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EDITORIAL

An update of the Worldwide Integrated Assessment (WIA) on systemic insecticides

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A. The Task Force on Systemic Pesticides (TFSP) and the WIA

A steep decline in insect populations started in the decade 1990–2000 (Bijleveld van Lexmond et al. 2015; Vogel, 2017; Sánchez-Bayo, 2019). In the early 1990s neonicotinoids were introduced into the pesticide market to provide systemic protection for crops from a wide range of insect pests, and they have been blamed to be responsible at least in part for these declines (Woodcock et al. 2016).

The Task Force on Systemic Pesticides (TFSP), an independent group of scientists from all over the globe, came together to carry out a comprehensive, objective, scientific review and assessment of the impact of systemic pesticides on biodiversity. Findings and evidences around the role of neonicotinoids and fipronil in

the collapse of global fauna have been presented and discussed in the TFSP working meetings. From the foundation of the TFSP (Bijleveld van Lexmond et al., 2015), members came together in working meetings, which took place in Paris (France 2010), Bath (UK 2011), Cambridge (UK 2012), Tokyo (Japan 2012), Montegrotto (Italy 2012), Louvain-la-Neuve (Belgium 2013), Tokyo (Japan 2013), Legnaro (Italy 2013), Ostheim (France 2014), Padova (Italy 2016), Padova (Italy 2017), Paris (France 2018) and Orléans (France 2019).

In 2015, the “Worldwide Integrated Assessment on the risks of Systemic Pesticides to Biodiversity and Ecosystems” (WIA), has been published as a synthesis of more than 1200 published peer-reviewed studies until June 2014, including industry-sponsored ones. It has been the first comprehensive synthesis of the state of knowledge on the risks to biodiversity and ecosystem functioning posed by the widespread global use of neonicotinoids and fipronil (Bijleveld van Lexmond et al., 2015).

The WIA of 2015 assessed respectively the trends, uses, mode of action and metabolites of these insecticides (Simon-Delso et al., 2015); their environmental fate and exposure (Bonmatin et al., 2015); effects on non-target invertebrates (Pisa et al., 2015); direct and indirect effects on vertebrate wildlife (Gibbons et al., 2015); risks to ecosystem functioning and services (Chagnon et al., 2015) and explored case studies of sustainable pest management practices that can serve as alternatives to the use of neonicotinoids and fipronil (Furlan and Kreuzweiser, 2015). The WIA of 2015 concluded that the existing literature clearly showed that levels of contamination of all environmental compartments with neonicotinoids and fipronil, caused by authorized uses, frequently exceed the lowest observed adverse effect concentrations (LOAEC) for a wide range of non-target species, and are thus inevitably to have a wide range of negative biological and ecological impacts (van der Sluijs et al., 2015).

The EASAC, the European Academies Science Advisory Council, in their report references the WIA of 2015 and comes to similar conclusions especially in terms of agricultural ecosystem services and for restoring biodiversity (EASAC, 2015). The IPBES, the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services on pollinators, pollination and food production, also references the WIA of 2015 in its report (IPBES, 2016a). Particularly, it was found that pesticides, including neonicotinoid insecticides, threaten pollinators worldwide, although the long-term effects are still unknown (IPBES, 2016b).

In the conclusive paper of the WIA of 2015 (van der Sluijs et al., 2015), a series of key knowledge gaps were highlighted:

- For most countries, there were few or no publicly available data sources on the quantities of systemic pesticides being applied;
- Screening of neonicotinoid and fipronil residues in environmental media was limited, especially in marine systems;
- Knowledge on environmental fate of neonicotinoids and fipronil and their metabolites was extremely limited, especially concerning their possible accumulation in soil and plants after repeated treatments;
- Long-term toxicity and effects of long-term/chronic exposure for susceptible organisms was unknown;
- Additive or synergistic effects due to simultaneous exposure to multiple compounds (neonicotinoids bind to the same nAChRs in the nervous system) were not studied;
- Interactions between systemic insecticides and other stressors, including other pesticides, were not studied;
- Impacts of these systemic insecticides on the delivery of a wide range of ecosystem services were uncertain;
- The short- and long-term agronomic benefits provided by neonicotinoids and fipronil were unclear.

After publication of the WIA of 2015, the TFSP was asked to contribute the expertise of its members to explore alternatives to systemic insecticide use. This was done by co-organising scientific and outreach symposia focussing on impacts and alternatives to these insecticides. These events were held in Paris (France 2015), Berlin (Germany 2015), Toronto (Canada 2016), Ottawa (Canada 2016), Montréal (Canada 2016), Manila (Philippines 2016), Tokyo (Japan 2016), Hangzhou (China 2017), Nay Pyi Taw (Myanmar 2017), Belmopan (Belize 2017) Toronto (Canada 2017), Davao (Philippines 2018), Taipei (Taiwan 2018), Pretoria (South Africa 2018) and Orléans (France 2019). In the same time, the TFSP continued its integrative works based on new published studies showing evidences on mechanisms and impacts of neonicotinoids and fipronil on biodiversity and ecosystems. This constitutes the present updated WIA on these systemic pesticides.

B. Main conclusions and knowledge gaps issuing from this updated WIA

Numerous research studies were undertaken in response to large gaps of knowledge, as attested by an exponential increase of publications on neonicotinoids and bees in the past five years. At the same time, manufactures have been expanding the neonicotinoid family, marketing new products under different sub-groups of neonicotinoids. In this update of the WIA, we have reviewed the peer-reviewed literature published after June 2014. Further discussions will address whether the newly published scientific literature fills the knowledge gaps highlighted above and highlight new emerging issues.

B.1. New molecules, metabolism, fate and transport (Giorio et al., 2017)

New evidence around the mode of action of neonicotinoids has revealed additional targets, together with neurological and genotoxic effects previously unknown. Research has also discovered new degradation products and metabolism pathways of neonicotinoids, in particular for the new and fourth generation of neonicotinoids.

Organisms are exposed to a cocktail of pesticides and affected by other stressors in the environment. Recent research started to investigate this aspects. Interestingly, some mixtures of neonicotinoids seem to have antagonistic effects, whereas exposure to several neonicotinoids is generally known to lead to synergistic toxicity. Other combination of stressors, including *Varroa* mite, microsporidian *Nosema spp* or some honeybee virus with exposure of honeybees to neonicotinoids also triggers synergistic effects.

Concerning environmental dispersion, new research confirms and supports previous findings on the contamination of air, soil and food. Beyond the archetypical neonicotinoid imidacloprid, the persistence of other neonicotinoids has been shown in the environment. Recent water surveys in more than a dozen countries highlighted a widespread contamination of surface waters around the world. Worryingly, current wastewater treatments seem to be inadequate to degrade and remove neonicotinoids, fipronil, and their toxic metabolites.

Knowledge gaps remaining are:

- Synergistic effects of pesticide cocktails and other environmental stressors.
- Identification and toxicity of metabolites and degradation products of new molecules.
- Persistence of new compounds and their metabolites in soils and contamination of subsequent crops.
- Screening of the environment for toxic metabolites and degradation products.
- Dispersion of dusts and spray drifts in the environment, their atmospheric lifetime and fate, including contamination of urban environment through atmospheric depositions.
- Biological and photochemical degradation in soils and sediments.

- Efficiency of translocation of active ingredients from treated seeds to plant tissues.
- Residues in fruits, vegetables, foodstuffs and animals, all over the world.
- Effective remediation strategies, especially given the widespread water contamination.

B.2. Impacts on organisms and ecosystems (Pisa et al., 2017)

An enormous research effort carried on bees has revealed new aspects of sublethal effects, including the reduced fecundity of queen bees, impairment of sperm in drones, negative interactions with parasites (e.g. *Varroa* mites) and on the immune system. Research on wild bees has shown that they are more sensitive to neonicotinoids than the honeybees. A few studies showed a correlation between the use of neonicotinoids and the declines in wild bees and butterflies in Europe and America, since the mid-1990s.

Toxicological effects of neonicotinoids extend far beyond the selected pest targets. Detrimental effects have been evidenced on predators and parasitoids of pests, thus confirming the unsuitability of neonicotinoids for integrated pest control programs.

Concerning the aquatic environment, studies have shown how the current contamination of surface waters are negatively affecting insect communities, which constitute a food source to fish, birds and other insectivorous vertebrates. There are now sufficient data to set protective limits for aquatic invertebrate communities in the legislation.

Concerning terrestrial vertebrates, fipronil and the neonicotinoids imidacloprid and clothianidin exert sublethal neurological effects in rats and bats. Moreover, ingestion of treated seeds by birds can cause not only sublethal effects on immunity but also lethal effects.

The negative impacts of neonicotinoids on terrestrial and aquatic invertebrates can translate into indirect impacts for the entire ecosystems.

Knowledge gaps remaining are:

- Monitoring of population trends of wild pollinators (e.g. bees, butterflies) in regions contaminated with these residual systemic insecticides.
- Effects of these insecticides on a large set of typical invertebrate species that are representatives of terrestrial invertebrate biodiversity.
- Susceptibility of beneficial non-target invertebrates (e.g. predators, parasitoids) to new neonicotinoids.
- Recovery of beneficial arthropods in areas treated with neonicotinoids and fipronil.
- Effects on soil biota (e.g. grubs, earthworms) and their impact on soil fertility.
- Monitoring of aquatic invertebrate biodiversity in waters contaminated with these systemic insecticides.
- While laboratory studies suggest that neonicotinoids and fipronil can kill or harm vertebrates, and inferences can be made from laboratory studies adopting field-realistic conditions, there are only a few studies of their impacts on vertebrate wildlife in their natural environment. Even fewer studies have investigated indirect (e.g. cascades through the food-chain) and population level impacts.
- More than half of all vertebrate studies were done of five species. Given the large variation in sensitivity to systemic pesticides among species, extrapolating results from such a small number of species to all vertebrates carries great risks, as they may not be representative.
- Lack of data on the characterisation and quantification of the impacts on ecosystem functioning and services.

B.3. Resistance and alternatives to systemic insecticides (Furlan et al., 2018)

First, prophylactic use of neonicotinoids does not guarantee an increase in crop yield. Second, when necessary, the use of systemic insecticides should be restricted to the specific areas affected by pest outbreaks. Pest control, on the other hand, can be implemented effectively using integrated pest management tools. In particular, case studies on economic insurance initiatives, as for maize crops in Italy, can provide reimbursements to the farmers for yield losses in case of economic damage.

Increasing resistance to neonicotinoids is now common and is affecting most crops worldwide. Replacement with new chemicals from the same class does not solve the problem, as all neonicotinoids target the same type of receptors and the resistance mechanisms are similar for all these compounds. The solution, therefore, is not to develop new chemicals with the same mode of action, but to favour the natural systems of pest control, such as predators and parasitoids because the latter's prevent the outbreak of pests in the first place. Many alternatives to systemic insecticides are efficient and already available. Interestingly, in 78% of the 152 authorized uses of neonicotinoids in France, there is an efficient and environmentally friendly alternative to neonicotinoids, this without any insecticide (Jactel et al., 2019). Alternatives allow to increase the net revenue for farmers. Actually, farmers can i) save money with less pesticides, and ii) sell their production at a higher price because of a better quality. However, these alternatives need to be adapted, crop by crop, to various landscapes in various countries. Furthermore, farmers should be helped (independent advises and funds) for such a transition towards a more sustainable crop production.

C. Regulations and conclusions

The WIA of 2015 has been submitted to the European Food Safety Authority (EFSA) in charge of performing, for the European Commission, a risk assessment for bees concerning the use of neonicotinoids and fipronil in seed and granular treatments currently under a EU moratorium (EC, 2013a & 2013b). To date, most of neonicotinoids uses are (or are planned to be) suspended in Europe, with the exception of acetamiprid. Here it is interesting to note that acetamiprid appeared one of the less toxic neonicotinoid for pollinators, but it is one of the most worrying neonicotinoid for human health (Ichikawa et al., 2019).

France banned fipronil for all agricultural uses late 2004. After a series of some use suspensions between 1999 and 2015, France decided in 2016 to totally ban all neonicotinoids for agricultural uses, with a very few number of exceptions. This total ban applied in 2018 (AN, 2016). Furthermore, France decided by law to ban all new molecules having the same mode of action (AN, 2018). This particularly applies for sulfoxaflor and flupyradifurone. However, special derogations has been granted in 2020 in France and in several European countries, for a limited time, for sugar beet production.

A few other initiatives occurred after publication of the WIA 2015. For instance, in the Philippines, C. O. Reyes, the Governor of the island province of Marinduque, has taken the decision to ban totally the use of neonicotinoids and fipronil in order to protect the butterfly industry of this province. Another example is given in Canada. Starting from 1st July 2015, the Canadian province of Ontario decided to restrict some use of neonicotinoids by 80% in a few years (ERO, 2015). However, there is no reliable data to support the results of such restrictions and the process is still in progress for corn and soybean seeds (ERO, 2019). At the national level, Canada is now consulting about 5 neonicotinoids for protection of aquatic life (CCME, 2020).

However, despite the evidence of negative effects on ecosystems as far as sediments (Bonmatin et al., 2019), and little productivity gains in food production, worldwide use of these and other insecticides continues to grow unabated with only a few exceptions as exemplified above. A new framework for a truly sustainable agriculture that relies mainly on natural ecosystem services instead of pesticides is required (Goulson et al.,

2018). It should be based on sound scientific knowledge and robust assessment, the precautionary principle (Patterson et al, 2018) and use the diverse range of alternative tools available through integrated pest management for pest control or organic farming (Brühl and Zaller, 2019; Wyckhuys et al., 2020).

Finally, there is an increasing set of data showing that the deleterious effects of these systemic insecticides are not restricted to invertebrates (e.g., Hallmann et al, 2017; Krupke and Tooker, 2020; Pelosi et al., 2020; Ewere et al., 2021) but affects also vertebrates, directly or indirectly (Paquet-Walsh et al., 2019; Eng et al., 2019). In addition, there is also growing evidences that mammals (including humans) can be directly affected by these insecticides (Taira, 2014; Cimino et al., 2016; Caron-Beaudoin et al., 2017; Wang et al., 2017; Berheim et al., 2019; Ospina et al., 2019; Ichikawa et al., 2019; Wang et al., 2020; Thompson et al., 2020; Oya et al., 2020; Bonmatin et al, 2020); this in sharp opposition to what was expected at the time of their registration.

Biographies



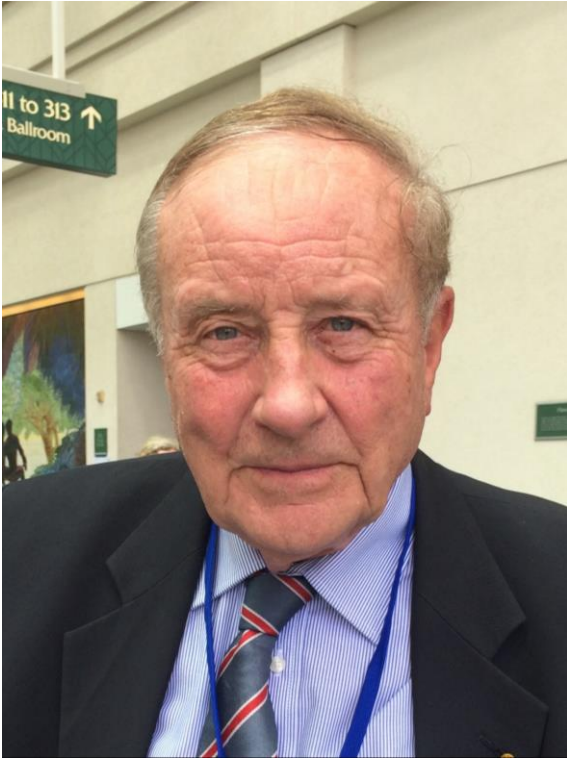
Dr Jean-Marc Bonmatin is researcher for the Centre National de la Recherche Scientifique (CNRS, France). He completed his thesis in 1987 in Chemistry and Physics (Bordeaux, France). Then, he worked for the National Research Council of Canada (Ottawa). He joined the Centre de Biophysique Moléculaire (CNRS) late 1989 in Orléans where he started his researches on structure-activity relationships of toxic molecules to their target (antibacterial, antifungal and neurotoxins, from bacteria and arthropods). From 1988, J.-M. Bonmatin was involved during twelve years in European programs on the so-called Colony Collapse Disorder (CCD) of honeybees, especially concerning analytics of pesticides in the environment and toxicology of pesticides on insects. He joined the Task Force on Systemic Pesticides (TFSP) from its very beginning in 2010, and he is now vice-President of the TFSP (www.tfsp.info). At the national level, he is currently an expert for the scientific committees of ITSAP (French Institute of Bee and Pollination) and of ANSES (French Agency of Environmental and Food Safety). He is the author of more than 80 publications. His book co-edited with Sánchez-Bayo F. and Janairo, J.I.B, entitled “Systemic Pesticides”, has been awarded with the first prize from the National Academy of Sciences of Philippines in 2018. Nowadays, he becomes more and more involved in risk assessment for public health.



Dr Chiara Giorio is lecturer at the University of Cambridge (UK). She received her Master's degree in Chemistry in 2008 from the University of Padua (Italy), where she then completed her PhD in Molecular Sciences in 2012. She was postdoctoral researcher at the University of Cambridge (UK) until the end of 2016, researcher at the Centre National de la Recherche Scientifique (CNRS, France) until the end of July 2017 and tenure-track Assistant Professor at the University of Padua (Italy) until the end of February 2020. She has also been Honorary Research Associate at the University of Birmingham (UK) since 2009. Her research interests concern formation pathways, processes, and impacts of atmospheric aerosols; and trace analysis of contaminants in remote, rural, and urban environments. She came into contact with the world of bees in 2008, participating to a project to study the translocation of neonicotinoids from treated seeds to seedling guttation drops as possible route of exposure of honeybees to neonicotinoids. Later on, she investigated the environmental dispersion of neonicotinoids from dusts emitted by seeders during sowing of corn seeds treated with neonicotinoids, and the consequent in-flight contamination of, and toxicity for, honeybees. She also worked on testing abatement devices to reduce emissions of neonicotinoids-bearing dusts during sowing operations.



Dr Francisco Sánchez-Bayo is Honorary Associate at the School of Life & Environmental Sciences of the University of Sydney, Australia. He obtained a Master's degree in Environmental Sciences and a doctorate in Ecology at the Autonomous University of Madrid. After some post-doctoral years in Australia, he became Assistant Professor at Chiba University (Japan), where he taught ecotoxicology and risk assessment of pesticides and became concerned about the ecological impacts of neonicotinoids in paddy fields. Upon his return to Australia, he was Research Associate at the University of Technology Sydney, worked in the Ecotoxicology laboratories at the Office of the Environment & Heritage NSW, and at the School of Life & Environmental Sciences, University of Sydney. Dr Sánchez-Bayo is author and co-author of over ninety scientific articles and book chapters on the environmental impact and risk of pesticides, ecology and related subjects, and is editor and author of the well-known online book "Ecological Impacts of Toxic Chemicals". He serves as Associate Editor of the journal *Entomologia Generalis*, as reviewer of over 60 international journals and as expert assessor for evaluation of scientific projects in eight countries.



Dr Maarten Bijleveld van Lexmond is a biologist and conservationist by training. He studied at Leiden and Amsterdam Universities obtaining his PhD. in 1974 with the publication of his first book: *Birds of Prey in Europe*. As one of the founders and Hon. Secretary for ten years of the World Wildlife Fund in the Netherlands, he joined the WWF international secretariat in Switzerland and later led the Commission on Ecology of the International Union for the Conservation of Nature (IUCN). In the mid-eighties he founded the Swiss Tropical Gardens in Neuchâtel, now in Kerzers (Switzerland), in parallel with the Shipstern Nature Reserve in Belize, Central America. For many years he also served as President of the Foundation for the Conservation of the Bearded Vulture which succeeded in reintroducing the species into the Alps and other parts of Europe. At present, dividing his time between Switzerland and the south of France most of it since 2009 is taken up by his function as Chairman of the international Task Force on Systemic Pesticides (TFSP) which now looks into the worldwide impact of these chemicals on biodiversity and ecosystems, and in particular on pollinators such as honey bees, bumble bees, butterflies, but also at suspected consequences for public health.

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Conflicts of interest

The authors declare no conflict of interest.