WP2 From grams to kilograms

WP2 addresses the challenges in operating continuous processes at the 'Miniplant' (kg's/day) and production scale. Data obtained in WP1 will be combined with process parameters (physiochemical properties, mixing, mass and heat transfer phenomena) and modelling to enable reactor design and scale-up. Moreover, we will develop optimal continuous flow processes that integrate multiple modular units of operation (telescoping reactors and separation units) and recycles. Novel concepts of process safety will be investigated, as well as the implementation of appropriate inline process analytical tools (sensors and detectors) to monitor performance and product quality. A seamless flow of data along the innovation chain will enable the use of digital twin technology to configure and operate novel process control strategies (WP3). Ultimately, we envision the delivery of an autonomous system that can be operated safely and continuously with minimal human intervention.

Exothermic reactions (OF4). There are many highly energetic reagents or reactions that cannot be handled safely or reliably executed on a large scale in existing batch reactors. However, many reactions involving highly reactive intermediates, such as diazomethane, are highly atom-economical, *i.e.* generate very little waste or by-product, thereby simplifying and lowering the costs of downstream processes. However, highly reactive compounds, tend to be intrinsically unstable and hazardous. Their corresponding reactions are likely to be extremely fast and highly exothermic. Therefore, suitable reactor/process design and careful heat management is needed to make sure that the process is high selectively and safe, e.g. microstructured flow reactors with a lower hold-up of hazardous material, which incurs lower cost for secondary containment. Furthermore, by coupling in-situ generation of the reactive species with its subsequent reaction with the substrate in a 'telescoped' process, will reduce the amount of highly energetic reagents to a minimum.

Process integration (OF5). Taking a chemical reaction from the lab to production scale requires design of not just the reactor, but also accompanying separation units, regeneration loops, and heat integration, which will determine the economics and sustainability of the product. Building on the results from screening and optimization (*OF3*), a design of a production process will be produced, with appropriate mass and heat transport characteristics (mixing and cooling), for the construction of a 'miniplant' for testing and experimental validation. Opportunities of process intensification and the separation and work-up procedure as a function of the product stream composition will govern the degree of telescoping with effects on the robustness of process control, investment and operating cost, and product quality. Finally, the business context of the product will determine the required degree of process flexibility. Therefore, this OF will develop concepts for modular plants and flexible process control. Conversely, safety engineering is highly regulated and extremely important in industry, yet has been traditionally underrepresented in academic research. As speciality chemicals are mostly made in batch and continuously operated, world-scale processes face different constraints and possibilities, there is a lot of room for innovation and IP in safety engineering of speciality processes. This is particularly true of the fields of inherent safety, digital monitoring and pattern recognition of deviations from the desired state of a process, and opportunities for Hazard and Operability Analysis (HAZOP) of flexible plants and the direct transfer of safety-relevant information from a lab-scale to a production process. Moreover, (inexpensive) safety concepts enabled through flow chemistry will make chemical transformations possible that would never be approved in batch operation, bearing the potential for great benefits relating to cost of goods and sustainability.

Distributed manufacturing (OF6). Prior to 2020, chemicals production has favored world scale plants for their economy of scale and the benefits of heat and mass flow integration. The rise of globalized supply chains has enabled the industry to source materials and precursors from the cheapest suppliers. While this drives down the price of products, it can lead to negative social and environmental impacts, as products produced in low-waged economies are often produced with little oversight or regulations. The outbreak and ongoing impacts of COVID-19, enhanced by the recent geopolitical conflicts affecting energy supplies, and the transition from fossil to renewable energy that is de-centrally produced and available, highlighted the need for innovative production concepts to improve the resilience and sustainability of chemical production. Distributed manufacturing relies on a network of geographically dispersed manufacturing facilities that can be coordinated using information technology. This approach can be particularly effective for sourcing precursors for small-scale pharmaceutical products, which can utilize renewable electricity in the most efficient way. By decentralizing manufacturing, it offers opportunities of creating a brand-new value chain; including providers of bespoke equipment, instruments, consultancy, engineering services, outsourced remote process control, etc, bringing production and jobs even to rural areas that currently suffer from being detached from the prosperity of business hubs. OF6 is also closely associated with supply and value chain aspects in WP3.