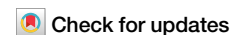


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Progress and future outlook towards a safe and sustainable production and use of chemicals



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The demands on chemical industry to transform towards safety and sustainability will require multi-disciplinary research and development where experts on chemistry and chemical engineering, toxicology, ecotoxicology, and life cycle assessment collaborate to develop novel production methods, chemicals and materials. Here we summarise the results of the Mistra SafeChem programme which has yielded considerable output in the areas of catalysis/bio-catalysis, hazard screening for humans and ecosystems and life cycle assessment with chemical footprints, both as individual scientific achievements and as part of an integrated approach to assess safety and sustainability of novel chemicals and chemical synthesis processes, in chemical value chains and across collaborations between industry- academia/ industry-industry. The outcomes from the programme are summarised and discussed and experiences from dialogues on the future of safe and sustainable chemistry are presented.

The chemical industry in Europe is facing challenges both in terms of the global market competition and expectations to contribute with new chemicals and materials necessary to fulfil the EU Green Deal¹. The latter includes the further development of a safe and sustainable industry sector, with increasing demands on climate neutrality and chemical safety. Meeting these challenges is necessary to achieve sustainable development and a long-term competitive European economy.

These challenges are, to a large extent, presented in the EU Chemical Strategy for Sustainability (CSS)² launched in October 2020. The CSS represents a major initiative and a major step forward towards a safer production and use of chemicals and materials. Both the CSS and chemical industry organisations emphasize that new chemicals and materials are expected to contribute to the green and sustainable transition that is ongoing in Europe, and to the fulfilment of the global Sustainable Development Goals (SDGs)³. The challenge is thus to maximise the benefits of

chemicals and new materials contributing to the green deal transformations while reducing the associated risks. The actions defined in the strategy provides a framework for this. One key action in the CSS is the introduction of the concept Safe and Sustainable by Design (SSbD)⁴. SSbD is a voluntary assessment framework that is under development and aimed at integrating aspects for the domain of safety, circularity and functionality of chemicals and materials, with sustainability consideration throughout their lifecycle. SSbD aims at facilitating the industrial transition towards a safe, zero pollution, climate-neutral and resource-efficient economy, addressing adverse effects on humans, ecosystems and biodiversity from a lifecycle perspective¹. Although the SSbD framework is seen as important for the transition towards safety and sustainability by stakeholders (e.g. by Cefic, The European Chemical Industry Council⁵), there are some challenges to consider⁶ including the need for high level of expert knowledge when assessing the chemical at the earliest stages of development. The expectations on the

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industry to deliver novel functional, safe and sustainable chemicals and materials will require large research and innovation efforts as well as the development of methods and procedures to ascertain the safety and sustainability of these new products. The recently presented EU Chemical Industry Action Plan⁷ also emphasizes the need for research, innovation and investments to ensure the future competitiveness of a sustainable EU chemical industry.

The Mistra SafeChem research programme is a large 4+4-year effort and has a vision to promote and enable a safe and sustainable chemical industry. In its first phase, involving 6 research partner institutions, as well as 14 companies representing industries from basic chemical and pharmaceutical producers to automobile producers and suppliers of cosmetics producers. The programme was started before the launching of the EU CSS, but research conducted in the programme is to a large extent relevant to the strategy, especially for the development and implementation of the SSbD-framework^{4,6,8} and providing suitable models and tools for SSbD assessment.

One key aspect of chemical manufacturing is the use of catalysts to accelerate reactions to industrial relevant timescales. Catalysis has a strong tradition in Sweden, for instance the Arrhenius equation (Svante August Arrhenius) and fundamental chemical concepts introduced by Jöns Jacob Berzelius. At the centre of the Mistra SafeChem programme is the development of novel synthesis processes based on catalysis, bio-catalysis and processes to enable circular use of raw materials. Equally important is the development of models and methods for hazard and risk assessment to allow early-stage assessment of the safety and environmental sustainability of these new synthesis processes and the chemicals and materials produced. To ensure that hazards and risks can be assessed over the life-cycle of the chemical and/or product, models and approaches for assessing exposure and risks need to cover the production, use and disposal stages in line with the concept of SSbD as presented by the EU Commission⁴.

In the Mistra SafeChem programme, chemists, biochemists, chemical engineers, toxicologists, ecotoxicologists, and life cycle assessment (LCA) experts cooperate to fulfil the research tasks aimed at making chemical and material development safe and sustainable from the early design and research phase through to large-scale production and use.

The participation of industry in the programme has proven to be a key strength, with contributions including a continual dialogue on the relevance of the research activities, as future end-users of the results, and by active participation in the basic research. Industry partners have also actively participated in internal and external communication activities, training and staff exchange. Implementation of results is an important aspect of this research programme and industry partners participate in the programme with a range of expectations. In some cases, industry has a direct interest in specific results such as novel synthesis routes for specific chemicals or valorisation of waste materials (see below) that can be integrated in future production processes. In other cases, industry partners are seeking to increase the knowledge base on specific topics of sustainable chemistry and to contribute to the training of PhD and Master students in selected areas making them attractive for future employment and continued research and development in a commercial setting.

A schematic description of the programme's main research components is presented in Fig. 1. The first phase of the programme started in December 2020 and closed in June 2024, while the second phase is currently ongoing until June 2028. Mistra SafeChem is funded by Mistra, an independent research foundation in Sweden, with additional contributions from industry and research partners. More information can be found on the programme website www.mistrasafechem.se⁹.

The first phase of Mistra SafeChem programme has yielded a significant scientific output in the form of over 100 published papers and technical reports, largely contributing to a more sustainable way of working in relation to chemicals. Results have recently been summarised and communicated in the Mistra SafeChem “toolbox” available on the programme website¹⁰.

Here, we present key achievements from the programme in three main areas: Hazard and exposure screening; LCA and management, focussed on

potential impacts of chemicals exposure, and Catalysis, biocatalysis and materials circularity. In addition to the three main research areas, a series of *case studies* were also conducted in the programme where the aim was to apply the knowledge gained to achieve integrated and multi-disciplinary research aiming towards a safe and sustainable production and use of chemicals. We discuss the way forward with focus on needs for research and innovation for a green and sustainable chemical and materials industry as well as a safe and sustainable use of chemicals in society.

Key achievements

The research in Mistra SafeChem has proven to be relevant for the development of new and modified chemicals and materials, implementing state-of-the-art knowledge and tools within organic chemistry, catalysis and biocatalysis, in combination with novel approaches for hazard and exposure assessment as well as LCA. This multi-disciplinary approach challenges and goes beyond the use of traditional scientific (mono)disciplines and requires both a common vision that can engage scientists from different disciplines and a learning process where knowledge on basic principles and possibilities of the necessary research can be exchanged. It is not unlikely that the same challenge will be faced in industry for implementation of SSbD, which will require collaboration between experts on chemical synthesis and design, and experts on chemical hazards, exposure, risk and sustainability. Here, the challenge to develop suitable metrics and quantitative tools to assess and evaluate sustainability are urgently needed.

Specific experiences from the programme include:

- The development of *hazard screening tools* is progressing rapidly and needs to expand to enable expedient and accurate hazard and risk assessment for a wide variety of chemicals with potential human and ecosystem effects/end-points. The development must focus on regulatory relevant end-points with uncertainty estimates and needs to be applicable in areas of high industrial importance.
- The *assessment of chemical hazards and exposure in the full life cycle of chemicals and materials* (and products/articles) needs to ensure that all relevant exposure pathways are covered. With the introduction of the concept of SSbD, models need to consider both the chemical risks and other criteria for environmental sustainability making a multi-disciplinary approach necessary in both method development and implementation.
- *Catalysis, biocatalysis and processes for waste valorisation* in combination with hazard screening and LCA provide a basis for the development of future safe and sustainable chemical processes for existing and new chemicals and materials. This will also form a basis for future sustainable methodology development in the field of organic chemistry and ensure aligning biosynthesis with sustainable manufacturing. Early assessment using applicable tools for hazard screening and (prospective) LCA needs to be used as a basis for evaluation, decision-making and planning in the innovation process.

Screening of human and environmental hazards and effects

The overall objective of this research is to provide a fit-for-purpose screening framework combining *in silico* (computational), *in vitro* (cells and organisms) and bioanalytical methods which will both utilise existing data and provide new experimental data for focus on comparative hazard predictions. The framework also includes methods to evaluate exposures, particularly with respect to multiple chemicals in the “exposome”, and tools to assess environmental fate (biodegradation, bioaccumulation, adsorption/desorption etc), all thus providing key data for supporting risk assessment. It is the aim to produce a robust framework which is accessible and tailored to a variety of applications of a safe, green and sustainable chemistry.

In silico tools. Computational tools have been developed with advanced machine learning and AI-based methods focussing on human end-points such as mutagenesis, eye irritation¹¹, cardio-vascular disease¹² and hormone disruption¹³. On-going work is focussed on clustering these methods into a user-friendly interface¹⁴, which is supported by

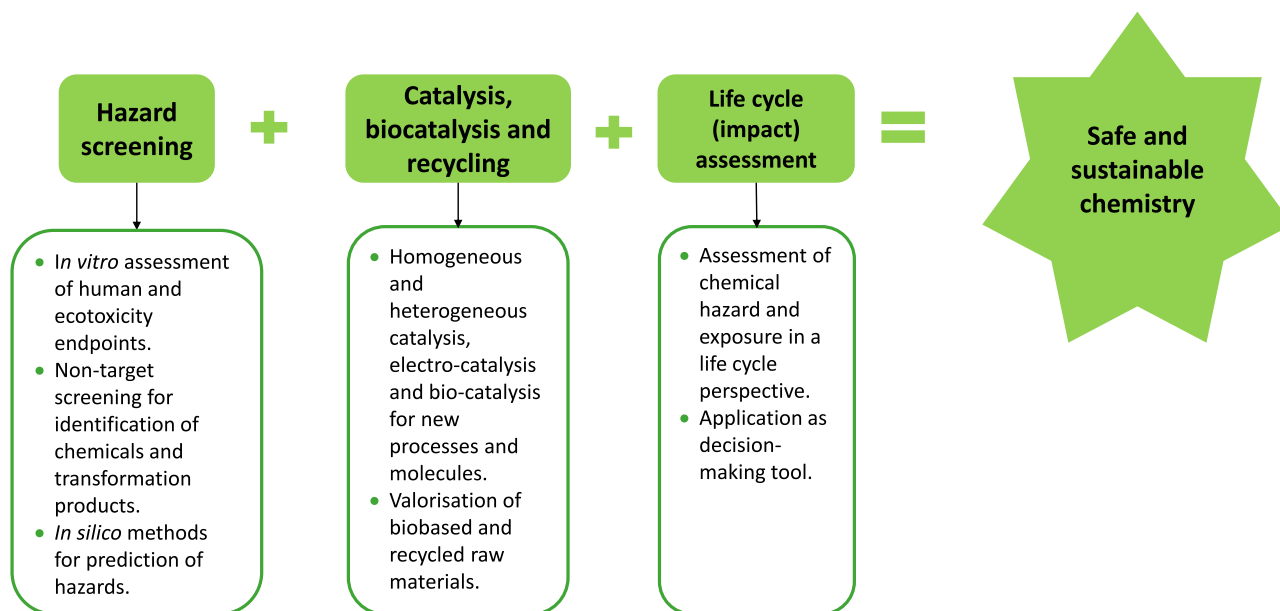


Fig. 1 | The main research components of the Mistra SafeChem programme. The schematic figure describes the contents of the main research components of the Mistra SafeChem programme and how they are combined to achieve results contributing to a safe and sustainable chemistry.

information concerning their validation as well as guidance in the interpretation of results and their use in decision-making. A key feature is the use of conformal prediction theory providing uncertainty parameters and applicability domain measures per model and prediction¹⁵.

Another cutting-edge attempt is introducing non-descriptor based structural designation features based on molecular graphs, i.e. atomic environment characteristics, by “molecular embeddings” when developing deep learning tools. We have also introduced computational tools to predict metabolic stability or breakdown of compounds in the human body and the ecosphere¹⁶. Recent developments include models for conformal predictions using H-phrases from REACH/CLP¹⁷.

The *in silico* tool suite allows direct access for early hazard screening of reagents, reactants, intermediates and products formed during the development of new chemical synthesis processes. This is clearly of value to e.g. industrial partners when following the emerging application of the EUs SSbD criteria, particularly steps 1 and 2. Proof of application value has been obtained in a number of industrial cases (see below).

Analytical exposure screening tools. To support the identification of potentially hazardous substances in chemical processes and applications, and to enable assessments of human and environmental exposures of increasing complexity, advanced analytical workflows have been developed. The workflows enable time-efficient and simultaneous screening of a broad range of chemical classes in a given environmental sample, material or process^{18,19}. The non-target screening tools are based on high-resolution mass spectrometry (HRMS) with gas chromatography (GC) or liquid chromatography (LC), and use of chemical informatics and computational workflows to rapidly identify or predict the structures of unknown and potentially hazardous substances. For complex effluents and polluted waters, over 39,000 molecular features can be detected by LC-HRMS, and all data-processing workflows for molecular annotation and structural identification can be accomplished using open science tools and spectral resources²⁰. Moreover, the data-rich output of these nontarget analyses, with accompanying MS2 spectra for thousands of unknown features, can be rapidly screened for toxicological hazards (e.g. acute fish toxicity) by MS2Tox²¹, a machine learning model that predicts toxicity from mass spectral information²². Additional analytical methods have been specifically developed for textile processes and textile materials²³. The ATD-GC/MS requires a minimum of sample

preparation, is solvent-free, and much faster than conventional methods for textile analysis.

Rapid biological hazard screening of chemicals. Current ecotoxicological testing strategies do not keep up with the demands and fail to sufficiently protect biodiversity. We have therefore developed innovative high-content screening (HCS) methods to determine hazard properties and better predict ecotoxicological effects in aquatic keystone species. To this end, we are combining multiplexed staining protocols, automatic high-throughput microscopy and image analysis²⁴ with a capacity of imaging more than a million samples per week with high-quality images. In addition to these advancements, we have developed *in vitro* mechanistic toxicology methods using fit-for-purpose HCS protocols. We have established the cell painting assay, which enables detailed phenotypical cell profiling by employing HCS, multiplexing six stains, and automatic image analysis^{25,26}. This novel tool captures large amounts of unbiased information, quantifying the cellular state after chemical perturbation. Our research has focused on both single compounds and mixtures, including evaluating differences in toxicity among PFAS alternatives.

Life cycle assessment and management

Life cycle thinking is key to achieving safety and sustainability of chemicals and the products, materials and articles they’re used to produce. LCA is a methodology for quantifying the environmental impacts of products or services covering the whole life-cycle (cradle -to-grave). The basic components of the methodology are: an inventory of all chemical, material and energy inputs in each step in the life-cycle, quantifying the releases of substances (or other flows) potentially harmful to climate, environment or human health and estimating the impact of these releases in each stage. Results are often summarised and aggregated to allow comparisons of alternative products or production processes. LCA can also be used as a tool in the innovation process to guide the development towards more sustainable alternatives. The life cycle-based assessment toolbox (LCBA) has been explored for decision support both in process optimisation in early design stages^{27,28} and in substitution assessment^{29,30}. We show how early screening LCA studies including “chemical footprint” (ecotoxicity and human toxicity impact indicators) can be useful for understanding and improving the environmental performance of lab scale routes, important

information for potential future scaleup. In a substitution case study for siloxanes (see below), chemical footprint and LCA were integrated in an SSbD assessment following the JRC framework.

The LCBA consists of two existing model systems: USEtox, a scientific consensus model for characterising human and ecotoxicological impacts of chemicals (<https://usetox.org/>), and ProScale, a method providing a hazard and exposure based scoring system for comparing chemical risks associated with products in a life cycle perspective (<https://proscale.org/>). At the onset of Mistra SafeChem the USEtox scope was mainly aquatic ecotoxicity and human health impacts from environmental exposure. The ProScale scope was mainly on workplace-related toxicity impacts. Both models are already used in industry and academia and have been further developed to broaden their respective scopes, and applied in this programme. USEtox advancements included a methodological framework and global recommendations for characterising freshwater ecotoxicity impacts from chemical emissions and chemicals in products³¹ and for advancing near-field/far-field exposure (i.e. direct exposure from emissions from product or process vs. exposure from chemical occurrence in background media) and human toxicity characterisation³². Based on the latter, USEtox has been developed and made available as beta-stage version 3, which can be accessed at <https://usetox.org/>. ProScale methodological advancements included laying the ground for ProScale on ecotoxicity³³, contributing to the further development of ProScaleE³⁴, as well as its possible inclusion in company-internal product LCA-s³⁵ and in a product environmental footprint (PEF) assessment³⁶. USEtox and ProScale, including the above-described advancements, provide possibilities for state-of-the-art LCIA (Life Cycle Impact Assessment) on ecotoxicity and human toxicity.

In addition to expanding the scope of the LCIA models by including more exposure pathways and impact categories, programme research has also focussed on increasing the coverage of the chemical space. By use of advanced digital methods, including automatized high-throughput workflows and machine learning, we are developing procedures to populate USEtox and ProScale with substance property data to increase their coverage of chemicals and make possible high-throughput assessment. To achieve this, a prioritisation framework has been developed to assess the potential of developing machine learning based approaches to fill input data-related gaps in human and ecosystem toxicity characterisation³⁷. A database of chemicals with measured parameter data available from public databases or published literature was used for the analysis. After assessment of data availability and uncertainty, thirteen out of 38 chemical-related parameters were prioritised for development of machine learning approaches including data for environmental partitioning and degradation, toxicity and ecotoxicity. The ML model was then applied to a data base on marketed chemicals from U.S. EPA's CompTox Chemicals Dashboard v2.1 (<https://comptox.epa.gov/dashboard/>). For these data on marketed chemicals, measured data was found to cover only 1–10% of the prioritised parameters. Applying the machine-learning based method, the resulting potential to fill data gaps covered 8–46%, depending on parameter, of the global space of marketed chemicals. To fill these data gaps and provide full transparency on the reliability of model predictions, uncertainty aware machine learning models are developed for prioritised parameters in USEtox³⁷. The uncertainty aware models provide predictions with fully quantified confidence intervals which also enable propagating uncertainty through impact assessments and thereby support the integration of predicted and measured data in comparative analyses.

While focusing research efforts on advancing the LCIA, equally important has been the development of a guidance document to accompany the toolbox with illustrative examples from a number of case studies³⁸.

Catalysis, biocatalysis and valorisation of waste

The purpose of this research is to develop, test and evaluate innovative chemical synthesis processes relevant for industrial production of components for new materials, speciality chemicals and pharmaceuticals, with an overall focus to reduce the inherent carbon footprint and increase the safety aspects in selections of chemicals used. Catalysis (mainly metal-based) and

biocatalysis (enzymes) plays a pivotal role in the chemical industry. The challenge now is to advance the state-of-the-art in catalytic processes for chemical synthesis to ensure sustainability while optimising the efficient use of existing resources. In Mistra SafeChem, the research has also focused on material re-use and recycling for maximum benefits for resource efficiency and sustainability, and on green chemistry industrial processes to reduce or replace toxic chemicals and minimise waste. Key areas include the design of early transition metal and enzyme catalysts, scaling up catalytic processes towards industrial scale, development of methods to define and quantify resource efficiency and circularity of value chains and evaluation and understanding toxicology determinants of products and processes.

Novel sustainable catalytic processes have been developed which can be used in organic chemical applications including biocatalysis and novel oxidation methods, and for new methods to construct carbon-carbon and carbon-heteroatom bonds selectively under mild reaction conditions^{39–43}. In this way, toxic by-products and waste can be avoided thus minimising exposure to hazardous solvents and substances. Hybrid catalysts⁴⁴, bifunctional catalysts⁴⁵ and chemoenzymatic cascades have also been developed⁴⁶. These catalysts mediate more than one transformation in a single synthetic step, avoiding isolation of intermediates and significantly reducing the environmental impact of a chemical process. The development of catalytic systems able to use carbon dioxide for the synthesis of organic compounds has been studied as well^{44,47}. A major focus in all metal-catalysed reactions⁴⁸ developed within the Mistra SafeChem framework has been the development of recyclable catalysts, as well as their substitution for catalysts based on abundant metals as compared to commonly used late transition metals, where both overall carbon footprint and the scarcity makes sustainable use thereof problematic.

Upcycling of textile waste. Textile recycling typically involves either mechanical, chemical, or biological methods, which rarely lead to the creation of higher-value products. In Mistra SafeChem, conversion of textile waste streams into nanomaterials is evaluated as an attractive approach for producing advanced materials with enhanced economic value⁴⁹. In this research, we explored multiple routes for extracting cellulosic nanomaterials, in the form of nanocrystals and nanofibers, from both pure cotton and blended fabrics (cotton/polyester and cotton/acrylic), investigating their properties, and demonstrating their use in high-performance lightweight materials such as foams and nanopapers^{23,50}.

Initial work focused on upcycling post-consumer textiles into nanocellulose using sulphuric acid hydrolysis (conventional route) and resulted in the development of a new processing route using the milder citric acid. The cotton fraction of the textiles was upcycled into cellulose nanocrystals (CNC) while the polyester or acrylics fractions were recovered without any decrease in molecular weight^{49,51}.

Metal catalysis. Heterogeneous nanocopper catalysts, where nanocopper particles are immobilized on microcrystalline cellulose (MCC), have opened novel synthetic methods. These catalysts are of importance in the pharmaceutical industry, since they are inexpensive and can be recycled many times. They also have the potential to be used in flow chemistry. A nanocopper catalyst developed in the programme demonstrated synthesis of complex organic molecules with importance for pharmaceutical applications. The carrier MCC is readily available and contributes to a lower carbon footprint compared to more established carriers such as polystyrene and perfluorinated carriers. No similar catalysts have been reported in the literature up till now. These catalysts have been proved useful in carbocyclisation⁵² and in the synthesis of enantiomerically pure allenes⁵³, offering a sustainable alternative to late transition metals.

A novel electrochemical palladium-catalysed method for the synthesis of biologically relevant enallenols was developed. In addition to the palladium catalyst, an electron transfer mediator is used in catalytic amounts to facilitate the anodic oxidation. In the initial publication CO is used as a

reagent in the oxidative carbonylation reaction⁵⁴. Ongoing potential development of this electrochemical method involves the direct use of CO₂ to generate CO in-situ via cathodic reduction.

The reduction of unsaturated C–C bonds is a common reaction in the production of pharmaceuticals, agrochemicals, and other materials. Traditionally, this process is carried out using catalytic systems based on rare metals such as Pd or Pt, in the presence of H₂ as the reductant. As these are catalysts based on scarce metals alternatives based on abundant metals should be developed. Research in Mistra SafeChem has yielded a method using Ni instead of Pd, and acidic water instead of H₂ for the electrochemical reduction of unsaturated C–C bonds, making it possible to avoid the use of both rare metals and fossil-based H₂ gas^{28,55}. Results from a screening LCA comparing the Pd and Ni catalysts is further discussed below.

Late-stage functionalization (LSF) is a chemoselective transformation on a complex organic molecule, such as a drug or a pharmaceutical, to provide at least one analogue in sufficient quantity and purity for a given purpose. This approach enables the rapid and efficient production of matched molecular pairs or drug-like analogues in a single chemical transformation, offering new potential drug candidates while saving resources, particularly chemical ones, such as organic solvents^{43,56,57}. We have developed catalytic system for the LSF of pharmaceuticals via the direct functionalization of carbon-hydrogen (C–H) bonds. The biological properties of the new drug analogues were analysed, and improved biological properties were identified. These compounds are currently being further evaluated by the pharmaceutical industry^{41–43}. The sustainable synthesis of enantiomerically pure chiral organic molecules, including important natural products and biologically active compounds⁴⁵ has also been a focus in Mistra SafeChem. Specifically, we have developed new homogeneous and heterogeneous recyclable metal catalysts to construct enantiomerically pure chiral organic compounds. One of them is a heterogeneous palladium catalyst immobilized on crystalline nanocellulose for selective oxidative carbonylation, which could be recycled up to nine times without any significant change in yield⁴⁵.

Enzyme catalysis in vitro and ex vivo. Biocatalyst stability is a key challenge that needs to be overcome to enable industrial application of enzymes. To overcome this bottleneck, research in the programme set out to develop a universally applicable pipeline for designing robust biocatalysts from sequence space, without the need of structural information.

This was achieved by a sequence-based protein engineering pipeline/method to generate biocatalysts with enhanced robustness^{39,58}. Our findings stressed the importance of generating a robust protein backbone that could be used as starting template in further engineering to modulate specificity while maintaining stability. Utilising this concept, we could generate a panel of cyclase enzymes with applications in C–C bond formation reactions and even retrieve their 3D-structures. We further explored the safety and sustainability of this pipeline in biocatalytic amide bond synthesis by applying tools developed and applied in Mistra SafeChem (see below).

Another challenge facing biocatalysis is the limited repertoire of reactions accessible to existing enzymes. Strategies to overcome this bottleneck includes enzyme discovery, engineering to enhance promiscuous activities and integrating chemical- and bio-catalysis by chemoenzymatic cascades. For the latter, we generated a chemoenzymatic approach to upcycle inert terpene-based building blocks from wood into activated monomers that could be chemically polymerized into a novel family of bio-based polyesters with high rigidity and with potent applications as bio-based coatings⁴⁶. We also showed how CO₂ could be used as feedstock to make the chemical building block furan dicarboxylic acid (FDCA) for material applications by synthetic biology. Whole-cell catalysis was employed and founded on simply adding one exogenous (de) carboxylase gene to *Escherichia coli*³⁹. This biocatalytic system could readily carboxylate furoic acid into FDCA under mild conditions and at elevated substrate loadings of relevance for industrial applications. With the recent emergence of AI-assisted generative protein design methods, enzyme catalysis will increase its impact on the chemical industry by

providing an array of new-to-nature reactions that were previously not accessible.

Valorisation of forestry residues. This research has resulted in novel methods for production of thermosets, fibres for textile and BX chemicals from kraft lignin^{59,60} beetle infected spruce⁶¹ and tops and branches⁶². Furthermore, we have depolymerized PET to regenerate the molecules enabling synthesis of virgin material⁶³.

To assess the sustainability of production of textile fibres from tops and branches, an LCA has been performed, showing advantages in comparison to conventional cotton fibre production in four out of five impact categories⁶⁴.

Multi-disciplinary approach towards safe and sustainable by design

To apply and demonstrate the implementation of the tools developed for hazard and exposure assessment and LCA, a number of case studies were performed on a selection of the novel processes for synthesising industry-relevant chemicals and materials, and specific challenges from industry^{29,38}. Tools developed in the programme were applied to assess e.g. the presence of hazardous substances, characterisation of hazardous properties of identified chemicals and life cycle sustainability. The case studies represent demonstrations of adaptation of the innovation process, with associated assessment of safety and sustainability, to the SSbD framework.

Upcycling of textile waste. In the development of processes for textile recycling, non-target screening of chemical content and a screening LCA were performed to inform process development in textile recycling to produce CNC. The screening LCA was employed to compare production using either a traditional process with sulphuric acid, or from a new citric acid process as well as the use of wood or discarded textile as starting materials. The results showed that producing the CNC from textiles has a significant environmental benefit over wood as the source. However, the environmental burden is high when using citric acid hydrolysis which initiated the development of a method to recover around 60 percent of the citric acid with a purity above 90 percent⁴⁹.

A comprehensive chemical screening with LC/MS to follow the fate of chemicals in the process, including starting material, acidic waste effluent, polyester waste, and the product (CNCs), was performed to follow the fate of chemicals in such a process. The final product, CNCs, was found to contain considerably less chemicals compared to the starting material with most chemicals remained in the polyester residual. Furthermore, the concentrations found in the process waste effluent were found to be predictable using a model based on solubilities under acidic conditions. A hazard ranking was made based on toxicities of quantified textile chemicals⁶⁵.

Sustainability assessment of a novel hydrogenation reaction process. Hazard assessment and LCA were employed to support the development of a catalytic method for reduction reactions, a crucial process in industrial applications. The new method replaced scarce metals (Pd or Pt) by more abundant metals (Ni). Hydrogen gas from fossil resources was replaced by hydrogen produced electrochemically from water. The reactions were performed in a water-based reaction medium. The case study includes an assessment of further optimisation possibilities by application of non-target screening combined with hazard assessment and LCA. The results show that the Ni foam catalyst can be recycled at least 15 times. A screening LCA was carried out to compare the environmental impact of the nickel foam hydrogenation in comparison to the palladium/carbon catalytic process. The assessment was carried out with a cradle-to-gate perspective i.e. with considerations of emissions and resource use from all activities from raw material acquisition to the production of the substance. The actual use stage is not included since it is not specified, but further treatment of waste streams generated in the process was. The impact categories, with indicators calculated with the USEtox model, included: acidification, climate

change, eutrophication potential (freshwater and marine), resource use (mineral and metals), ecotoxicity and human toxicity (cancer and non-cancer).

The results of the LCA showed that the nickel foam method showed potentially larger impacts for all considered categories with the platinum counter electrode being the dominant contributing factor from the Pt production and electricity use stages. For the Pd/C method the electricity usage and Pd catalyst production were the major hotspots. The results of screening LCA could become more favourable for the nickel foam hydrogenation method if the energy mix assumed in this study is updated to a future (more sustainable) scenario and if utilisation of the produced excess hydrogen gas is included in the assessment. Additional improvements of the environmental characteristics could be achieved by replacing the Pt counter electrode, and graphite rods were suggested as alternatives to explore. The assessment of safety aspects shows that the nickel foam method avoids the risks associated with the pyrophoric Pd/C system and the hydrogen gas use, since the hydrogen is produced internally from water. The hazard assessment identified low yields of chemical by-products and concluded that leakage of Ni from the system is very low, in addition to being in the form of NiSO_4 , known to pose a lower risk than other Ni-salts.

LCA and hazard assessment proved to be complementary and provided relevant insights for further process development before scale-up²⁸.

Safe-by-design biocatalysis for drug discovery. While the development of more sustainable biocatalytic reactions has been in the spotlight, significantly less attention has been given to human toxicity and environmental aspects of the underlying substrates and the associated products. We advocate that any chemical process needs to start from the reagents from both an environmental and safety perspective. Here, we address this gap by an exploratory approach according to the concept SSbD framework in biocatalytic amide bond synthesis. We highlight that generating chemical diversity is possible while navigating under a controlled and safe chemical space, and we coined the term “SafeChems” for the associated building blocks that we predicted were SSbD⁴⁵.

This case study was designed to develop and validate a biocatalytic pipeline for safe drug discovery chemistry with amide-bond synthesis, ranked as the second most important challenge in key green chemistry research by the ACS Green Chemistry Institute⁶⁶. As a starting point, *in silico* models were employed to filter all possible starting reagents (amines and acids) from a toxicological and pharmacological perspective. USEtox was then employed to evaluate the environmental fate and exposure of the filtered building blocks identified in the first step and the final products (amides). The results show that amides were in general predicted as more toxic compared to the starting acids and amines^{40,41}.

Using the enzyme engineering toolbox discussed above, we further showed how engineered enzymes were amenable to upcycle such filtered building blocks predicted to be safe into a plethora of amides under mild reaction conditions into building blocks of high commercial value; including skeletons that form integral part of e.g. anticancer drugs.

Siloxanes and silicones in cosmetics. This case study aimed to investigate the environmental effects of siloxanes and silicones from a life cycle perspective and to identify and evaluate possible substitutes²⁹. More than 175 alternative ingredients to silicones in foundation and lotions were identified using a systematic search strategy. A screening assessment using existing data to follow step 1 in the SSbD framework (i.e. initial hazard assessment of the substance being investigated based on their intrinsic physico-chemical, toxicological and ecotoxicological properties) as proposed by JRC was established and used for a first prioritisation. In total, 67 ingredients were further assessed and prioritised with the Mistra SafeChem toolbox. This methodology could simplify screening and prioritising among substances for use in a formulation or when choosing chemical products. Input from the study has been provided as feedback to JRC with a focus on user-friendliness and needs from an SME (Small and Medium Enterprises) perspective.

Cyclic siloxanes are a subgroup of silicones, listed as Substances of Very High Concern in REACH⁶⁷, since their properties fulfil the criteria for Persistent, Bioaccumulative and Toxic (PBT) chemicals. The case study was done from the perspective of a brand or retailer (high TRL) that uses different silicones in their cosmetic products and aims to find safe and sustainable alternatives. D5 (Decamethylcyclopentasiloxane, CAS 541-02-6) was selected as a reference substance to present a procedure for the chemical substitution using the LCBA toolbox.

In the chemical substitution case of D5 the LCBA toolbox was used to conduct a chemical alternative assessment based on the SSbD framework proposed by the EU⁴. The workflow was also inspired by life cycle-based alternatives assessment for chemical substitution approach suggested by Fantke et al.⁶⁸. Many of the functional alternatives to D5 identified were esters. In SSbD Step 1, 26 ingredients received the highest safety scores based on known hazard data. Further prioritisation was conducted using the *in silico* toxicity toolbox, where several ingredients were flagged for potential endocrine activity and skin sensitisation. Three esters were selected for further assessment in SSbD Steps 2–4 (i.e. human health and safety during the production process, environmental and human health risks in the use phase and environmental impacts along the entire life cycle). Using the ProScale model, Ester 1 showed significantly lower impacts during production for both dermal and inhalation exposure compared to D5, while Ester 2 and Ester 3 showed higher impacts. In Step 3, human and ecotoxicity impacts during the use phase of a liquid foundation, assessed with the USEtox model, indicated reduced exposure risks and lower impacts for Ester 1 compared to D5 and the other esters. A cradle-to-gate LCA (Step 4), performed as a broader environmental sustainability assessment, showed that all three esters had lower impacts than D5 in the toxicity-related impact categories (cancer, non-cancer, and ecotoxicity), as well as in several other environmental footprint (EF) categories. This assessment highlights the importance of considering multiple aspects, not just a single criterion, when identifying the safest and most sustainable ingredients for use in products.

Additional case studies²⁹ with application of the Mistra SafeChem tool for sustainability were conducted for industrial production scale-up²⁷ and for substitution of plasticisers in car interiors materials³⁰.

Regulatory perspective - The EU Chemical Strategy for sustainability and legislation

Apart from the mentioned CSS aiming to strengthen EU legislative work, many current regulations and directives cover safety and environmental protection related to chemicals⁶⁹. These existing regulations also include requirements on industries to ensure the safety of their chemical use and to report results from testing and assessments. With the introduction of SSbD⁴, a novel procedure to assess and report the results, it is of importance to strive for harmonisation of data availability and knowledge base for the assessments, criteria for risk assessment and reporting, to avoid multiple standards and overlaps. The announced EU reform “One substance, one assessment”⁷⁰ and associated initiatives^{71,72} may contribute to this. Hopefully, the efforts underway to develop tools and methodologies for SSbD assessment by the JRC and supported by research in Mistra SafeChem⁹ and other initiatives such as PARC⁷³, will contribute to this.

The REACH data, as published online by the European Chemicals Agency⁷⁴, currently represents one of the most comprehensive databases on chemicals. Proposed updates of REACH^{67,75,76} include registration requirements with increased information on hazards of concern, safe use documentation, registration of certain polymers or e.g. adding the information on chemical footprint. Furthermore, it is proposed to reform the authorisation and restriction process, add mixture assessment factor, simplify the communication in the supply chains, revise the dossiers/substances evaluation and finally revise the enforcement in member states (European Commission, Inception Impact Assessment, 2021⁷⁷). These updates will, when implemented, contribute to filling current data gaps on e.g. hazards related to e.g. CMR (Carcinogenic, Mutagenic and Reprotoxic), neurotoxicity or endocrine disruption.

REACH does not require new studies on substances if available data already exist. Nonetheless, in instances where there is an absence of relevant information, it is essential to generate new data to address these knowledge gaps. Before any new data generation, existing data, QSARs and data from structurally related substances (read-across approach) can be applied for assessment. The Mistra SafeChem tools¹⁰ can potentially support this process with e.g. hazard screening (in silico or analytical methods) to prioritise which substances should be further tested and/or to provide input for chemical footprint assessment.

Overall, the ongoing regulatory developments and market demands are strong drivers for industry's sustainable transition. In a broader perspective of the CCS² and the Green Deal action plan⁷² includes either banning the most harmful chemicals in consumer products or phasing out per- and polyfluoroalkyl substances (PFAS) in the EU, unless use is essential⁷⁸. The already implemented changes in the EU consist of new hazard criteria under the CLP regulation⁷⁹. Currently⁸⁰, substances and mixtures have to be classified and labelled when fulfilling the criteria for endocrine disrupting substances; Persistent, Mobile and Toxic and very Persistent and very Mobile substances (vPvM) and PBT and very Persistent, very Bioaccumulative substances (vPvB). Similar regulatory trends are emerging worldwide, where many countries either propose their own PFAS restrictions or bans^{81,82}, or revise local Globally Harmonised Standard implementations^{83,84}. In a global perspective, the agreement to the Global Framework on Chemicals was proposed by the United Nations Environment Program (UNEP) in 2023 providing a vision for a planet free of harm from chemicals and waste, for a safe, healthy and sustainable future⁸⁵.

The Ecodesign for Sustainable Products Regulation (ESPR) entered into force in July 2024 (Regulation (EU) 2024/1781)⁸⁶. The new ESPR applies to a broad range of products and is a framework legislation with product rules (performance and/or conditions) to be set progressively over time. Here, companies must ensure that design of their products will minimize the life cycle impacts.

To further address chemical pollution, climate change and contribution to UN SDGs, the EU has established an action plan "Towards Zero Pollution for Air, Water and Soil" as part of a vision for 2050 (European Commission, 2021)⁸⁷. The *Industrial Strategy* was updated with defined steps required to achieve the green transition of the chemical industry (European Commission, 2023: Transition Pathway for the Chemical Industry)⁸⁸. The proposed PEF method to evaluate the environmental impacts of products also advances clear EU recommendation towards LCA-based methods (Commission Recommendation (EU) 2021/2279)⁸⁹. The recently presented EU Chemical industry Action Plan⁷ includes a number of measures including further simplification of the regulatory system and actions to stimulate innovation in the chemical sector.

The already heavily regulated chemical industry is subjected to significant regulatory pressure to enhance the innovation of more sustainable and safe chemicals and materials. To meet the needs of the climate transition, and at the same time reduce the toxic pollution pressure, will be a competitive strength of European companies. This is a great challenge, and we believe that Mistra SafeChem provides useful examples and tools to promote and facilitate the transition to a more safe, sustainable, and green chemical industry.

Lessons learned and future outlook

Mistra SafeChem has also provided the opportunity for dialogues with representatives from research, authorities and industry to identify challenges and opportunities in the transition to meet the future demands of the chemical industry. General lessons learned from these dialogues are:

- The on-going implementation of the EU CSS provides a strong and coordinated opportunity to develop the European chemical industry and the societal use of chemicals in a green and sustainable direction and to contribute to the green transition. The SSbD framework should be integrated in newly started EU initiatives for research and innovation on new materials such as the Advanced Materials 2030 Initiative (AMi2030)⁹⁰. The focus on sustainability and chemical safety

must also remain at the forefront in the future implementation of the EU Chemical Industry Action Plan.

- Research, innovation and investments are central to the future development including, for example, specific challenges and knowledge requirements for definition and development of methods to operationalise and implement SSbD that are not too complex and time-consuming, and for development of innovative production processes for chemicals and materials. Examples of challenges for implementation of SSbD in the innovation process is the availability of rapid methods for early hazard assessment (Step 1 in the SSbD process) that can be applied with reasonable efforts and that need to be reliable with documented accuracy/uncertainty. For the following steps (2–4), which include assessment of both human and environmental impacts in the production and use phases, availability of LCA-methods that are capable of both incorporating chemical risks and of simulating upscaled production processes as well as use and disposal/recycling phases.
- The implementation of the SSbD framework needs to be sensitive to the complexity and heterogeneity of chemical industries, chemical processes and value chains. The sector includes activities ranging from small-scale production of speciality chemicals, the pharmaceutical industry, up to large-scale production of base chemicals for a variety of applications and value chains. These value chains are also complex, international/global and include all societal sectors. Mapping chemical production and use with the purpose of analysing risks and prioritising areas for action/development is thus difficult and involves many actors.
- Digitalisation and artificial intelligence (AI) are important parts in the development of sustainable chemical innovation and sustainable chemical value chains, and its importance will likely increase further. Of specific relevance to the Mistra SafeChem programme is early hazard assessment including predictions of potential risks in a life-cycle perspective. Specific areas of development include collection and evaluation of data on chemical properties and functions from existing databases as well as from experimental results from e.g. non-target screening, structural predictions and advanced biological test methods. AI-based computational models to predict endpoints and effects of new chemicals on humans and the ecosystem can provide input to hazard assessments and environmental fate and for pharmaceutical applications. The possibility to streamline data generation, systematic and rapid hazard and risk assessment with life-cycle assessment will provide powerful and applicable tools for early-stage decision-making in innovation processes. The main challenges associated with digitalisation and AI-applications are the applicability of the tools developed and accuracy of the results. For AI-generated results to be used in decision making, results need to be of a documented certainty/uncertainty and trustworthy.
- A shift towards renewable energy and biobased raw materials is currently the highest priority in society. When implementing solutions for the climate challenge in the chemical industry, it is important to have access to adequate LCA- and risk assessment tools to allow the assessment and comparison of different technologies and raw material sources as well as to minimise potential chemical risks and potential harm to other planetary boundaries, e.g. biosphere integrity.
- For the growth and expansion of a circular economy, the re-use and recycling of materials is essential. For research and innovation, the challenge is both to develop processes for recycling of existing and produced materials, as described above for textiles and wood waste, and to develop new materials that can be easily disassembled and recycled. We must ensure that future materials do not contain potentially hazardous or unwanted chemicals that may interfere with the future circular material use or lead to risks for exposure in future use.
- For the continued development of a safe and sustainable chemistry, there is a need for continued research and innovation focussing on resource-efficient and safe synthesis processes for basic and speciality chemicals as well as for new molecules and materials needed for the

green transition and a sustainable future. To achieve this, there is also a need to integrate fast, manageable and reliable methods for early-stage hazard screening and prospective risk assessment into digital tools for chemical research and development. This will require not only computational or experimental methods development covering individual molecules or processes, but also to cover the full life-cycle of new molecules, materials or products. It is also essential to integrate concepts of safe and sustainable chemistry in the education of future chemists, chemical engineers and material scientists.

- The initiative to launch a research programme focussing on green and sustainable chemistry and the research outcome summarised in this paper is very much in line with the five recommendations presented in the Stockholm Declaration on Chemistry for the Future, launched at the 2025 Nobel Symposium on 'Chemistry for Sustainability' on May 23, 2025 (<https://www.stockholm-declaration.org/>). The declaration is currently signed by more than 1700 signatories and organisations across the globe. This declaration highlights the critical role of sustainable chemistry in addressing global challenges stating that "The Stockholm Declaration on Chemistry for the Future is a call to action urging scientists, industry, educators, students, and policy makers to collaborate on implementing solutions for human well-being while preserving and protecting our environment. By embracing this vision, we can harness chemistry's full potential as a catalyst for a fairer, more sustainable, and resilient world". This declaration will continue to provide inspiration and guidance, and an increased interest and awareness in society, during the remaining years of Mistra SafeChem and beyond.

Finally, the strong engagement from major chemical and pharmaceutical industries in the Mistra SafeChem programme, as well as in other research initiatives funded by e.g. the EU Horizon Europe programme, is a strong indicator of the relevance and importance of multidisciplinary research to integrate safety and sustainability in product assessment and in decision making in the innovation process.

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Author contributions

J.Mu. conceived and drafted text, all authors (L.B., D.B., I.C., A.-K.H., H.H., M.J.J., R.L., A.J., J.Ma., B.M.-M., A.M., T.R., L.S., M.W., P.-O.S.) contributed

to the research in the programme and to writing and editing. All co-authors had leading roles as WP leads, WP co-leads, case study leads or chair of the industry group in the Mistra SafeChem programme phase 1 and made significant contributions to the research, the management of the programme and communication of the results. Participants in phase 2 are presented on www.mistrasafechem.se.

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