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A Perspective on Chemistry and Society

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

Chemistry and the Environment & Green and Sustainable Chemistry

A Roadmap Towards Sustainable Chemical Products and Processes for Switzerland

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Pollution of the environment with man-made chemicals is an issue of increasing concern with scientists, society and legislators. Environmental chemistry and (eco-)toxicology research provide evidence for the disruptive effects that many synthetic compounds have on ecosystem and human health. Involved scientists also point out that problems recognized some 30 years ago (*e.g.* with persistent organic pollutants) continue, while the market is flooded with new chemicals that exhibit similar properties or even raise new concerns.[1–3] In light of this, one may question the impact the '12 principles of green chemistry' have had, which John Warner and Paul Anastas had formulated in 1998 to guide chemical research and industry towards greener chemical processes and products.[4]

More recently, however, the sense of urgency has increased, with society by large recognizing and agreeing on the fact that chemical industry must move towards sustainable business and consumption models that are significantly more environmentally benign, and that it must do so fast as consumption and hence use of chemicals continues to speed up.[5] An increasing number of industry commitments towards green and sustainable chemistry, either as part of corporate social responsibility programs or large initiatives (*e.g.* Innovative Medicines Initiative (IMI) research projects iPiE, ChEM21,[6] PREMIER) has, finally, been matched with clear agenda setting at the EU political level in 2020. Most prominently, the 'Chemicals Strategy for Sustainability Towards a Toxic-Free Environment' of the European Commission[7] formulates a new framework for how chemical risk should be dealt with in the future. One of its core aspects is the 'toxic-free hierarchy' of actions to protect health and the environment and to encourage innovation (Fig. 1). While the 'toxic-free hierarchy' recognizes that there is obviously still much need to assess, reduce or eliminate existing pollution problems, it clearly puts the development and use of safe and sustainable chemicals, as well as clean production processes for those chemicals, on top of the hierarchy of priorities for action.

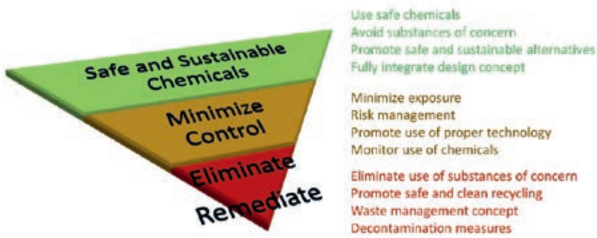

Fig. 1. The toxic-free hierarchy, adapted from ref. [6].

Switzerland has been at the forefront of chemical product discovery and production, witnessing such milestone compounds as DDT, benzodiazepine or cyclosporin, which revolutionized our understanding of how chemicals could impact our life, both positively and negatively. Switzerland has been and remains a landmark for chemistry, home to many of the biggest chemical, agrochemical and pharmaceutical companies worldwide. We would like to take the opportunity of the 75th anniversary of CHIMIA, the journal who has witnessed and communicated most of that development in Switzerland, to highlight the unique opportunity and obligation we have as a scientific community to reflect on how the specific Swiss industrial and academic environment could be leveraged to move towards more sustainable chemical products and processes, and what immediate next steps need to be taken to move into that direction.

Current Practice in Chemical Product and Process Design

Chemical product design, particularly for new active ingredients for medical and agricultural purposes, two key areas of chemical industry in Switzerland, is a highly targeted and time-consuming process that requires significant investments. Its primary goal is to discover and refine new chemical principles that have highest possible intrinsic activities to fulfill their purpose, *i.e.* a specific activity on a target disease, pest, or health outcome. These goals are increasingly challenged by growing resistance to currently used classes of bioactive compounds, most widely known by the example of resistance to antibiotics in human pathogens, but also observed, for instance, as emerging resistance of target pests in agriculture to currently used plant protection products.

Typically, the development of a new agrochemical product takes over 10 years and costs over 200 Mio Euros.[8] In the research phase, which takes up about one third of time and costs of the whole R&D process, hundred thousands of candidate structures are screened and finally reduced down to 1–2 lead structures that are taken into development, registration, and ultimately commercialization. Up to far in the development process, limited characterization of potential adverse environmental fate properties or ecotoxicological effects required for ultimate potential market registration of those lead structures will have taken place, at least for agrochemicals.

For active pharmaceutical ingredients, because of the importance of excluding severe side effects, hit-to-lead and lead optimization of potential scaffolds during the late stages of the research phase do consider human toxicity through a number of bioassays (*e.g.* genotoxicity P450 inhibition, hERG assay *etc.)*. However, also for pharmaceuticals, consideration of potential environmental health outcomes takes place only late in the development process.

In both cases, when it comes to chemical process development, the conceptual steps that routinely take place are as follows:

1. Route design: elaboration of sequence of events from commodities to desired targets; manually or *via* computer-aided approach (rule- or AI-based)
2. Decision on better options commonly driven by economic, intellectual property, scalability, robustness, safety, process readiness and developability, technologies, regulatory, productivity/expediency aspects; might optionally go through feedstock considerations or consider overall environmental impact of project
3. (Semi)-automation to identify the optimal choice of reagents, solvents; some process simulation is utilized to increase productivity and identify the best solution; time allowing, optimization to improve overall process intensification with one or the other technology incorporated (*e.g.* flow, robot…)
4. Process understanding to optimize process design; time allowing, typically conducted in parallel to previous activities to minimize risks of discarding wrong options
5. Waste management, and potential life cycle activities to reduce waste (*via* recycling, waste valorization)
6. Optionally, if time allows and for some industries, full revisit of the overall process in a holistic manner to streamline solvent or purification strategies and maximize overall throughput.

Environmental fate, *e.g.* biodegradability, and ecotoxicological properties of the process wastewater are typically considered relatively late in process development and based on measured data. They can therefore only be generated for already advanced campaigns, thus reducing the chances to change in a meaningful way a process if undesirable outcomes are observed. Also, there is hardly any opportunity for process design to feed back into the early stages of product research, such as the smart integration of relevant (bio-)feedstock or valorized materials within syntheses and processes.

Major Obstacles Impeding Change towards more Sustainable Chemical Products and Processes

The development of new chemical products is highly challenging and complex due to the many requirements and boundary conditions imposed by the targeted application itself. Additional requirements for the products and processes to be more environmentally benign and sustainable top those with a plethora of new requirements that may exhibit complex interdependencies or may not be very well defined (*e.g.* they may be subject to change depending on how the system boundaries are defined). Also, requirements on the application side may stand in contradiction to requirements on the environmental safety side. Organofluorine compounds, for instance, are constantly rising in products for both medical and agrochemical applications due to their advantageous properties for fine-tuning physico-chemical properties, increased stability and ease of synthesis.[9] Yet many of these compounds containing aliphatic C–F-bonds – the most stable chemical bond known –are close to impossible to being broken down by any environmental degradation process available. As a consequence, environmental pollution by highly persistent (per)fluorinated compounds is increasingly being recognized as major environmental threat.[10]

Yet, while we agree that these problems are challenging, we believe that they should be and can be solved, particularly in a country as rich in know-how, skillsets and talent pool as Switzerland. However, success will require processes and conditions that are adequate to tackle the complexity of the problem, which, in our opinion, is not the case for at least five reasons: First, the complexity of the agrochemical and pharmaceutical business has led to fragmentation of activities. A lot of responsibilities are split in organizations, creating silos, short-term visions, missed opportunities or the pursue of sub-optimal leads. Second, at least up until recently, there was limited recognition of the environmental agenda, and a lack of appropriate incentive systems in companies. In most industries, even when committed to sustainability, decisions tend to be taken on purely financial grounds, rather than value creation. For instance, the notion of fairness inherent in conducting the production in one or the other location alters the assessment of a process. Neglecting it may lead to the wrong decisions being taken (*i.e.* typically more ‘polluting’ standard chemistry, intensive in human work, being preferred over innovative and capital-intensive fine chemistry, although scalable for the next projects), and thus prevent significant environmental improvements and economic savings. A related aspect is short-term financial accounting, with the amortization, in case of capital investment, being calculated project per project. Instead, allowing amortization to be spread out over multiple projects would allow for a more long-term planning of capital-intense but sustainable modifications in production processes and facilities. Third, the incentive problem is aggravated by a lack of flexibility and speed in the regulatory acceptance of, *e.g.* 2nd generation synthesis processes. With current regulatory constraints, very few organizations take the efforts to go through re-registration of a new synthesis and/or process, although much improved alternatives may have already been demonstrated. As a consequence, it is estimated that only a small fraction of the commercial syntheses and processes in the pharmaceutical industry are optimal, both from an economical and environmental perspective. Fourth, there is a lack of tools such as models or high-throughput assays that are fast and accurate enough to consider the environmental risk of chemicals early in the research process. Also, tools that quickly match lead structures to the feasibility and sustainability of synthesis routes are still in their infancy. Fifth, we notice a striking lack of education of chemistry students, and even chemistry practitioners in large, in green chemistry and related topics such as life-cycle analysis, environmental chemistry, ecotoxicology, system design *etc.* throughout most Swiss universities. Prominent examples have been the loss of chemical safety and environmental technology programs at key Swiss institutions.

Roadmap towards Change in Switzerland and the Potential Role of SCS

To take full advantage of the unique Swiss research ecosystem, we suggest the following actions enhancing collaboration and science for the acceleration of best practices in sustainable chemical product and process design (see Fig. 2).

Fig. 2. Roadmap towards best practice in sustainable chemical product and process design in Switzerland.

Align the community: An overview of actors in academic and industrial research across Switzerland in the broad area of sustainable chemical product and process design should be gained. Thematically, this should go well beyond current efforts in catalysis research, such as in the frame of NCCR Catalysis, and broadly include research on chemical-intense products and processes, such as, for instance, new energy technology materials. Drawing this map of actors is necessary, but requires manpower and resources not currently available at any one institution. This raises the question whether there could be a role for the SCS, potentially in collaboration with the chemistry platform of SCNAT, in supporting such a future-oriented endeavor?

Educate the next generation: Considerable efforts are needed to mainstream green and sustainable chemistry (GSC) education into classical chemistry education, including gathering and disseminating best practices.[11] Teaching materials supporting such activities are starting to emerge.[12,13] In line with the call for considering environmental aspects early in product and process design, basic GSC principles should already be taught at the bachelor level. As chemistry bachelor programs are typically densely packed with theoretical classes and laboratory courses teaching traditional, disciplinary chemistry knowledge, finding space and the best format for introducing GSC principles requires concerted action at the level of curriculum design and hiring strategies. Respective endeavors are also an important part of the ongoing NCCR Catalysis.

Educate leaders: We need to raise the awareness of those who take decisions in our organizations, whether industrial, governmental or regulatory, about their social duty. This should best be achieved through communicating real-life examples of product and process improvements that have had real impacts on their environmental footprint, the companies' reputation, and/or for society. Such success stories should be communicated internally and externally, *e.g.* through road shows *etc*.

Generate action: We should jointly take all efforts needed to foster a community focusing on sustainable chemical product and process design that is in intense exchange and that profits from and maintains the competitive advantage of the Swiss chemistry research ecosystem. These goals can be partly achieved by defining joint actions between the SCS Sections on 'Green & Sustainable Chemistry' and on 'Chemistry and the Environment'. Yet, as a community, we should also aim to initiate ambitious, pre-competitive national collaborative projects on the subject, *e.g.* by exploiting the NCCR and NRP formats offered by the Swiss National Science Foundation. The map of actors will be an important basis upon which such initiatives can be built. We hope that the SCS will play an important role in these actions.

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