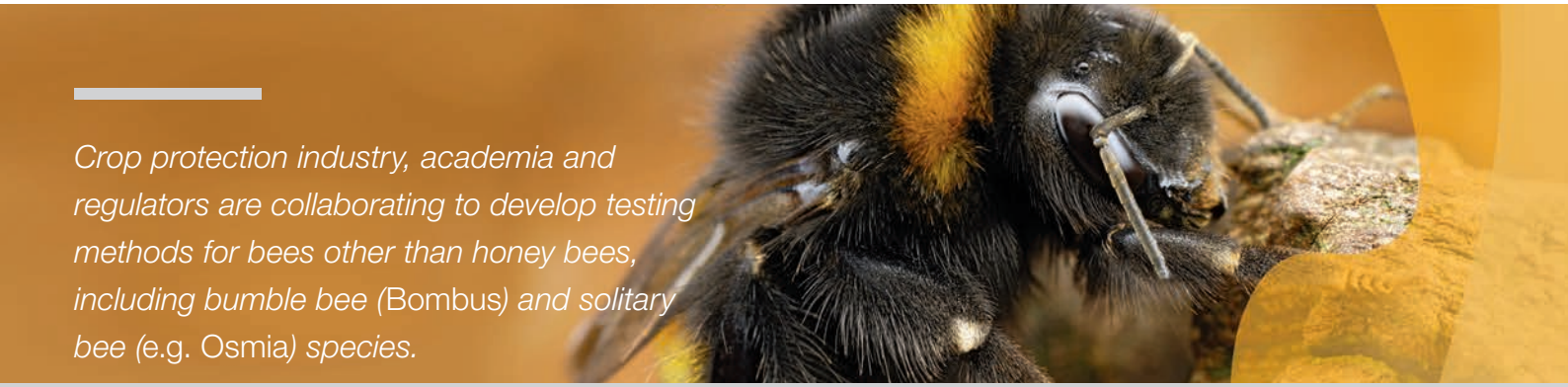
As in any rapidly evolving field of scientific research, there will be ups and downs and bee health testing is no exception. Finding the right balance between what is theoretically possible and what is practical is especially important when it can significantly affect the livelihood of a farmer or beekeeper. It is essential that regulators come to a consensus on how best to conduct meaningful risk assessments that will allow for the protection of crops and at the same time protect the health of bees.

In a global economy, the need for harmonization of protocols is becoming even more urgent as development of sophisticated systems of bee testing and risk assessment continues to expand in other countries, such as Brazil and China. The following examples of new regulatory requirements being developed in the United States and Europe reveal the evolving and sometimes divergent direction of bee testing, but also clearly demonstrate the need for more practical and realistic considerations. This is particularly striking when looking at the study and risk assessment requirements relied on in the recent evaluations of the potential impact of neonicotinoid insecticides on honey bees.

In North America and Europe, all pesticides are subject to periodic reevaluation to ensure they are continuously evaluated to comply with the latest standards of safety to protect human health and the environment. In the case of neonicotinoids, a class of insecticides, this reevaluation process was accelerated and expanded to answer additional, specific questions regarding bee safety in the United States as well as in the European Union. The US Environmental Protection Agency (EPA) recently evaluated the neonicotinoid, imidacloprid, on the basis of extensive higher-tier exposure studies over more than 20 bloom seasons (periods of time when treated crops are in bloom), involving more than 8,000 residue samples. By comparison, this is ten times the number of residue samples that would be needed to support a human dietary assessment on the same group of crops.

In response to public concerns about honey bees and other pollinators, the European Food Safety Authority (EFSA) issued a new Draft Bee Guidance Document in 2013 (EFSA, 2013), which proposes strict and very extensive new requirements for product testing and risk assessment.

The new EFSA Draft Bee Guidance Document mandates **six new routes of exposure, 46 additional risk calculations, and increases tier 1 testing requirements from two to twelve studies or extrapolations from honey bees to other bees** (i.e. predictions for other bee species, as bumble bees or solitary bees, based on honey bee data).

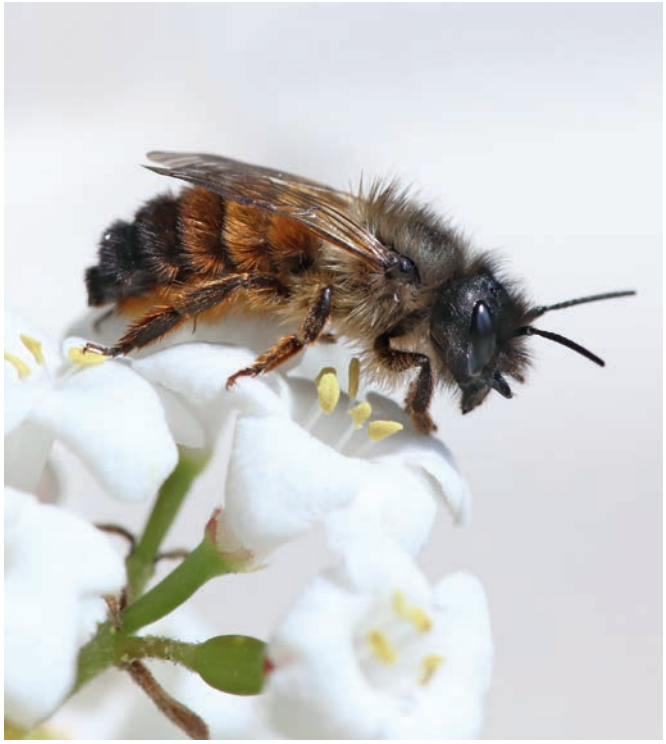


*Crop protection industry, academia and regulators are collaborating to develop testing methods for bees other than honey bees, including bumble bee (*Bombus*) and solitary bee (*e.g. Osmia*) species.*

An adoption of the EFSA Draft Bee Guidance Document's additional, extremely conservative evaluation factors, in combination with unrealistic protection goals, effectively eliminates the possibility to conduct higher-tiered and more realistic field testing for most crop protection products. For example, in order to identify that a pesticide does not cause unacceptable effects, it has to be shown that it does not cause more than 7 % reduction in colony size, this whilst natural fluctuations in colony strengths due to e.g. weather conditions or availability of forage, are often much higher. Methodologies for many of the new studies have not been developed or validated yet. Also, as currently written, the proposed requirements for higher-tier testing are impossible to fully implement from a practical point of view. A single field study would, for instance, require testing areas exceeding the land size of Malta to reach the statistical significance required.

Although EFSA's draft guidance document has not been approved by the EU Member States, the selective implementation of the key principles on which it is based, with respect to the re-evaluation of the neonicotinoids, has resulted in the suspension of numerous uses of these important products throughout the European Union. As a result of the impractical aspects of the new testing requirements, the urgent need for a revision of the proposed document is seen by many stakeholders, including bee experts in the environmental protection agencies of various Member States of the European Union. The crop protection industry remains open to discuss ways to improve this process with European regulators. Further collaboration between EFSA and the industry is clearly needed because, if the same criteria were applied to all other registered crop protection products in the EU, virtually every insecticide, as well as many fungicides and herbicides, would fail to satisfy the basic requirements for registration.

Bumble bee (*Bombus terrestris*)



Solitary bee (*Osmia bicornis*)

In the future, harmonization of different regulatory approaches to bee testing is needed to ensure that scientific risk assessment is sound, transparent and meaningful.

Looking to the future

Over the past decade, our understanding of the many factors affecting bee health has significantly improved. While new studies have revealed the importance of factors such as parasites, diseases, foraging habitat and nutrition to honey bees, by far the greatest amount of research has been directed at the potential impact of crop protection products on bees. And what we have learned over the years has confirmed the environmental safety of these important agricultural tools, which have been approved on the basis of sophisticated testing and risk assessment. This is supported by the fact that it has been clearly shown in many bee health monitoring programs in various countries on different continents that the main causative factors impairing bee health on a large scale are parasites and diseases, rather than pesticides.

Today's system of bee testing involves a series of stepwise processes that work together to ensure the safe use of registered products to honey bees following modern agricultural practices. It begins with lower-tiered laboratory tests and moves to higher-tiered field studies, where necessary, to evaluate potential risk. Under this system, products that fail to meet these rigorous criteria will not see the light of commercial reality. Finally, the adoption of label use restrictions, often supplemented by enhanced stewardship efforts, further minimize the chance of unwanted exposures.

The further development and extension of appropriate assessment schemes and scientifically robust methods to determine the safety to other bee species, beyond the honey bee, is one of the main challenges that regulators, scientists and industry will face in the coming years.

While there is much debate as to the suitability of using the honey bee as a surrogate for other bee species, it is clear that developing protocols for each of the more than 20,000 bee pollinators is impossible, from a purely practical perspective. In addition, since there is an incomplete understanding of the biology, ecology and potential risks (sensitivity and exposure) for these pollinators in the agricultural environment, plant protection industry, academia and regulators are collaborating to develop tier 1 testing methods for some of the most important ones, including bumble bee (*Bombus*) and solitary bee (*e.g. Osmia*) species (Dietzsch et al. 2015; Sandrock & Candolfi, 2015; Van der Steen et al. 2015). While tier 1 tests can determine the sensitivity of these non-Apis species towards pesticides, the absence of validated higher-tier testing methodologies makes it challenging to perform meaningful risk assessments at this time.

Despite the common use of crop protection products over many years, routine incident monitoring reports have documented relatively few instances of harmful pesticide-pollinator interactions. In their 2016 preliminary pollinator risk assessment of imidacloprid, US regulators noted very few bee incidents over many years of use. In fact, there has not been a single documented honey bee colony loss in the United States that can be attributed to exposure following a legal application of imidacloprid, despite its widespread use in agriculture. Annual monitoring reports confirm that the number of harmful incidents remains low, with further decreasing trends, in European countries, such as the UK and Germany (Jones, 2016; Thompson & Thorbahn, 2009), as well (*figure 4*).

The number of studies required to assess the risk potential of crop protection products to bees has grown at an amazing rate in recent years and it is certain that new study protocols will continue to evolve, concurrent with our understanding of bee biology and behavior. Despite this welcome progress, there is certainly room for improvement. There are serious questions regarding the usefulness of some of these new protocols, particularly in Europe, which must be resolved if agriculture and apiculture are to coexist. In the future, harmonization of different regulatory approaches to bee testing is needed to ensure that scientific risk assessment is sound, transparent and meaningful.

Selected supporting references

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The authors

Coralie van Breukelen-Groeneveld
Global Head Bayer Bee Care

Coralie van Breukelen-Groeneveld is Head of the Bayer Bee Care Center at Bayer, Division Crop Science, in Monheim, Germany. With her team, she steers the Bayer Bee Care Program, coordinating and uniting Bayer's collaborative activities in the pollinator health and safety areas. The program enables Bayer to combine and better utilize its in-depth expertise and experience in the fields of crop protection and animal health to really make a difference to the health of bees and other pollinators.

Dr Christian Maus
Global Lead Scientist Bayer Bee Care

Dr Christian Maus is Global Lead Scientist Bayer Bee Care and Pollinator Safety Manager at Bayer, Division Crop Science, in Monheim, Germany. He is responsible for pollinator health and safety within the scope of agricultural pest management and works with all stakeholders at the interfaces of science, politics and regulatory affairs.

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