PESTICIDES MODES OF ACTION AND RESISTANCE: A PERSPECTIVE FROM THE 2019 IUPAC CONGRESS

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Figure 1. Ghent Historical City Centre.

Introduction

The International Union of Pure and Applied Chemistry (IUPAC) federation has organized congresses on diverse topics related to chemistry for one hundred years. The 2019 IUPAC Crop Protection congress was held from May 19–24 at the International Convention Center in Ghent, Belgium (Figure 1). This meeting assembled crop health experts to share their expertise and discuss emerging issues of global significance in agriculture. This year's meeting was particularly large, as it included the 14th International IUPAC Congress on Crop Protection, the European Crop Protection Association (ECPA), and the International Symposium of Crop Protection (ISCP).

Ghent proved to be a delightful location to hold this congress as this historical city has been the home of technology and innovation since the middle ages and is now a bustling and lively spot where it is a pleasure to live, work and study. It is also the home of Ghent University, whose own reputation is matched by its important role in the history of crop protection. Indeed, the First International congress for Plant Protection was held in Ghent in 1946. Similar meetings and symposia have been held in this region nearly every year since.

The congress was chaired by Prof. Pieter Spanoghe (Figure 2) and Dr. Nathan De Geyter (Ghent University, Belgium), who relied on more than 50 renowned scientists from around the world to assemble an excellent scientific programme. The meeting was attended by more than 1500 crop health specialists from 82 countries and was represented by approximately 60% industry representatives and 40% academic researchers, as well as governmental agencies, policymakers and others. A total of 350 oral contributions and 325 posters were presented during the congress. The meeting was designed to provide ample opportunities to network with our fellow crop-health experts (Figures 3 and 4).

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Figure 2. Prof. Pieter Spanoghe from Ghent University (Belgium) and Prof. Dayan from Colorado State University (USA) visit during the opening reception of the congress.

Figure 3. Attendees during one of the poster sessions.

The scientific congress started with a plenary talk by Fraser Stoddart, Board of Trustees Professor of Chemistry at Northwestern University (Illinois, USA) and 2016 Nobel laureate of Chemistry. His presentation entitled 'Research Excellence Through Innovation: Doing One's Own Thing' challenged us to produce revolutionary ideas by carrying transformative research rather than simply replicating what has been done in the past. He admonished administrators and governmental agencies to consider funding this type of high-risk, high-reward research and allowing a high degree of personal freedom to seek out truly innovative concepts.

Following this stimulating and challenging call for excellence, the congress, whose overall theme was **Crop Protection: Education of the Future Generation**, started the following day. There were 9 main themes:

Figure 4. Prof. Stephen Powles from the Australian Herbicide Resistance Institute (Australia), Dr. Roland Beffa from Bayer CropScience (Germany), Prof. Ralf Nauen from Bayer AG (Germany) and Prof. Franck Dayan from Colorado State University (USA).

1. Stewardship, regulation and communication: Future challenges
2. Novel agricultural technologies
3. Discovery and optimization of crop protection products
4. Formulation and application technologies
5. Non-dietary human health hazard, exposure and risk
6. Food quality and safety
7. Environmental fate, transport and metabolism
8. Ecosystem and ecological risk assessment
9. Mode of action and resistance

While all these themes are worthy of their own highlights, this report focuses on theme 9: Mode of Action and Resistance, that was organized by Ralf Nauen and Thomas van Leeuwen, and a scientific committee composed of experts in the areas of herbicides, fungicides, insecticides, nematicides, and genome based technologies.

Herbicide Mode of Action and Resistance

This session was chaired by Drs. De Cauwer (Ghent University, Belgium) and Dayan (Colorado State University, USA). Agriculture is facing a mounting problem of resistance to commercial herbicides, targeting most modes of action, primarily through the selection of mutations providing target-site resistance (TSR) or enhanced herbicide metabolism providing non-target site resistance (NTSR). While there has not been any new mechanism of action (MOA) introduced in

the last several decades, the need for new tools is more dire than ever. Consequently, it was a great pleasure to have several new MOAs and chemistry introduced during this congress.

Regarding new MOAs, Dr. Koskull-Doering from Bayer reported that aclonifen (Figure 5) causes bleaching of treated plants by inhibiting solanyl diphosphate synthase (SPS), a key enzyme involved in plastoquinone synthesis. There are 3 genes encoding this enzyme, two encoding for proteins localized in the chloroplast (SPS1 and SPS2) and one mitochondrial isoform (SPS3). SPS1 and SPS2 are inhibited whereas aclonifen does not affect SPS3. Mitsui Chemical Agro Inc. reported the discovery and development of cyclopyrimorate (Figure 5) as a new herbicide for weed management in rice paddies. This bleaching herbicide acts by inhibiting homogentisate solanesyltransferase (HST), a downstream enzyme of hydroxyphenylpyruvate dioxygenase (HPPD) in the plastoquinone biosynthesis pathway. Further work demonstrated that cyclopyrimorate was a proherbicide requiring bioactivation to act on HST.

Drs. Gutteridge and Shelby from FMC Agricultural Solutions reported a new herbicide mechanism of action targeted by tetflupyrolimet (new aryl pyrrolidinone anilide chemical class) for grass control in rice. The target site is dihydroorotate dehydrogenase, a key enzyme in pyrimidine biosynthesis.

Tang and Jacobsen from UCLA reported an innovative resistant-gene directed discovery approach that led to the discovery of the herbicide target site of the natural product aspterric acid. This metabolite inhibits dihydroxy-acid dehydratase DHAD. One of the advantages of this approach is that it also led to the discovery of a herbicide-resistant form of DHAD in the organism producing aspterric acid.

Regarding MOAs, Dr. Dayan and his group from Colorado State University reported new insight on the factors contributing to the contact activity of glufosinate. They demonstrated that glufosinate triggers a rapid and massive production of reactive oxygen species driving the catastrophic lipid peroxidation of the cell membranes and rapid cell death. Also, a research group Central China Normal University presented two lectures on HPPD. The first one provided new molecular insights into the mechanism of 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibition that may explain the slow binding properties of HPPD inhibitors. This group subsequently discovered a novel quinazoline-2.4-dione (code Y13161) with promising herbicidal activity.

In addition to tetflupyrolimet and cyclopyrimorate mentioned above, Sinochem Agrochemicals R&D Co. Ltd reported the discovery of another novel class of uracil herbicides containing an isoxazoline ring (Figure 5). These compounds effectively control economically important monocotyledonous and dicotyledonous weeds while safe to wheat, corn and rice. Scientists from the Institute of Pesticide and Organic Chemistry of Central China Normal University reported the herbicidal activity of novel cyclic methylphosphonates that target the pyruvate dehydrogenase complex (PDHc). They also developed highly predictive models that were used to design highly active compounds particularly effective on broadleaf weeds. Dr. Viner from Syngenta highlighted the current understanding of the binding of inhibitors to imadazoleglycerol phosphate dehydratase (IGPD), a key step in the biosynthesis of histidine. Early work identified a triazole analog of glyphosate (code C348) with herbicidal

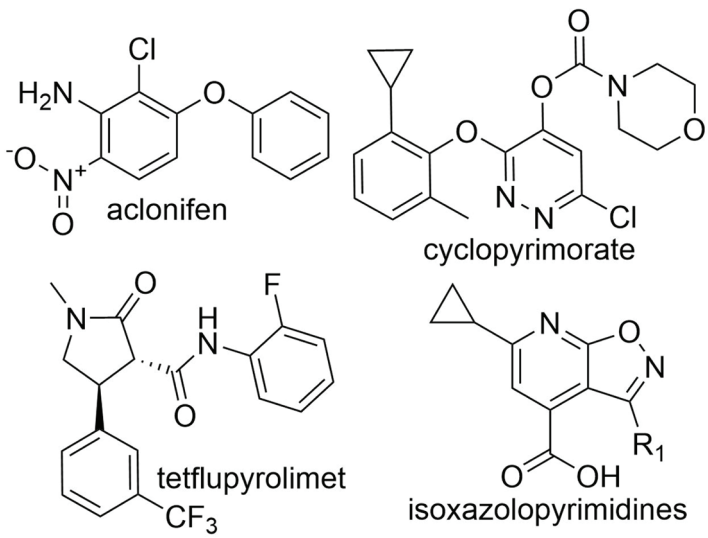

Figure 5. Structures of novel herbicides mentioned in the text.

activity that did not inhibit EPSPS. C348 competes for the binding of the substrate. Finally, Dr. Seitz from BASF introduced a new class of herbicides based on an isoxazolopyridine scaffold with a yet to be determined MOA (Figure 5). Some of the compounds have excellent cross-spectrum post-emergence control of broadleaf weeds. Selectivity to monocotyledonous crops is achieved through metabolic degradation of the active ingredient. These molecules are phloem-mobile in dicotyledons and appear to affect carbohydrate metabolism.

A couple of presentations discussed issues related to herbicide resistance. Dr Nichols (Cotton Inc.) reported on the patterns of molecular evolution and population genetics of glyphosate resistance in *Amaranthus palmeri*. This weed is now one of the most problematic plants in US crop production (see this issue of *Outlooks*). While there is a general good correlation between EPSPS gene copy number and resistance, it is not always the case. Dr. Beffa, from Bayer's Weed Resistance Research discussed the implication of non-target site resistance and its implication on managing weed resistance. Particular focus was placed on cytochrome P450 monooxygenases and GST imparting resistance to certain acetyl-CoA carboxylase (ACCase), acetolactate synthase (ALS) and very long chain fatty acid synthase (VLCFA) inhibitors.

Finally, Dr. Giannakopoulos from Newcastle University discussed the crop specificity of the maize herbicide safener cyprosulfamide with reference to the xenome. The xenome describes the overall response of a plant's xenobiotic detoxifying machinery to foreign molecules. The main conclusion was that cyprosulfamide's specific action depends on both its fate and xenome-inducing capabilities, therefore both need to be studied for the elucidation of its molecular mechanism. Metabolites of cyprosulfamide had no safener activity.

Fungicide Mode of Action and Resistance

This session was chaired by Drs. Haesaert (Ghent University, Belgium) and Mehl (Bayer AG, Germany). Resistance against fungicides is still a large problem in many crops. For the recent broad-spectrum succinate dehydrogenase inhibitors (SDHIs), two types of populations were detected with being either

sensitive (S population) or lower sensitive (LS population) to SDHIs which have a pyrazole-carboxylic acid moiety, such as penthiopyrad and fluxapyroxad. Recent studies observed the presence of multi-resistant populations of *Cercospora beticola* (Cercospora leaf spot disease or CLS) as a consequence of intensive use of single site fungicides, i.e. benzimidazole (MBC), azole (DMI) and strobilurin (QoI). With the development of multi-resistance, sugar beet production in Serbia is faced with the loss of all of the curative fungicides labeled for CLS management. The mechanisms of *Zymoseptoria tritici* (septoria leaf blotch of wheat) fungicide resistance have been well investigated and several studies have reported the preponderance of such mechanisms in the field populations of the fungus. However, abiotic factors such as temperature influence the expression of resistance.

For bulked samples and field populations, application of quantitative technologies such as quantitative PCR or pyrosequencing can provide an accurate estimate of resistance frequencies. It is increasingly evident that the simultaneous detection and quantification of several point mutations will be needed in the future, also for a faster change of resistance management recommendations, when appropriate.

New techniques (i.e. quantum chemistry, computational chemistry-based workflows as well as artificial intelligence-based predictive models) are used to determine the mode of action of new active ingredients. This targeted design enables development of novel agrochemical products as well as optimization of active ingredients for known targets. The increasing amount of biological data along with the development of sophisticated algorithms and tools will have a tremendous impact on the ability to overcome Target Specific Resistance (TSR). Approaches based on these advancements will enable prudent selection in advance of both biological targets of interest and compounds that are most-promising as starting points for discovery/optimization.

New actives ingredients from different chemical families were presented: Amino-pyrazoles are analogues of the 2-aminopyrimidine fungicides dimethirimol and ethirimol and are active against powdery mildews. Revysol® (common name: mefentrifluconazole) (Figure 6) is a novel triazole fungicide inhibiting the fungal cytochrome P450 sterol 14αdemethylase (*CYP51*). It provides excellent efficacy against a wide spectrum of foliar diseases including key diseases like septoria leaf blotch (*Zymoseptoria tritici*), brown rust in wheat (*Puccinia triticina*), apple scab (*Venturia inaequalis*), powdery mildew (*Uncinula necator*) in grapes and various diseases in corn, soybean, rice, turf and vegetables. Aminopyrifen (Figure 6) is a novel 2-amino nicotinate fungicide and has a novel mode of action. The compound is not cross-resistant to other commercial fungicides. Aminopyrifen showed high fungicidal activity against various plant pathogens including gray mold (*Botrytis cinerea*), sclerotinia rot (*Sclerotinia sclerotiorum*), powdery mildew (numerous diseases), apple scab (*Venturia inaequalis*) and anthracnose (*Colletotrichium truncatum* species). Isotianil, a plant defense inducer (PDI) with strong efficacy against rice blast (*Magnaporthe oryzae*), is a good candidate to control wheat blast (*Magnaporthe grisea*) without any risk of resistance development.

A number of presentations addressed issues related to plant resistance. For cotton, two new genes encoding for germin-like proteins (GLPs) and phytoalexin-deficient 4, respectively, are important in the hormone-based plant defense signaling pathway were described. Expression of the genes enhances resistance against *Verticillium* and *Fusarium* wilt in cotton. A negative relation was found between the expression of cotton wax synthesis regulator, GhWSR, and *Fusarium oxysporum* resistance.

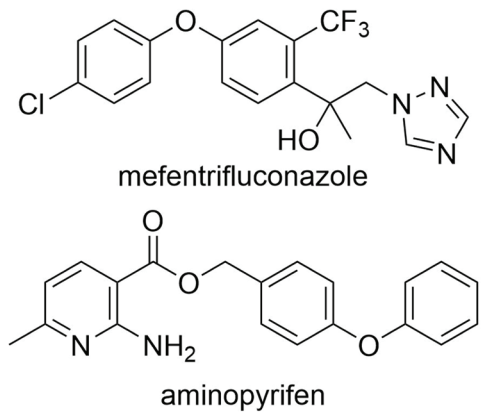

Figure 6. Structures of novel fungicides mentioned in the text.

Insecticide Mode of Action and Resistance

This session was chaired by Drs. Nauen (Bayer AG, Germany), Van Leeuwen (Ghent University, Belgium) and Vontas (Institute of Molecular Biology and Biotechnology, Greece). One of the major challenges of the crop protection industry is to develop insecticides with novel modes of action targeting binding sites not yet addressed by existing chemical classes. More than 150,000 compounds need to be screened for each new insecticide launched to the market after approximately 11 years of development and fulfilling increasingly stringent regulatory requirements, including for example resistance risk assessment, in European legislation pathways. New modes of action are of utmost importance to overcome resistance issues to established compounds, particularly in insect crop pests which can only be kept under economic damage thresholds by frequent applications. Many of the most destructive insect pests have developed high levels of (cross)resistance against different chemical classes of insecticides, either by the overexpression of metabolic enzymes rapidly detoxifying insecticides or by the selection for rare mutant alleles conferring target-site resistance. This is particularly observed in pests of intense agronomic cropping systems where chemical insect control options are limited, and where repeated applications of the same mode of action target consecutive generations of the same pest. Sustainable yields in many crops largely depend on the number of modes of action available for pest control, because resistance management strategies rely on the alternation of a certain diversity of chemical classes targeting different modes of action. The importance of *Insecticide Mode of Action and Resistance* in crop protection research is reflected by the fact that this particular IUPAC section included 20 oral presentations and spanned over two days. However a few selected presentations are briefly highlighted below.

Ozoe *et al.* from Shimane University, Japan, in collaboration with Nissan Chemical Cooperation investigated

critical determinants of binding sensitivity of ligand-gated chloride channels for the new arylisoxazoline ectoparasiticide fluralaner (Figure 7). Glutamate- and GABA-gated chloride channels are important insecticide targets and arylisoxazolines particularly active on the latter. The authors reported that a single amino acid change in glutamate-gated chloride channels increased sensitivity to fluralaner, but a loss of sensitivity to ivermectin, a member of the macrolid class of avermectins including commercial insecticides.

Crossthwaite and colleagues from Syngenta Crop Protection reported on a new insecticide, isocycloseram (Figure 7), addressing the same binding site as fluralaner, but under development for agricultural pest control. It is a broad spectrum insecticide and acaricide, including activity against lepidopteran, hemipteran, coleopteran, thysanopteran and dipteran pest species. Isocycloseram acts as a non-competitive GABA-gated chloride channel antagonist at a site different from known antagonists such as fiproles and cyclodienes.

Cordova *et al.* from FMC Agricultural Solutions highlighted work on the discovery of a new chemical class of insecticidal ryanodine receptor (RyR) activators, pyrrole-2-carboxamides. Today anthranilic and phthalic diamides are the only known commercial chemotypes selectively addressing insect RyRs. The new chemical class was identified by a target-based screening approach, but despite high binding affinity to RyRs *in vitro*, this class failed to overcome target-site resistance to diamides based on an amino acid substitution in the RyR transmembrane domain. Thus indicating a shared binding site between diamides and the novel class of pyrrole-2-carboxamides.

Flemming *et al.* from Syngenta Crop Protection reported on the discovery and mode of action of spiropidion (Figure 7), an insecticide under development targeting a number of important sucking pest species. Spiropidion is a pro-insecticide and belongs to the same chemical family as spirotetramat and other commercial ketoenols that inhibit lipid biosynthesis by targeting acetyl-CoA carboxylase. Alongside specific insights into its chemistry it was highlighted that a diversity of biochemical and genetic approaches helps to identify target proteins in crop protection research.

Huang *et al.* from Zhejiang University, China, presented new insights into the mode of action of flonicamid (Figure 7), a carboxamide pro-insecticide acting on sucking pests as a modulator of chordotonal organs with an undefined target-site. Experimental work with the model insect *Drosophila melanogaster*, revealed significant differences in flonicamid toxicity between wildtype flies and mutant flies lacking serotonin receptors. The serotonin receptors are expressed in several types of proprioceptive neurons in the chordotonal organ, suggesting serotonin receptors as a potential target for flonicamid.

Vontas (IMBB-FORTH, Greece) and co-authors presented work on how genetic manipulation and genome modification in *Drosophila* can help to dissect individual contributions of different molecular mechanisms of insecticide resistance present in a single phenotype. Genome editing by CRISPR/Cas9 helped to reverse genetically validated target-site based resistance mechanisms, whereas metabolic mechanisms of resistance have been addressed in parallel by the heterologous GAL4/UAS overexpression of candidate detoxification genes such as cytochrome P450s. Such model insects can serve as screening tools to identify new chemical classes of insecticides overcoming known resistance mechanisms.

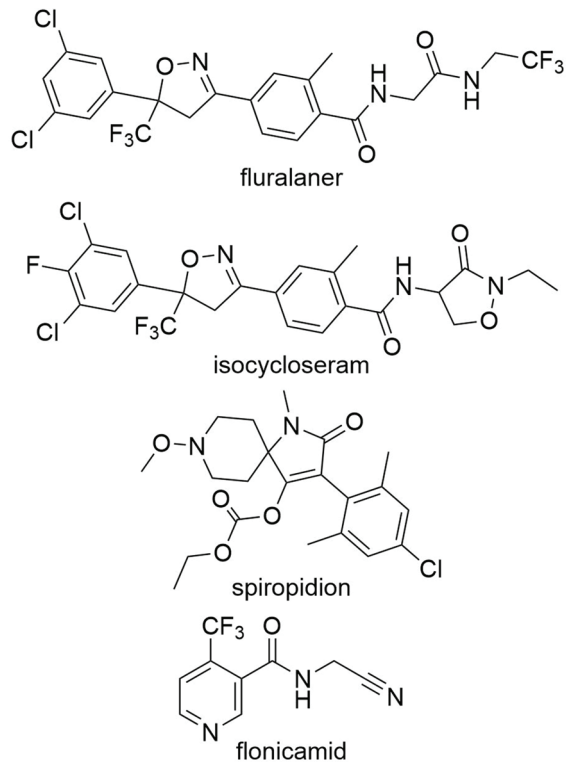

Figure 7. Structures of insecticides mentioned in the text.

Sabina Bajda from Ghent University provided an interesting experimental analysis on fitness costs of point mutations conferring resistance to different classes of acaricides in two-spotted spider mites (*Tetranychus urticae*), an ubiquitous mite pest in many agricultural and horticultural cropping systems. Major point mutations present in different acaricide target-sites such as cytochrome b, chitin synthase 1 and glutamate-gated chloride channels were selected, and their impact on fertility life-table parameters and life history traits were compared among 15 near isogenic mite lines. The findings will help to define better resistance management strategies and to support integrated mite management programmes.

Boaventura and Nauen from University of Bonn and Bayer Crop Science division, respectively, investigated the mechanism of *Bacillus thuringiensis* Cry1F toxin resistance in fall armyworm (*Spodoptera frugiperda*) populations from Brazil. Fall armyworm has recently spread outside the Americas as it invaded the African and Asian continents in 2016 and 2018, respectively. Cry1F resistance was conferred by a two amino acid deletion in one of the extracellular loops of the ATP-binding cassette transporter C2 (ABCC2). This novel mutation was characterised by molecular techniques such as recombinant expression of different ABCC2 variants in insect cell lines. The study will help to design future control strategies against fall armyworm.

Nematicide Mode of Action and Resistance

This session was chaired by Drs. Holden-Dye (University of Southampton, UK) and Wesemael (ILVO, Belgium). Two intersecting approaches may be used for chemical discovery for crop protection; target-focussed rational discovery

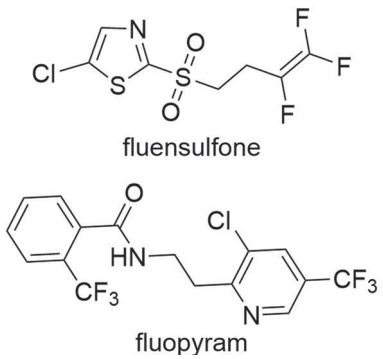

Figure 8. Structures of nematicides mentioned in the text.

programmes or phenotypic-based discovery. The former is typically based on a molecular target which, on the basis of its comparative physiological and biochemical properties, is predicted to be an efficacious target with good prospects for low off-target toxicity. It has the advantage that from the start the target is known. Optimisation during the development programme can fine-tune chemicals for the specific molecular target in the pest. The latter has the benefit of being a completely unbiased approach that can deliver new chemical structures with potent pesticidal action. However, in this case the challenge of resolving the molecular target remains. This is of key importance for chemical development, for regulatory considerations and also for understanding prospects for resistance. These two approaches intersect as a new chemical entity discovered through a phenotypic approach can spotlight a molecular target that can subsequently be subject to a more rational approach for chemical screening and design. The talks in this session touch on all of these aspects with respect to new nematicides. They span a discussion of putative new targets in the serotonin signalling pathway, recent insights into the mode of action of fluensulfone (Figure 8), molecular determinants of the efficacy of the succinate dehydrogenase inhibitor fluopyram (Figure 8) and exploring the mode of action of monoterpenoids.

Genome based technologies in MoA and resistance research

This session was chaired by Drs. Van Leeuwen (Ghent University, Belgium) and Crossthwaite (Syngenta Crop Protection, UK). To address the challenges in resolving the molecular genetic mechanisms of resistance, but also to elucidate the mode of action of new molecules more efficiently, the use of (gen)omics and advanced computational approaches has become more and more crucial. How new technologies have impacted mode of action diagnosis over the last 20 years was perfectly illustrated by the plenary talk of Dr. Earley from Syngenta (UK), who explained how the challenge of elucidating mode of action has driven biochemists to new approaches based on bioinformatics, genomics and high throughput analytical sciences.

Snoeck and colleagues form Ghent University showed how high-resolution bulk segregant analysis could be used to map accurately resistance genes in spider mites resistant to three Mitochondrial Electron Transport Inhibitors (site I). It was argued that such hypothesis-free mapping approaches will also become more and more in reach for non-model organisms, as long as a genome sequence is available. The work revealed a mutation in the PSST subunit of complex I, and a potential role for the cytochrome P450 reductase and a novel class of NHR96-like receptors in *Tetranychus urticae*.

Dr. Beck and colleagues from Bayer AG, Germany, argued that next to more common computational approaches, quantum chemistry can in principle accurately describe the electronic structure of molecules and that application of methods for protein-ligand interactions have become more feasible. A few examples are presented, including investigation into the mode of binding of nicotine and imidacroprid to insect and vertebrate nicotinic acetylcholine receptors.

Dr. Inbal form agPlenus, Israel, presented the company's aims to develop safe and effective agrochemicals based on the utilization of proprietary computational and predictive technologies. Examples were given to illustrate how the increasing amount of biological data can be used to overcome target-site specific resistance by prudent selection of both target-site and molecules. The last presentation by Dr Fan from Nankai University outlined the discovery of a number of molecules that act via plant-induced resistance.

Conclusion

These sessions concluded with a lively plenary discussion on the theme "Crop protection: fact-based science and science-based policy". These discussions included public interaction and was led by a professional moderator. In summary, the 2019 IUPAC congress highlighted the current effort by industry, academia and governmental organizations to address the need for new chemistry and new mechanisms of action. By and large, it appears that the call for action has been answered and a number of new chemistries and, more importantly, several novel mechanisms of action have been reported.

Dr. Dayan received his PhD from Auburn University in 1995. He has worked as a Research Plant Physiologist with the USDA-ARS Natural Products Utilization Research Unit for 20 years. He is now full professor in the Agricultural Biology Department at Colorado State University. His work covers the mechanisms of action of natural and synthetic herbicides and the mechanisms of herbicide resistance in plants, as well as chemical ecological studies of plant biotic interactions. Franck is (co)-author of than 169 peer-reviewed publications and 61 book chapters and reviews (https://scholar.google.com/citations?user=CojvaIAAAAJ&hl=en).

Dr. Geert Haesaert is full professor at the faculty of Bioscience Engineering of Ghent University. He is an agronomist involved in more than 40 national and international research projects. His research focus on sustainable crop production and – protection in moderate as well as in tropical agro-ecological zones. Recent interests are bio-control microorganisms toxigenic fungi (especially *Fusarium* spp.) and their associated mycotoxins. Geert Haesaert is (co)-author of more than 100 international peer-reviewed – and more than 200 technical publications (https://biblio.ugent.be/person/80200016806).

Dr. Andrew Crossthwaite received his PhD from Kings College London in 2002. He joined Syngenta's Jealott's Hill UK Research Station in 2005 and is head of Insecticide Bioscience. Located in the UK and Stein, Switzerland the groups

research aims at elucidating mode of action, understanding insect ADME and diagnosing mechanisms of insecticide resistance. Supporting synthetic, biological and natural products from discovery, through development and into commercialisation. He is also the current IRAC (Insecticide Resistance Action Committee) Mode of Action work group lead.

Dr. Nauen is an insect toxicologist and received his PhD from Portsmouth University, UK, for his work on insecticide toxicodynamics and pharmacokinetics. He is a Research Fellow and Chief Scientist at Bayer Crop Science Division in Germany. His work on insects covers mode of action studies, functional (toxico)genomics, insecticide resistance, mechanisms and management. He is appointed visiting Professor by CAAS, lecturer at Bonn University, Fellow of the Entomological Society of America and Fellow of the Royal Entomological Society (London).

Dr. Lindy Holden-Dye graduated with a BSc Hons in Physiology from the University of Wales, Cardiff and then moved to the University of Southampton where she studied for a PhD in Neuropharmacology with Professor Geoffrey Woodruff. She has pursued a long-standing interest in using invertebrate systems to provide insight into neural mechanisms of behavioural plasticity and the mode of action of neuroactive drugs. This has encompassed industrial collaborations to pursue novel anti-parasitics, in particular nematicidal chemicals. She holds a personal chair in Neuroscience in the School of Biological Sciences at the University of Southampton, UK.

Similar articles that appeared in *Outlooks on Pest Management* include – 2010 **21(6)** 288; 2014 **25(5)** 304