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# Case Study Summary Report

## Summary of WP6 of Mistra SafeChem

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MISTRA SAFECHEM

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# Abstract


The ambition of Mistra SafeChem has been to make an impact on the quality of life for humans and animals as well as ensuring a thriving environment. To be able to fulfil part of the programme goals, **Work Package 6** (WP6) was developed for coordinating work with specific case studies performed within academia and industry.

The specific objects of WP6 were: *i*) To coordinate the interaction between the case studies and the various tools and methods generated in WP3, WP4 and WP5; *ii*) To transform industrial challenges into cases fit for the programme and evaluation of the tools; and *iii*) To formulate the results from the case studies into general conclusions with respect to efficiency and reliability of the toolbox.

The included case studies have been chosen to enable assessment of various aspects of the molecules, processes, by-products from processes and/or non-target screening of recipients.

The tools used by all collaborators have been developed within the Mistra SafeChem programme and belong to three overarching groups of tools. The first group represents tools for **Hazard and exposure screening**, comprising of Chemical screening, *In vitro* prediction, and *In silico* prediction. The second group of tools belong to **Process design and optimization** tools, subcategorised into Catalysis/biocatalysis, Electrochemical methods, Textile recycling, and Valorisation of forest residues. The third and last group of tools were the one for **Life cycle based assessment**. This group have mainly three different sustainability tools with the following grouping: Life cycle assessment, Chemical footprint assessment, and Life cycle based alternative assessment. As a result of WP6 all tools have been compiled into a toolbox, which is published on the Mistra SafeChem webpage (www.mistrasafechem.se).

# Background

**Work Package 6 contained case studies aiming to verify tools developed in other parts of the programme, specifically in Work Packages 3, 4 and 5, commonly known as the Mistra SafeChem Toolbox on industrial products, processes and/or other challenges. Thus, Work Package 6 acted as an interface between the development of the toolbox system, primarily carried out in the academic circle, and the implementation of the same system, or parts of it, on industrial cases.**

Work Package 6 (WP6) was the point of entrance for new industrial partners to gain access to the developed tools and methods within Mistra SafeChem.

For Mistra SafeChem to have any actual impact on the quality of life for humans and animals and on the environment in which they thrive, the program needs to be implemented on existing systems within society. Hence, several detailed case-studies were performed, involving actual industrial challenges, to verify the applicability of the toolbox system developed in WP3, WP4 and WP5.

# Aim

The specific objectives for WP6 were:

- To coordinate the interaction between the case studies and the various tools and methods generated in WP3, WP4 and WP5.
- To transform industrial challenges into cases fit for the programme and evaluation of the tools.
- To formulate the results from the case studies into general conclusions with respect to efficiency and reliability of the toolbox.

The included case studies have been chosen to enable assessment of various aspects of the molecules, processes, by-products from processes and/or non-target screening of recipients.

# Case studies in WP6

Work Package 6 was designed to incorporate three industrial case studies focussing on substitution in different value chains. Three case studies based on research on design and management of chemicals, materials, and processes (from WP4) were selected to completement the larger ones. Together the results and progress within each case study will enable the achievement of the aims of WP6. The case study on indoor quality air inside cars and the case study on siloxanes and silicones in cosmetics were described and planned in the proposal. The other four was developed during the program.

## Indoor air quality – materials inside the car cabin

A car cabin is a microenvironment that the human population is exposed to and that is affected both by ventilation and emissions from interior materials. The material composition within a car cabin is complex and includes different substances with the purpose to achieve desired functions such as flame-retardance, limited ageing or soiling. Therefore, studying and improving this microenvironment is in-line with the overarching vision of Mistra SafeChem, to enable and promote the expansion of a safe, sustainable and green chemical industry in Sweden and to reduce hazardous chemical exposure of the human population and the environment. The focus of this case study was on the end-product, i.e. the car, and evaluation of exposure to certain chemicals as well as identification of strategies to decrease or substitute these substances with better alternatives from a health and environmental perspective.

### Aim

The aim was to evaluate substances used in or entering a car cabin with respect to toxicology and substitution. To reach these goals, two main tracks were pursued in this case study:

1. An assessment of current and alternative plasticizers used in artificial leather to investigate safe substitution.

2. An analysis of CMR (Carcinogenic, Mutagenic, Reprotoxic) substances present in the indoor air environment and an analysis of which substances to be prioritized for substitution with a safer alternative.

### Results

A separate summary report for case study 6.2 is available for download from the Mistra SafeChem website. To summarize some of the key achievements:

- *In silico* prediction tools were used for the hazard assessments of plasticizers used in car interior materials as well as to generate data to be used in the different tiers of the life cycle based alternative assessment. The results from the *in silico* predictions confirm that the chemicals in focus are likely either CMR chemicals or have an endocrine disrupting potential. Based on these results, all chemicals in focus should be prioritized for substitution, if they are found to be present in the car cabin.

- For the LCA based alternative assessment, the project made use of USEtox version 3.0 beta 6c and the LCAA framework by Peter Fantke et al (Fantke *et al.*, 2017). Four alternatives were found to have a lower hazard compared to the others. However, the uncertainty associated with the hazard classification, mostly based on QSAR predictions was very high and should be taken into account. In addition, the results indicated that the difference in the potential human toxicity impacts between different compounds (calculated using USEtox) were too small in relation to the estimated uncertainty, to draw any conclusions.

- Two sampling campaigns were carried out within the scope of the case study, with a different vehicle each time. The samples were analyzed by targeted screening for a list of CMR substances reported in the literature from measurements in car environments (see summary report 6.2 for details). The vehicles were different in age and material specifications but similar in model and size. Polydimethylsiloxane (PDMS) sheets were used for both air sampling as well as for contact sampling of the material surfaces inside of the car cabin.
  - Substances belonging to chlorinated phosphates group were detected in almost all the locations and showed the highest levels.
  - Generally, the dashboards of both cars showed the lowest levels of detected substances, while steering wheels and seats were at the other end of the scale.
  - Car 2 showed overall higher levels of detected substances, by the longer sampling time for the samplers at elevated temperatures and the use of different materials and parts between the two cars.
  - The contact samplers provided valuable information to identify potential emission sources.
  - The measurements show that differences can be observed between the different areas in relation to the emission from the specific surfaces. The measurements are in line with what would be expected from the different parts (engineering judgement).
- A framework was provided on how the substitution process could look like and how the different tools could be used.
- A wide range of tools from the SafeChem toolbox were used, tested and evaluated. Feedback on what worked well and what could be improved had been provided to the developers of the tools and is summarized in the summary report for the case study.

*Table 1. External deliverables that will be made available on the Mistra SafeChem webpage.*

| Deliverable number | Deliverable name |
|---|---|
| **D6.2.4** | WP6 case study summary: Indoor air quality - materials inside the car cabin |

## Cyclic siloxanes and silicones in cosmetics

Due to their unique functions, various silicone-based chemicals are used in cosmetic products. Due to potential negative environmental and human health impacts, concerns have been raised for some silicone cosmetic ingredients. The cyclic siloxanes Octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5) and dodecamethylcyclopentasiloxane (D6) are listed on the REACH candidate list as substances of very high concern (because of existing or predicted persistent, bioaccumulative and toxic properties). Furthermore, there are restrictions on how they can be used in cosmetic products in the EU. Whereas there are wider restrictions of the cyclic siloxanes under review, there are currently no limitations of using linear or branched silicones. Cyclic siloxanes can be used either as such, or as precursors to silicone-based chemistry. Silicones are used in many other applications and not only in cosmetics.

**Aim**

The aim of the case study was to investigate the environmental effects of silicones and when necessary, identify or develop suitable substitutes or alternative processes. The case study was therefore built on the following two pillars:

1. To investigate the potential concerns with siloxanes and silicones from a life cycle perspective, a qualitative life cycle impact mapping was performed using literature and the Mistra SafeChem toolbox considering both human and environmental effects.

2. To find, assess and prioritise possible alternatives to targeted siloxanes and silicones in selected cosmetic products from a life cycle perspective. The case study has tested the proposed SSbD procedure (that was introduced after the start of the program) and made a prioritisation of possible alternative ingredients assessing function, intrinsic hazard (step 1), occupational exposure and risk (step 2), human exposure and risk during use (step 3) and life cycle impacts (step 4).

**Results**

The results from the case study are summarized in a bulleted list:

- The SSbD framework has been applied to guide substitution of silicones in cosmetics using a novel combination of lifecycle based chemical assessment tools.

- Steps 1- 4 in the SSbD framework have been assessed which includes intrinsic hazard, occupational, human and environmental exposure and impacts that together provide a comprehensive picture of potential hazards and trade-offs.

- The focus of the case study was finding alternatives to cyclic siloxanes as a solvent in liquid foundations, and dimethicone as a skin conditioner in foundations and lotions. Solvents in foundations should have high spreadability, and evenly distribute pigments while providing a smooth and non-tacky skin feel. Skin conditioning agents should form an occlusive layer hindering moisture from evaporating while providing a smooth and non-tacky skin feel, and anti-foaming effect.

- Over 170 possible alternatives were identified using different search strategies for the required function of the chemical alternative. The alternatives were categorised into the functional groups: alcohols, alkanes, esters, ethers, fatty alcohols, hydrogenated oils, polymers, triglycerides and vegetable oils.

- All ingredients were provided an intrinsic hazard score (safety level) based on the SSbD criteria defined by the Joint Research Centre (JRC). Skin sensitization (H317) was prioritized higher due to the final application being cosmetics and was moved from criteria H2 to criteria H1. The alternatives were classified into the following safety levels: cut-off (n=14), safety level 1 (n=24), safety level 2 (n=25), safety level 3 (n=26), with No. 3 representing the highest safety level and data gaps (n=84). The biggest category of alternatives were exceedingly esters either biobased, partly biobased or petroleum (n=63), followed by vegetable oils (n=32) and hydrocarbons (n=14). Availability of SMILES-code varied depending on category for example 97% of vegetable lacked SMILES-code compared to 11% of esters.

- Out of the 63 identified esters, 44% were classified as datagap, compared to 78% of vegetable oils, and 14% of hydrocarbons. Esters were deemed as the more promising category of alternatives to assess further.

- Further assessment and prioritisation were done using the Mistra SafeChem *in silico* prediction tools from WP3 allowing assessments of chemicals with data gaps as long as the structure is known.

- Ingredients that were predicted positive for CMR, ecotoxicity, skin sensitisation and with over 8 positive predictions among all endocrine endpoints were excluded from the list of prioritised ingredients with safety score 3. Selected ingredients that were promising from a functional perspective but were classified with a lower safety score or data gap but had no positive predictions in the *in silico* screening were added to list of prioritised ingredients.

- The case study has provided data for comparing the Mistra SafeChem *in silico* prediction models with other models for the same endpoints from Vega (v1.2.3). With a suite of 100+ models from the MSC (v 1.0) toolbox and Vega, consensus scores were calculated for 20 “general” endpoints considering both the reliability and the general agreement between models.

- Some ingredients were predicted to have a positive impact with high reliability for CMR, skin sensitisation and various endocrine endpoints and should be assessed further in literature and tested in vitro to investigate potential hazards further. Although the alternative may not be of concern, they were not prioritised in our assessment of possible alternatives. Many cosmetic ingredients end up in wastewater and potentially in the environment like cyclic siloxanes. Therefore, possible biodegradation products and ecotoxicity were modelled for a selection of the prioritised ingredients. Predicted metabolites were screened with the Mistra SafeChem (v 1.0) toolbox and with 100+ models using Vega (v1.2.3) and consensus scores were calculated. None of the modelled ingredients seemed to form any metabolites with a positive prediction with high reliability for aquatic acute toxicity, bioaccumulation, and persistence. The match function in Excel was used to search for alternatives with input data in the USEtox database. The input data needed are various physicochemical properties, ecotoxicity effect data (HC20) and human toxicity effect data which are not known for many substances. Three of the esters, i.e., diethylhexyl sebacate, diisopropyl adipate and decyl oleate were selected for SSbD step 2 – step 4 based on availability of input data in USEtox database. The alternatives were prioritised based on available data, rather than function with the purpose of method development. The three esters were compared to cyclic siloxane D5 as benchmark.

- ProScale was used to assess occupational exposure and risk during production (SSbD step 2). The ProScale score of both diisopropyl adipate and diethylhexyl sebacate were higher compared to D5 for both inhalation and dermal exposure. The ProScale score for decyl oleate was lower compared to D5.

- USEtox personal care interface was used to assess human exposure risk during use (SSbD step 3). The input exposure scenarios were: 20% ingredient in a liquid foundation (0.51 g/day), and 2 adults + 1 child household (236 m3).

- The results from USEtox show that only one ester (decyl oleate) had a lower human toxicity exposure risk and a lower ecotoxicity impact score than D5. Diisopropyl adipate had a hazard quotient (HQ) of 11.5 (HQ>1 is considered as high risk) whereas D5 and the other two esters had a HQ below 1.

- A cradle to gate LCA for D5 and the three esters was used to assess environmental impacts (SSbD step 4). The Environmental Footprint 3.1 method was used with toxicity impact categories calculated with USEtox 2.13. The 3 esters performed better compared to D5 in 13/16 impact categories. The biobased origin of two of the esters contribute with a higher impact in marine eutrophication, land use and water use. The modelling indicate that D5 has higher human toxicity and freshwater ecotoxicity impacts than the evaluated ester alternatives.

- To design safe and sustainable formulations such as cosmetics products, assessment of ingredients from a life cycle perspective should lay the ground for decision on which ingredients to use in the formulation if they also provide a targeted function. As of today, cosmetic ingredients display lack of data where many are not even registered in REACH due to low production volumes. Most of the ingredients lack human toxicity effects data such as ED10 or RfD (reference dose) which limited our ability to apply the SSbD-framework.

- SSbD was a relevant approach in the case study to guide decision from safety and sustainability perspective and reducing number of alternatives to focus on. Further development is needed of the toolbox to support the framework, especially for improved decision support when data is lacking.

*Table 2. External deliverables that will be made available on the Mistra SafeChem webpage.*

| Deliverable number | Deliverable name |
|---|---|
| **D6.3.2** | Assessment of alternatives to siloxanes and silicones in cosmetics |
| **D6.3.3** | Motivation for substitution of siloxanes and silicones |

## Environmental assessment in early process scale-up

The chemical industry is one of Europe's largest manufacturing sectors, representing around 7% of EU manufacturing by turnover, and comes third in $CO_2$ emissions following cement and iron/steel industries (EC, 2023). EU's chemical industry is a crucial provider of innovative materials and technological solutions on the EUs market. However, many of the produced chemicals have hazardous properties. Eurostat data (2023) show that the consumption of chemicals hazardous to health in the EU was 196 million tonnes in 2022.

The chemical industry in Europe is also highly regulated. New chemical substances placed on the EU/EEA market are subject to classification and labelling or registration prior to manufacture or import as required in the CLP and REACH regulations. As EUs REACH regulation aims for stronger protection of human health and the environment (by e.g., restrictions, authorisations, or consumers right to know), there is a commercial need for novel chemical substances having desired physico-chemical properties combined with benign safety and environmental profile. Additionally, to accelerate the innovation and safety, EU has taken on the Chemicals Strategy for Sustainability (CSS) and as part of the ambitious Green Deal plan that includes the recommendation on Safe and Sustainable by Design (SSbD). Therefore, it is important to monitor and improve the environmental performance of the production of new chemicals as well as production of chemicals currently in use. To ensure that safe and sustainable chemical products are put on the market, an early assessment during the planning of the upscaling of chemical production is needed. By including environmental assessment and green chemistry principles in early chemical process scale up, optimization of the process is possible and the most feasible process settings from an environmental perspective can be identified.

**Aim**

The main objective of this case study was to identify and assess the environmental impact of a new chemical using a life cycle assessment screening. Furthermore, the processes and activities that contribute most to the environmental impact were also investigated.

This study's overarching goal was to help assess whether an alternative chemical and its production are more sustainable than the chemical it is intended to replace, and thus minimize the risk of unwanted substitution, already during planning and upscaling. The scope also included the modelling of chemical processes for upscaling and the generation of (eco-)toxicological parameters for the chemical of interest.

Such simulated model and (eco-)toxicological parameters were not only aimed as input for the LCA of the upscaled process, but also for future scenarios covering environmental impacts and process learning along with technological maturity.

**Results**

The studied system considered the production of a new chemical and was performed in cooperation with Perstorp. In order to meet the scope, the whole activity was divided into several subtasks: (1) Modelling and process optimization, (2) Degradability and breakdown products of aimed chemical, (3) LCA (Life Cycle Assessment) on the upscaled production and in future-oriented context and (4) Dissemination of the results.

We summarize the results and methods below in bullet point and for detailed information on this case study we refer to Mistra SafeChem webpage where the final report is published.

- Aspen Plus (AspenTech) was used to model and simulate the production of the new chemical.
- A working method was suggested for coupling the LCA with process simulation. We also proposed steps on how to create a multi-variate regression model in SIMCA, transfer the model to MATLAB and to further connect it with LCA computations. However, this case study proceeded with the LCA based on Aspen simulations as no reliable multi-variate model could be developed within the time frame and resources available.
- Aspen simulation experiments were evaluated in terms of their environmental scores (normalized and weighted according to EF 3.0). The lowest score was found at low temperature and low molar fraction.
- The modelling of the system has been conducted using the LCA-software "LCA for experts" by Sphera.
- (Eco-)toxicity impact category indicators were calculated with USEtox 2.12 and ProScale.
- The Mistra SafeChem *in silico* toolbox was used to predict substance properties in order to populate USEtox and ProScale for the further calculation of the characterisation factors.
- Based on this case study, a generic guideline on using the *in silico* toolbox for deriving ProScale hazard factors was developed.
- Other impact category indicators were calculated with EF3.0 as implemented in GaBi.

- LCA results showed that for the base case scenario the production of raw materials, as well as production of the catalyst are the major hotspots regarding the studied environmental impact categories.

- The cradle-to-gate ProScale results, for the new chemical showed that the raw material production contributes mostly to the total ProScale score, for both inhalation and dermal exposure.

- "Chemical footprint" was assessed by evaluating all toxicity-related category indicator results.

- The future improvement possibilities (in terms of environmental impacts) were investigated. Here, seven future scenarios were developed and analysed.

- The future improvement possibility for the total environmental score was found to be 10.3% for the best-case scenario. Additionally, the highest potential improvement that can be achieved was found for climate change impact, with a 26.5% decrease in the best-case scenario. For both mentioned here, the catalyst was the major contributor to the impacts.

- It was not possible to compare the environmental and (eco-)toxicity impact of the new chemical with currently used alternatives due to lack of data.

*Table 3. External deliverables that will be made available on the Mistra SafeChem webpage.*

| Delivery number | Delivery title |
|---|---|
| **D6.4.3-N** | A report summarizing the process optimization case study and its results (published on mistrasafechem.se) |
| **D6.4.4-N** | Dissemination of results to industry partners and researchers (as part of our Mistra SafeChem dissemination tour, where the programme gave presentations to industry partners, this case study was presented on 16th of February 2024 at the Perstorp site) |

**Summary of key achievements**

In this task we demonstrated that Mistra SafeChem toolbox can be applied in environmental impact assessment considering the production process of a new chemical. By using LCA assessment integrated with process modelling, and finding the best-case (manufacturing) scenario, we could identify which processes that contribute the most to the environmental and toxicity impact for the selected scenario. Next, by looking at future scenarios we could discuss recommendations for future improvement opportunities. The process LCA and chemical footprint investigation can indeed support the industry decision making and the shift towards eco-design. Furthermore, this case study also contributed by interacting with WP5 and WP3 in deliverables on suggested guidance on the use of the LCA toolbox, as part of WP5 delivering the LCA guidance and on the use of *in silico* models for hazard assessment in WP3.

## Textile recycling – Optimizing sustainability

Biobased nanomaterials such as cellulose nanocrystals (CNCs) have been increasingly explored to replace fossil-based materials in different applications. CNCs can be isolated from various cellulosic biomass sources. Textiles, which are mostly made of cotton, are an under-utilized biomass that after their lifetime is either burned or dumped into landfills.

This case study concerned the conversion of cotton-based textile into cellulose nanocrystals (CNC) using acid hydrolysis in a water-based system. The development of a new milder processing route was investigated from a life cycle perspective, where citric acid was used for acid hydrolysis instead of the traditional sulfuric acid. The aim was to develop safer process routes and reagent recycling for improved environmental performance compared to other textile recycling routes. By use of analytical non-target screening tools based on mass spectrometry, the content of potentially hazardous chemicals in both recycled material and waste streams were assessed and prioritised based on hazard.

**Results**

- The early-stage life cycle assessment (LCA) showed a significant reduction in the environmental burden of CNC extraction using post-consumer cotton instead of wood pulp, making clothing a good feedstock.
- The LCA modelling showed that the new extraction route using citric acid showed higher environmental impacts than the route using sulfuric acid in an initial set-up, mainly due to the upstream processes of citric acid. However, the high yield, and the properties of the CNCs when using citric acid encourage the development of more efficient routes for the recovery of citric acid. The current 58% recovery of citric acid by simple evaporation and crystallization already reduces the environmental impact and sets the foundation for a more environmental-friendly process that can be improved further.
- The case study showcases that early LCA studies can be useful for understanding and improving the environmental performance of lab-scale routes and providing essential information for future scale-up.
- Cotton fabrics may contain unwanted impurities from both their production and use, which can potentially limit the field of applications of the extracted CNCs.
- 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 chemical screening was done from the traditional sulfuric acid route.
- An important finding from the screening was the limited transfer of toxic substances to the finished product, CNCs. Only a few plasticizers, such as DEHP and DBP, were found strongly attached to the CNCs. This may have implications depending on the application areas and further use of this material. This is also true for the recovered polyester, which contained the vast majority of the identified textile chemicals.
- A hazard ranking was made based on toxicities of quantified textile chemicals as a prioritized list for future screening and quantification in new textile batches and the citric acid extraction route (that was the focus in the LCA assessment).
- In total, 24 chemicals were identified and quantified, and these were screened using the Pharos chemical and material database that aggregates and benchmark the inherent hazards of chemicals across a broad range of human health and environmental endpoints using over 70 hazard lists developed by state, national or international governmental agencies or science-based non-governmental organizations.
- Pharos applies a hazard ranking system based largely on the protocol of the GreenScreen for Safer Chemicals, scoring all chemicals against the GreenScreen List Translator (GSLT) to

identify chemicals of high concern. If there is a public GreenScreen assessment for a substance, the assessment hazards are displayed. The chemicals were sorted based on the hazard score from higher to lower concern based on what is known about the chemicals today. This ranking can be used to prioritize compounds to be analyzed during the recycling process.

The results of the case study have been published in several scientific papers:


- Ruiz-Caldas, M.-X., Carlsson, J., Sadiktsis, I., Jaworski, A., Nilsson, U., & Mathew, A. P. (2022). Cellulose Nanocrystals from Postconsumer Cotton and Blended Fabrics: A Study on Their Properties, Chemical Composition, and Process Efficiency. ACS Sustainable Chemistry & Engineering 10(11): 3787-3798.
- Ruiz-Caldas, M. X., Apostolopoulou-Kalkavoura, V., Hellström, A. K., Hildenbrand, J., Larsson, M., Jaworski, A., ... & Mathew, A. P. (2023). Citrated cellulose nanocrystals from post-consumer cotton textiles. Journal of Materials Chemistry A, 11(13), 6854-6868
- Ruiz-Caldas, M.-X., Apostolopoulou-Kalkavoura, V., Pacoste, L., Jaworski, A., & Mathew, A. P. (2024). Upcycling Textile Waste into Anionic and Cationic Cellulose Nanofibrils and Their Assembly into 2D and 3D Materials. ChemSusChem, in press, e202402103. Available at: https://doi.org/10.1002/cssc.202402103
- Åström, T., Ruiz-Caldas, M.-X., Skedung, L., Chelcea, I., Nilsson, C., Mathew, A. P., … Nilsson, U. (2024). The fate of hazardous textile pollutants in an upcycling process for post-consumer garments. Cleaner Engineering and Technology, 22, 100794.


## Safer and more sustainable by design in discovery chemistry

Generation of pharmaceuticals may suffer from hazardous reaction conditions, toxicity of intermediates and products and poor stoichiometry that do not fully align with the 12 principles of green chemistry. This case study was designed to develop and validate a biocatalytic pipeline for sustainable and safe drug discovery chemistry. To achieve this, a collaboration by the Mistra SafeChem WP3, WP4 and WP5 was initiated. WP3 was to filter all possible starting reagents from a toxicological and pharmacological perspective using *in silico* tools, enabling safer starting materials. WP4 then performed the laboratory tests to generate amides. WP5 performed USEtox to evaluate the environmental fate and exposure of the filtered building blocks identified by WP3 and used by WP4. Finally, WP5 is also working on preforming life cycle analysis (LCA) to benchmark the process compared to other methods.

**Results**

- The process of the first *in silico* hazard screening of the building blocks of amide formation, amines (n = 15374) and acids (n = 25994), gave a good starting point to avoiding the most toxic substances, and identified so called “safechems” (n = 288) for further consideration.

- The USEtox tool from WP5 was used to evaluate the “safechems” and corresponding amides for intrinsic properties of the compounds and to provide a risk assessment based on their fate and exposure.

The results of this case study have been summarised in a scientific article and published:


- Söderberg, E., von Borries, K., Norinder, U., Petchey, M., Ranjani, G., Chavan, S., . . . Syrén, P.-O. (2024). Toward safer and more sustainable by design biocatalytic amide-bond coupling. Green Chemistry, 26(22), 11147-11163.

## Sustainability assessment of a novel hydrogenation reaction process

In this case study a Ni-catalyzed electrochemical reduction of alkynes to Z-alkenes, and alkenes to alkanes, in a water-based reaction medium, was developed. Scarce metals were replaced by more abundant metals as the Pd catalyst is replaced by Ni. Hydrogen gas from fossil resources was replaced by hydrogen produced electrochemically from water. The case study includes an assessment of further optimization possibilities by application of non-target screening combined with hazard assessment and life cycle assessment (LCA).

**Results**

- Excellent to moderate yield was observed for a number of tri-, di- and monosubstituted enones and alkenes.
- The recyclability tests of the nickel foam catalyst showed a constant performance for at least 15 runs.
- The hazard assessment optimized the system from a hazard perspective via for example a recommendation of replacing methanol for ethanol.
- The screening LCA gave insights to further optimization possibilities. The LCA results identified the Pt counter electrode as a main contributor to the environmental impact from the nickel foam system which spur further research on alternative electrode materials.

The results of this case study have been summarised in a scientific article and accepted to Green Chemistry journal for publication:

- Tortajada, P. J., Kärnman, T., Martínez-Pardo, P., Nilsson, C., Holmquist, H., Johansson, M. J., & Martín-Matute, B. (2025). Electrochemical hydrogenation of alkenes over a nickel foam guided by life cycle, safety and toxicological assessments. Green Chemistry, 27(1), 227–239.

# Overall result of WP6

**This report summarises the results and overarching conclusions that can be drawn from all the case studies included in WP6. This includes parts of internal reports which can be made publicly available. Furthermore, the results also include all material that should have been reported in the delivery D6.1.3-N (Synthesis report from the four case studies connected to WP4) here.**

## Aim 1: To coordinate the interaction between the case studies and the various tools and methods generated in WP3, WP4 and WP5

The vision for Mistra SafeChem is to enable and promote the expansion of a safe, sustainable and green chemical industry in Sweden. Central parts of this interdisciplinary programme were to develop new processes for the industry and to develop a toolbox with models and methods that can be used for the risk assessment of chemicals. Safety and sustainability considerations should include the whole life cycle of chemicals, materials, or products, including their development and substitution. The developed toolbox, used by the different WPs in Mistra SafeChem includes new and more sustainable chemical processes, analytical techniques, predictions and testing of human toxicity and ecotoxicity, and methods for life cycle assessments including process safety and chemical footprint analysis. In total, 39 different tools have been developed or refined within the programme. Within WP6 all tools have been compiled into a webpage with a description of the tools and their maturity. For easy navigation the tools were grouped into the following categories:

- Hazard and exposure screening – 17 tools
    - Chemical screening
    - *In silico* prediction
    - *In vitro* prediction
- Process design and optimization – 15 tools
    - Catalysis / Biocatalysis
    - Electrochemical methods
    - Textile recycling
    - Valorization of forest residues
- Life cycle based assessment – 7 tools
    - Life cycle assessment
    - Chemical footprint assessment
    - Life cycle based alternatives assessment

Below is a short description of the aim and purpose for the main categories of the toolbox. For a full list of the tools, please visit the Mistra Safechem webpage, Toolbox - IVL.se (mistrasafechem.se)

**Hazard and exposure screening**

Defined approaches are characterised by the combination of *in littero*, *in silico* and *in vitro* hazard prediction methods in a decision framework for a specific purpose. The starting point is usually a situation where there is insufficient literature data to say whether a chemical is hazardous in a particular way.

If data is not available, *in silico* tools are applied as appropriate. The results can be used as the basis for a decision based on certainty, either to advise on hazard or to proceed to a biological test to confirm or not the hazardous property. Defined approaches are not necessarily regulatory compliant, based on acceptance guidelines, but allow screening decisions to be made. The current focus is on defined approaches for mutagenicity, endocrine disruption, and skin sensitization, where the decision points are clearly defined.

**Process design and optimization**

In the pursuit of enhanced safety and sustainability in the production of chemicals and materials, Mistra SafeChem is actively working on developing innovative tools and methods to achieve the following:

Replacement of virgin resources with recycled materials in the regeneration of textile fibres through cutting-edge spinning technologies. The primary emphasis lies in strengthening the mechanical properties of recycled fibres by incorporating novel, eco-friendly bio-based additives.

By incorporating novel fractionation technologies, the toolkit enables the substitution of virgin resources in primary production with secondary products or waste materials. This transformation primarily targets forestry and agricultural by-products or waste streams. The extracted fractions are then customised and recombined through sustainable chemistry approaches, yielding innovative composite materials.

Pioneering novel catalytic methods, including both enzymatic and metal-based approaches, to produce organic compounds of significant utility in various industries, particularly the pharmaceutical sector. The toolkit harnesses reagents and reaction conditions in line with the principles of green chemistry, with an emphasis on optimising atom economy, minimising waste, and using non-hazardous reagents or solvents.

The processes and optimization approaches use performance, toxicity and life cycle impact assessments as decision-making tools.

**Life cycle based assessment**

A life cycle based assessment toolbox is being developed to support the assessment of sustainability of chemicals. It is based on existing models already used in life cycle assessment (LCA) to assess the toxicity and ecotoxicity of chemicals, while taking into account advances in digitalization methods.

Substituting hazardous chemicals in industrial processes and consumer products requires not only the selection of less hazardous alternatives but also ensuring that the substitution does not lead to unacceptable trade-offs elsewhere in the chemical or product life cycle. Similarly, applying a systems perspective to process design and optimization is essential to avoid shifting the burden from one potential health and environmental impact to another.

Robust methods and tools are needed to address these challenges. Life cycle based tools need to take into account the hazardous properties of chemicals and materials as well as the risks of exposure throughout the life cycle.

The sustainability part of the toolbox is divided into three main parts: Life cycle assessment, Chemical footprint assessment and Life cycle based alternatives assessment.

**Coordination of case studies**

Furthermore, WP6 had a project leading role in the different case studies to coordinate and compile overall results. The task can best be described as transdisciplinary work, where substantial time has been dedicated into making sure that all partners from the different disciplines come together and understand each other's competences and areas. Each case study had the ambition from the beginning to use tools developed from each work package however, it would prove impossible for all studies, due to their nature and differences in the level of maturity of the tools to achieve this goal. For specific results of the case studies, see above for summary.

One successful outcome from the collaboration was the inter- and transdisciplinary collaboration approach with the integration of diverse expertise. Within the case studies experts from different fields were given the possibility to interact and gain knowledge from each other, to produce something new and reaching a collective understanding of the information flow that was necessary to reach the common goals.

## Aim 2: To transform industrial challenges into cases fit for the programme and evaluation of the tools

An important aim of WP6 was to provide case studies based on real industrial challenges to test and evaluate the use and performance of the toolbox and to map potential limitations of the toolbox for further development.

The work towards this aim was started in the application phase for Mistra SafeChem, in which three larger case studies were developed together with industrial partners. This included case studies on hazardous chemicals in the indoor air environment of a car, cyclosiloxanes and silicones in cosmetics and process optimization and intensification.

Throughout the course of the project, the work package contributed to this aim by:

- Reformulating one of the case studies on process optimization and intensification in collaboration with the industrial partner to take into account the lessons learned from the work already done in the first two case studies. The new case study focused on parts of the toolbox not yet included in the other case studies.
- Developing a new set of smaller case studies linked to the work in WP4, which was not previously included in any the case studies. In these case studies, WP6 played a coordinating role but partners from all case studies were included to ensure a cross disciplinary approach.
- Evaluation of the tools developed in the toolbox together with the industrial partners to test their usefulness for solving industrial challenges.
- Providing continuous feedback to the toolbox developers. In many cases, the toolbox developers were included directly in the case studies to provide assistance and support.

## Aim 3: To formulate the results from the case studies into general conclusions with respect to efficiency and reliability of the toolbox

The case studies were designed to make it possible to test and evaluate the tools developed in real scenarios. Several tools were tested in multiple case studies simultaneously and one of the aims of

WP6 was therefore to provide a synthesis on how the tools performed in the case studies and how they could be developed further.

The evaluation of the toolbox is discussed in the summaries of the different case studies, but also in Table 4.

*Table 4. Deliverables in the Mistra SafeChem programme referring to usage of the toolbox*

| Deliverable number | Deliverable Title |
|---|---|
| **D3.4.3** | Establish and routinize continued feedback to WPs 4-6 with relevant safety and exposure data, with a review every 6 months. |
| **D5.1.2** | Data requirements for LCA and feedback to WP3 and 4. |
| **D6.2.2** | Feedback on implementation of tools and methods from the case to WP3 and WP5. |
| **D6.3.2** | Assessment of alternatives to siloxanes and silicones in cosmetics. |

## Summary of conclusions for the three respective groups of tools

### Hazard and exposure screening tools

Chemical screening tools such as target, suspect and non-target chemical analyses were used in several of the case studies.

- In the car case study, target analysis was used in combination with a novel use for passive samplers of PDMS that were placed in direct contact with surfaces, to identify potential hazardous chemicals in the indoor car environment. In combination with passive air sampling, it provided a way to screen for hazardous chemicals in the indoor car air and then link it to potential emission sources, which would not have been possible to the same extent with just air sampling.
- In the textile and hydrogenation case studies, non-target screening was used to screen for transformation products, by-products and to map and trace hazardous chemicals through the production processes providing valuable information that could be included in the life cycle based alternative assessments.

When data regarding a chemical's properties, hazards and (eco-)toxicity is missing, *in silico* tools can be used to address these data gaps. In Mistra SafeChem three different *in silico* tools were developed, using machine learning and AI, covering a total of 67 newly trained prediction models:

- AI-based prediction tools, developed by Swapnil Chavan, RISE
- Machine learning tools, developed by Ziye Zheng, Cytiva
- Machine learning tools, developed by Ulf Norinder, Stockholm University

A summary of feedback collected for these tools is presented below:

- The tools were used to some extent in all case studies as it was often difficult to find sufficient data for all the substances of interest for a hazard screening/ranking.

- When performing the case studies, the user interface of the *in silico* tools in WP3 were not ready to be tested by the case study groups, but rather information on substances was distributed to the tool owner in the form of SMILES codes and results were then given to the case study group. The models will be easier to use in the future as WP3 is working on creating a common interface, connecting all three of the models, making the *in silico* toolbox a valuable addition to already existing models.

- The range of endpoints covered by the models was very broad.

- Model outputs were provided in an easy-to-use format (Excel), often with predictions regarding the confidence in the results, e.g., “Prediction with high confidence” or “Out of domain”.

- The tools are currently limited to hazard predictions (binary classification models) and do not yet match all needs for an LCAA (quantitative data). External tools and databases needed to be used to generate additional input data required for the use of the USEtox model in the case study applications. Future models will likely include quantitative endpoints and automated processes to generate data.

- The hazard prediction results from the tools can sometimes be hard to understand and the tools can feel like a black box. It is not always clear to the user which data is used to train the models and how certain outputs, e.g., substances predicted to have both antagonistic as well as protagonist effects for a certain endocrine disrupting endpoint, should be interpreted.

- The existing models currently cannot be used to predict hazards for substances such as metals, nanomaterials or natural oils as they fall outside the domain of these models. This is a general limitation of many existing *in silico* prediction tools. For companies focusing on screening alternative substances and materials using a different type of chemistry, this can be an issue. Several case studies reported that they had to exclude potential alternatives from the assessment due to a lack of data.

- Further testing of the tools by comparison with existing (experimental) results will increase the reliability and robustness of the model results.

As part of the *in silico* toolbox, the Mistra SafeChem project also developed a workflow for the prediction of bio-degradation and the formation of transformation products using existing external tools (deliverable D3.3.2, where parts of this work are accepted for publication in journal article, see Liagkouridis et al. (2025))

- This workflow was applied to the siloxane case to extend the alternative assessment to also look into potentially hazardous transformation products of the assessed alternatives, thereby further minimizing the risk for potential regretful substitutions.

- Ideally this workflow should be included into the *in silico* toolbox in the future to automatically predict endpoints for the chemicals of interest but also their potential transformation products.

A wide range of novel in vitro tools was developed in the Mistra SafeChem programme, including tools for high throughput and high content screening for (eco-)toxicity and epigenetics. As they were still under development when the case studies were planned, none of these tools could be tested in the case studies, during phase 1. But work is ongoing to quantify the health risks from exposure to chemicals in clothing, which is coupled to the textile case study. The availability of reliable (eco-)

toxicity data for a wide range of chemicals is essential to the input of many of the Mistra SafeChem tools used and for the development of better prediction models that can be used for a wide range of chemicals.

**Process design and optimisation tools**

The process design and optimization tools include a wide selection of tools and methods that can be used to replace virgin resources with recycled materials in manufacturing using novel catalytic methods.

The development and use of these tools were the core activity in WP4 and are commented on in other deliveries of the programme.

**Life cycle based assessment tools**

Life cycle based assessment tools included in the Mistra SafeChem toolbox, include USEtox and ProScale which are used to provide input for Life cycle assessments, chemical footprint calculations and life cycle based alternative assessments. In addition, Life cycle inventory process modelling was used for achieving data on relevant inputs and outputs on industrial scale level processes and to explore possibilities to use process simulations to generate LCA inventory data.

USEtox was used in almost all of the case studies, focusing mostly on indirect exposure during the use and end of life phases of the assessed chemicals. Its use varied from alternative screening in specific scenarios such as a car environment or the application of personal care products, to generating tox and ecotox input data for life cycle based alternative assessments. Below follows a summary on our experience with USEtox:

- USEtox was deemed to be a very powerful tool, in most of the cases, for screening chemical alternatives based on their (eco-)toxicity and to provide input to LCA based assessments, when data for the substances is available.

- The workshops and presentations on USEtox given within the Mistra SafeChem programme were informative and helped the case study participants understand the thinking behind the models and how they could be used. Direct contact with the USEtox developers that supplied the case study with input data (where available), bug fixes and feedback on the use of the model and recommendations regarding the data generation was also very helpful. It also highlights one of the potential challenges with USEtox however, in that it is a complex tool that requires training before it can be used to generate quality output.

- Before USEtox can be used routinely by the industry it will likely need an overhaul of the user interphase, making it easier to know what data input is required, where it can be found, and which output is relevant for the specific question. In scenarios where manufacturers rely on chemical substance data from their suppliers, it will not always be possible for the manufacturer to receive all the data required to run USEtox themselves due to data confidentiality. In that case, the suppliers would need to be able to run USEtox and provide the output to the manufacturers or have a third part collect the date and run it through the model under confidentiality agreements. Due to the complexity of the model, the latter is likely to be the preferred option as it minimizes the risk for mistakes in the use of the model and the interpretation of the results.

- It is currently difficult to address and quantify the uncertainty associated with the individual (eco-)toxicity impact predictions from USEtox.

- Several of the alternatives identified (e.g., substances derived from natural oils) could not be assessed properly because they fall outside of the domain of USEtox or the *in silico* toolbox from Mistra SafeChem.

- USEtox requires a large amount of quantitative input parameters to make accurate predictions. For new or lesser-known substances these input parameters can be difficult to obtain, meaning that accurate assessments for these substances cannot be made. Work is ongoing within Mistra SafeChem to improve the automated generation of these parameters using *in silico* tools. The current toolbox does not yet support the generation of quantitative data and is limited to qualitative output (e.g. if the substance is mutagenic or not), but work is ongoing to address this.

- Compared to ProScale, which includes a ”punish” value, that is used to take into account the lack of data for certain substances, this seems to this moment harder to establish in USEtox as it relies mostly on quantitative data.

- While the USEtox model is flexible enough to easily simulate different environments and scenarios, some parameters such as changing ventilation rates for the indoor exposure model were harder to work with within the time constraints of the project.

- In some of the case studies USEtox version 2.12 was preferred over the newer 3.0 version, due to differences in how the characterization factors (used as inputs to example Gabi, for LCA) are calculated.

- In the silicone case study characterisation factors for the three chemical impact categories from USEtox 3.0 were obtained but it was not obvious how these outputs were to be combined with the other environmental impacts in the LCA that was done using SigmaPro and the ecoinvent database. Instead output from USEtox 2.13 was used that was an incorporated method in SigmaPro. Three of the alternatives in the silicone case study were selected for SSbD step 2 – step 4 based on availability of input data in USEtox database. The alternatives were prioritised based on available data, rather than function with the purpose of method development. A couple of additional ingredients were in the database but were lacking human toxicity effects data such as ED10 of reference dose needed obtain the characterisation factors. Prediction of human effects data may be challenging but could allow more substances to be evaluated with the Mistra Safechem toolbox.

ProScale was also used in all three of the larger case studies, but often with a more pronounced focus on the manufacturing stage and direct exposure. Both ProScale as well as USEtox can be used for screening alternative chemicals and several of the studies included in the Mistra SafeChem programme used both models to get a more complete picture and to compare the outcome of the different models.

- Compared with USEtox, the data requirements for ProScale are much smaller as it relies mostly on qualitative rather than quantitative data, making it easier to use when input data for USEtox is not readily available. For some of the case studies for example, ProScale could be used to assess certain alternatives that could not be assessed with USEtox as there was no input data available for these substances.

- ProScale includes a ”punish” value, that is used to take into account substances for which data is missing. This is possible as the data requirements for ProScale are mostly qualitative.

- Further investigation is underway to assess situations where the two models generate differences in the outcomes, e.g. when applied to the indoor car environment case study. It is currently unclear if this is because of differences in the methods, the data selection or the uncertainty regarding the input parameters.

- As with USEtox, the uncertainty regarding the input and output data is an area that was flagged for further investigation. This included for example the uncertainty coupled to the use of QSARs for generating input data and uncertainties coupled to extrapolating data such as inhalation LC 50 values from oral LD values when other data is lacking.

# Synthesis of lessons learned

On a general scale the lessons learned from having case studies overarching several work packages, is that it facilitates transdisciplinary research with possibilities for collective learning within the specific case study. Another important general lesson is that transdisciplinary work does often take more time than first anticipated, hence scheduling of initial communication channels and workshops for coordinating work is an important aspect to consider. This enabled several of the case studies in MSC programme to keep all team members aligned and informed on work progress.

The value of having experts from different work packages (3, 4, 5) and industry involved in each of the case studies should not be underestimated. The knowledge gap between experts in work packages 3, 4, and 5 was to some extent significant but without a basic understanding of each other's fields and the possibilities and limitations of the different tools, it would not have been possible to provide the holistic approach required for developing green chemistry and methods. The case studies helped bring different experts together and greatly enhanced the quality of the research in the different work packages as well as the usability of the toolbox. The case studies provided essential feedback on how the tools could be used and developed further. In many cases the tools were used to answer complex questions that pushed the use of these tools to their limits.

Furthermore, these to some extent new collaborations were also beneficial for the case studies and facilitating sustainable and green development of chemicals, products, and processes. Attaining valuable information on for example ecotoxicity or human hazard risk, at an early stage in development by using the MSC toolbox helped several case studies in having iterations and adaptations along the way, to choose the correct chemicals from the start. This in turn led to avoiding for example regrettable substitution, or elimination of chemicals or processes. The iterative development of joint inventories for safety assessments and LCA underscores the effectiveness of this collaborative methodology, with each discipline contributing with insights and data. This adaptive approach was used to full extent in all of the research case studies, and also to some extent in the industrial case studies described above.

One of the more crucial lessons learned is perhaps the understanding that for the collaboration and interaction between different fields, the case studies must, to some extent, be designed from the methods and tools available already at the start. A recurring issue that was present in several of the case studies was the issue with lacking toxicity data as input data for LCA assessment and how to interpret the uncertainty in the model output. This is a well-known problem that is sometimes difficult to find a solution to. On the other hand, it is also difficult to design the studies in too much detail since this might limit certain aspects such as to include new tools or to address challenges during the course of the case study. Importantly, challenges will arise especially when working with real scenarios from the industry that may be difficult to solve with existing tools, and alterations will be needed to achieve the expected outcome.

Another conclusion is that the *in silico* tools are very valuable when it comes to designing new chemicals, since they are powerful tools that can screen multiple structures for hazard purposes, enabling exclusion of molecules at an early stage. However, one should know that the interpretation of the results may be difficult in reality when it comes to understanding how to use the results.

The overall conclusion of this WP is that we have within the programme of MSC come a long way towards the usability of the tools, although there is still more work to be done before the majority of them can be used as standalone tools for industry to use to enhance sustainable and greener chemistry.

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# About Mistra SafeChem

Mistra SafeChem is a research programme with the vision
to enable and promote the expansion of a safe, sustainable, and green chemical industry.

The programme is developed with the twelve principles of green chemistry as a fundament.

The research combines the potential of innovative manufacturing processes,
tools for hazard and risk screening, and life cycle assessment
with ambitions and opportunities for the development and growth
of a safe and sustainable chemical industry.

**More information:**
News from the programme, publications, and persons to contact
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