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A Perspective on Chemistry and Society

A Column on the Occasion of the 75th Anniversary of CHIMIA

Syngenta Crop Protection AG

Crop Protection Chemistry: Innovation with Purpose

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Jérôme Cassayre was born in Nancy, France (1973). He graduated from the Ecole Polytechnique (Palaiseau, FR, 1995) and obtained his PhD in chemistry at the Institut de Chimie des Substances Naturelles (ICSN, Gif-Sur-Yvette, FR, 1999, Prof. S. Z. Zard). He joined Novartis Crop Protection (which became Syngenta) as chemistry lab lead (Basel, CH, 2000). He became group leader (2008), then head of insecticide and seed care chemistry (Syngenta Stein, CH, 2011), followed by head of new active ingredient process technology (Münchwilen, CH, 2016). In 2018 he was appointed head of global research chemistry, Syngenta Crop Protection, Stein, Switzerland.

The SARS-CoV-2 pandemic crisis has put food security back at the center of the debate, with our western societies rediscovering the tremendous effort required to grow and supply food while other parts of the world already suffering from hunger and malnutrition before the virus became even more vulnerable during and likely will remain so after this crisis.[1] As the adage goes "every cloud has a silver lining", we can only welcome that the vital role of agriculture has been duly recognized, as well as society becoming more aware of the multiple challenges faced by farmers around the world including climate change, pest pressure, soil degradation, and the urgency to achieve greater sustainability and biodiversity. We may only wish that a similar awareness is drawn towards the recognition of science achievements which enabled agriculture to continuously improve productivity until today and the urgent need to accelerate innovation to secure future food security. In this perspective, I advocate for chemistry being part of the solution for sustainable agriculture but also explore how crop protection research may reinvent itself to better respond to growers' needs and restore the damaged but not broken link between agrochemical innovation and society.

Accelerate Innovation: Necessity Rather than Choice

Agricultural research has been the main contributor to the 60% increase of global agricultural output during the past 40 years while cropland has only increased by 5% during the same period.[2] Besides the rationalization of agronomical practices, crop protection products have played a major role in the productivity gains by preventing yield losses due to pest.[3] Crop protection chemists have been continuously innovating with the discovery of molecules acting at lower rate (a 10-fold decrease in average in the last 50 years) and displaying a much more favorable human and environmental safety profile.[4] However, a recent study confirmed and quantified that anthropogenic climate change has slowed global agricultural growth, an effect even more pronounced in the southern hemisphere.[5] With the impact of climate change expected to accelerate, it poses a serious threat to the delicate balance which exists between the constant development of pest shift and resistance, and our ability to innovate at a pace required for agriculture to sustain food production for a world population projected to reach *ca.* 10 billion by 2050.[6]

Accelerating innovation to help farmers become more resilient to the consequences of climate change while limiting its causes (food production represents 26% of anthropogenic greenhouse gas emissions)[7] is the great challenge for the next decade. The urgency to respond to the food security question in a world impacted by climate change should wind up the sterile debate between man-made or nature-made solutions, and encourage us to explore the complementarity and synergies between crop protection chemistry, biological control and modern agronomical practices.

Less is more: Expanding the Chemistry Toolbox

Modern farming techniques[8] enable the use of crop protection products at the right time (through sensing technologies), at the right place (through precision application) and at the right dose (through informed management systems), contributing to reduce the agrochemical input while optimizing output. This evolution also opens new territories in the chemical space so far largely uncharted in crop protection for cost limitations. Applying less product more precisely indeed allows for more diverse and complex chemistry to meet more stringent performance, safety and sustainability criteria while continuing to reduce the cost of application *per* hectare (Fig. 1). This will also unleash opportunities for synthetic modalities beyond small molecules following the trend observed in drug discovery in the last decade:[9] natural products already proved as a reliable source of agrochemical leads and novel modes of action,[10] peptides are emerging as promising agrochemical entities,[11] RNA interference technology has been explored for insect biocontrol,[12] and protein degraders (PROTAC technology) may also find their place in the crop protection toolbox.[13]

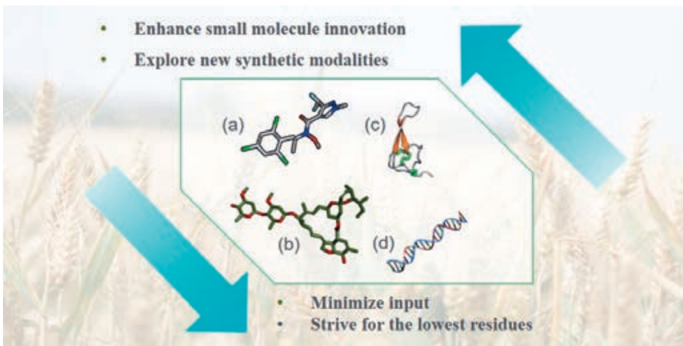

Fig. 1. Rate reduction expands the chemistry toolbox in crop protection: (a) small molecules (b) natural products, (c) peptides (d) RNA-based biocontrols.

The crop protection industry is thus committed to promote agricultural practices with less chemical input, and for chemists this is a chance to enhance and diversify small molecule innovation.

More is less: Greener Labs for Greener Products

Rethinking agrochemical innovation comes with the imperative to embed the sustainability principles in the design and synthesis of new active ingredients. Our 'sustainable design' framework, inspired by the circular economy,[14] embeds the entire lifecycle of an agrochemical product in molecular design (Fig. 2). Upstream considerations include synthetic feasibility from a cost and an environmental standpoint taking advantage of advances in synthetic tractability methods[15] and chemical complexity metrics.[16] There is also an opportunity to exploit renewable starting materials in discovery programs as alternatives to fossil-based feedstock; peptides fall naturally into this category but other options exist such as terpenes[17] and more generally through the valorization of biomass using chemo- or bio-catalysis. Downstream considerations on the other hand aim at designing compounds for optimal efficacy/selectivity ratio while considering the environmental fate of the active ingredient itself as well its metabolites.

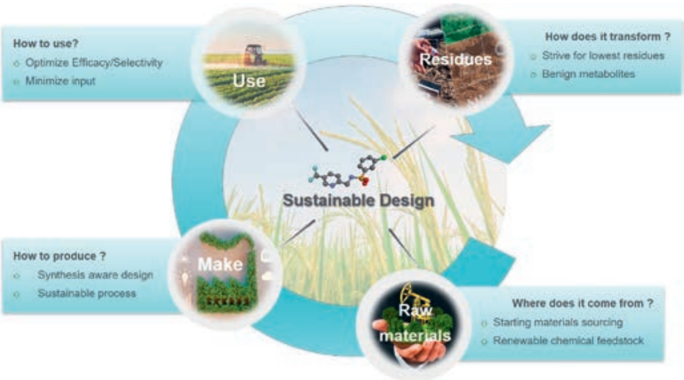

Fig. 2. A chemical design framework for sustainable crop protection innovation.

The 12 principles of green chemistry[18] provide an excellent framework to guide chemists in this quest for more sustainable innovation.[19] The change, however, starts at the laboratory doorstep: while the lab culture of safety and environmental risk assessment continuously improves, we may consider whether some hazards could be *avoided* before being *managed* thus creating a virtuous circle for adoption of more sustainable methods. We could show at Syngenta[20] that a drastic reduction in the use of seven of the most hazardous solvents (including the commonly used dichloromethane and dimethylformamide) was possible by raising awareness and promoting alternatives,[21] for example in the amide coupling reaction where effective substitutes exist[22] for the most usual solvents (DMF and CH_2Cl_2) and reagents (EDC and HATU) but wider adoption of these more sustainable solutions still requires a deliberate effort.

Hence, by consciously adopting more virtuous practices in our laboratories, we also promote innovation towards more sustainable crop protection products.

Digital Chemistry: Embracing Complexity

The design of modern agrochemicals in an enlarged chemical space and their optimization against more diverse criteria does obviously come with increased complexity for crop protection chemists. However, they find in the ongoing digital transformation a precious ally on their journey. The digitalization of the Design-Synthesis-Test-Analysis cycle,[23] at the heart of our agrochemical innovation model, can indeed transcend the usual boundaries of reductionist approaches and embrace the complexity of biological systems and chemical space to increase both quality and speed (Fig. 3). The collection of downstream data from R&D (*e.g.* field trials, product safety) but more importantly from customers (*e.g.* real-use data, agroecological biomarkers) can improve their translation into robust target functional properties, which themselves can serve as a basis for generative chemistry and multi-parameter optimization. This inverse design[24] paradigm shift brings the requirements from the customers, the regulators, and the society closer to the scientists thus increasing the quality of their research. At the same time, the convergence of technologies such as microfluidics, robotics, and artificial intelligence allow for more robust design of experiment and greater automation of chemical synthesis and biological testing thus significantly speeding up the optimization and selection of new active ingredients and ultimately accelerating the delivery of products to our customers.

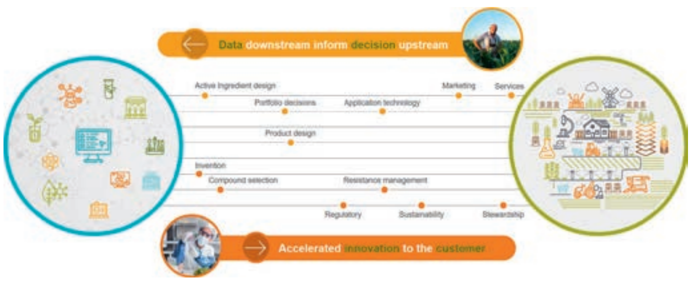

Fig. 3. Customer-centric accelerated innovation model enabled by digital chemistry.

Innovation with Purpose

The necessity to accelerate innovation in agriculture to support the growing demand for food is accentuated by climate change. While the evolution of agronomical systems and the emergence of biological solutions will contribute, chemists will continue to play the key role through the discovery of new molecules to prevent crop losses from pest, abiotic stress and more generally to improve plant and soil health. This chemical innovation imperative requires a delicate triangle balance between customer needs, regulatory standards, and society expectations. Driven by the meaningful purpose of sustainable agriculture, crop protection chemists are ready to take up this challenge and benefit from a growing innovation ecosystem both from a technology and a collaboration standpoint.

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