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Towards safe and sustainable chemistry

Guidance to the use of the Mistra SafeChem toolbox for life cycle based assessments

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MISTRA SAFECHEM

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Contents

Summary

This report provides information about life cycle based assessments to be used for developing safe and sustainable chemistry as they have been used in the Mistra SafeChem research programme. The requirement to consider a variety of aspects which are anchored in different research communities is rather novel, therefore it can be expected that adjustments and iterations will be necessary based on results from research programmes such as Mistra SafeChem.

Background on established assessment contexts for chemical alternatives assessment and life cycle assessment and the integrated chemical footprint assessment is provided. The key models applied for sustainability assessment are USEtox and the framework for life cycle alternatives assessment and ProScale – all of them are under development and testing for a selection of application cases is therefore intended as a contribution to identify user needs, drivers and barriers for application.

Separate case study reports are made available through the programme website for further reading on the current state of implementation. This report includes a synthetic case study to showcase application of tools and current challenges providing data, modelling and interpreting results. The Mistra SafeChem research programme will continue with more case studies and address gaps that have been identified in interdisciplinary work so far to enable the implementation of safe and sustainable chemistry principles.

Abbreviations

Life cycle assessment (LCA)
Chemical Footprint Assessment (CFA)
Chemical Alternatives Assessment (CAA)
Chemicals strategy for sustainability (CSS)
Environmental Product Declarations (EPD)
Life cycle alternative assessment (LCAA)
Life cycle based assessment toolbox (LCBA)
Life cycle inventory (LCI)
Life cycle impact assessment (LCIA)
Prospective LCA
(eco)toxicity
Safe and Sustainable by Design (SSbD)

1. Introduction

The present document is intended as a guideline to the structured application of tools for life cycle based assessment contained in the Mistra SafeChem toolbox. These tools, for evaluation of substances and processes, are intended to reduce hazards and environmental impacts along the entire life cycle of products. Two types of users are expected to work with this document, the first is LCA practitioners who need to add a broad set of impact categories, including (eco)toxicity, and want to understand underlying concepts and methodological choices. The second type of user is risk assessment practitioners who need to add life cycle thinking to their assessment, including information about the production routes and downstream fate and exposure of chemicals in relation to the target substances in an alternatives assessment. The integrated chemical footprint assessment, a concept within the Mistra SafeChem research programme, is designed to address both safety and sustainability aspects of chemicals. For comprehensive information about individual concepts and tools we refer to textbooks, reports and scientific publications.

This chapter lays the foundation for understanding the conceptual life cycle-based assessment toolbox (LCBA) and describes the scope and content of this report.

1.1. The conceptual Life Cycle-Based Assessment toolbox

Holistic environmental assessments are designed to address multiple protection objectives and the entire life cycle. This has more recently gained momentum, especially through work related to Green Deal policies including the Safe and Sustainable by Design (SSbD) framework. Existing tools that are evaluated and tested within the MSC toolbox predate this development and are thus not necessarily aligned with the entire SSbD framework, as an example they can focus on a smaller set of aspects or a part of the life cycle.

1.1.1. Policy initiatives on EU level

The European Green Deal's ambitious goals for climate neutrality, a circular economy and a toxic-free environment by 2050 initiated a number of regulations and directives related to handling of chemicals. A core element is the Chemicals strategy for sustainability (CSS) (EC, 2020), which prioritizes the adoption of SSbD chemicals and materials. This strategic approach aims to (re-)design and assess chemicals, processes, and materials, ensuring they maintain functionality while minimizing adverse health and environmental effects. To support this goal, the European Commission (EC) is developing a framework to assess if a chemical substance or material meets the SSbD criteria. The SSbD framework's (EC, 2022) main objective is to identify safety and sustainability hotspots early in the (re)-design of chemicals, processes, and products, thereby avoiding obstacles in later stages of innovation (Caldeira et al., 2022). For additional information regarding tools and policy drivers for development of chemical footprints see also a mapping study by Andersson et al. (Andersson et al., 2024).

1.1.2. Implementation levels and entry points

In the context of CSS, the pursuit of a sustainable chemical industry is increasingly recognized as critical. Central is the strategic substitution of hazardous chemicals in industrial processes and consumer products. Here is where the methodology Chemical Alternatives Assessment (CAA) plays a crucial role (OECD, 2021). CAA helps identifying and evaluating potential substitutes for chemicals to be phased out. Incorporating a life cycle perspective in CAA is essential to avoid the shifting of burdens along the life cycle and between different safeguard objects. However, this approach faces challenges due to the lack of standardization in life cycle thinking and the shortage of data, complicating comprehensive life cycle impact assessments.

Life Cycle Assessment (LCA) is an integral part of policy work both in EU and nationally (Suikkanen et al., 2023). Global standardization is implemented through ISO standards. For LCA-based environmental labels Environmental Product Declarations (EPD) are established (ISO, 2006a). More recently, an approach for LCA-based environmental labels is suggested in the European Commission Organizational and Product Environmental Footprint methodology (OEF and PEF). It includes guidance for product categories and organizational sectors through pilot studies for selected sectors and products (EC, 2013).

The chemical footprint assessment, a concept attaining increased attention and adopted within the Mistra SafeChem research programme, was designed to address both safety and sustainability aspects of chemicals integrated on an intermediate level. CFA is defined within Mistra SafeChem as "an aggregated indicator of chemical pollution that enables the assessment of the potential human toxicological and ecotoxicological impacts of the entire life cycle of a product or service". The key tools for evaluating the Chemical footprint in the conceptual toolbox are the LCIA models USEtox and ProScale, which are further described in Chapter 3.

1.1.3. Addressing toxicity

One of the significant challenges in human toxicity and ecotoxicity impact assessments is extensive data requirements for characterizing chemicals, products and processes. This includes a high level of complexity in supply chains, which induces time-consuming data collection and modelling effort required for life cycle-based assessments. Significant data gaps exist for providing life cycle inventories across all life cycle stages - from extraction, manufacturing to use and end of life, including emissions from both the process and product application. Characterisation factors for impact assessment modelling are equally missing. Detailed understanding of parameters such as chemical occurrence, emissions, fate, exposure and toxicity is vital to address these gaps. Parameterized models are also increasingly required to utilize digitalisation and *in silico* substance property predictions, as an approach to gather data for impact assessment models of a large number of substances.

1.1.4. Development of the Life cycle-based assessment toolbox

As an interim result of the Mistra SafeChem research programme, tools are arranged in a Life Cycle-Based Assessment (LCBA) toolbox. This is intended primarily for conducting environmental and human health assessment contributing to sustainability assessment within the chemical sector and its associated value chains. The toolbox is available in its current state and will be further updated and extended in phase 2 of the Mistra SafeChem research programme.

These tools need to be consistent with the assessments in CAA and LCA and use comparative metrics in each. In response to these needs, a conceptual life cycle-based chemical assessment toolbox is being developed as part of the Mistra SafeChem research programme (see Figure 1). This toolbox includes a concept for Chemical Footprint Assessment (CFA) and aims to address data gaps in assessing toxicity impacts on humans and freshwater ecosystems resulting from chemical production and usage integrating these assessments in both CAA and LCA.

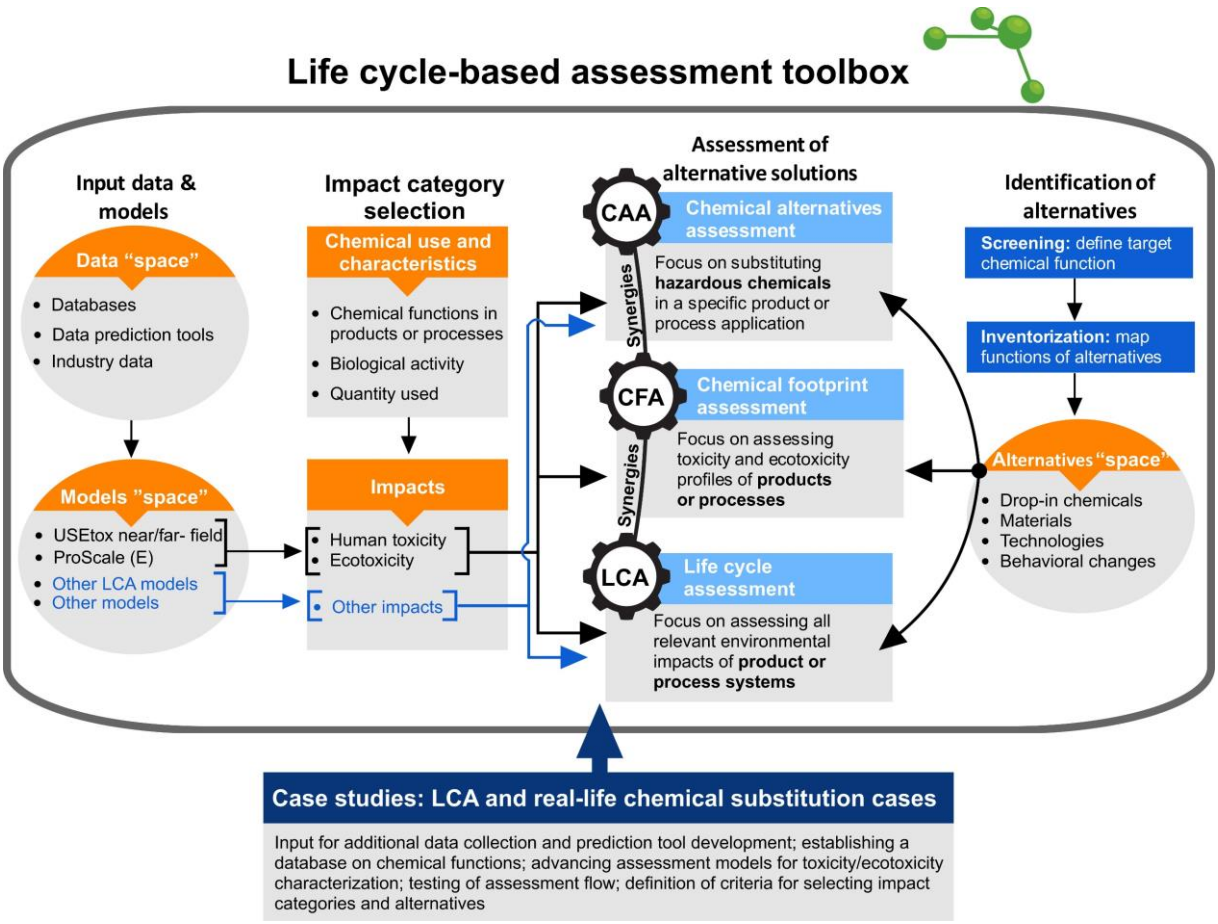


Figure 1 The Mistra SafeChem conceptual life cycle-based chemicals assessment toolbox.

1.1.5. Starting point of the Mistra SafeChem toolbox

The Mistra SafeChem life cycle-based assessment (LCBA) toolbox is inspired by a tiered Life cycle alternative assessment (LCAA) framework developed by Fantke et al.(Fantke et al., 2020). The framework, expanding from use-stage risk to encompassing the chemical value chain and product life cycle impacts, is consistent with the consensus-based model USEtox (USEtox) applied in LCA and aligned with the 2014 Framework for guiding the selection of chemical alternatives by the US National Research Council (NAP, 2014) . Building on this foundation, the LCBA toolbox was developed, and its primary aim is to extend beyond chemical-by-chemical substitution, giving access to concrete tools for allowing a wider perspective on early design of chemicals, processes and products, including material related issues, technology and behaviourial aspects.

ProScale is a life cycle-oriented tool (Lexén et al., 2017) designed to assess the direct toxicological potentials of chemical process and product systems. ProScale methodology is specifically designed to assess the toxicological potential resulting from direct exposure to hazardous substances present on their own, in a formulation or products throughout their life cycle.

The key tools, USEtox (see Rosenbaum et al., 2008, Fantke et al., 2021, Owsianiak et al., 2023) and ProScale have been tested in case studies and further developed within Mistra SafeChem. The potential of digitalization techniques has been explored and development started to address critical data gaps prevalent in existing CAA and LCA models, particularly for assessing emissions, fate, exposure, and (eco)toxicity effects across a wide spectrum of chemicals (von Borries et al., 2023).

The tools and the conceptual LCBA toolbox are still under development. A contribution of the Mistra SafeChem research programme is to test practical application in a number of case studies in collaboration with industry and various stakeholders. A case study demonstrates how the toolbox can be used to understand and improve environmental performance, providing decision support for chemical substitution. Separate case study reports address usage of tools in process design and optimization at low technology readiness level (TRL).

1.2. Purpose, scope and content of this report

This report aims to describe and illustrate, through case study examples, how the conceptual LCBA toolbox can be used in different contexts. It primarily addresses aspects relevant to the case studies conducted within the Mistra SafeChem programme.

1.2.1. Target audience

It is recommended to use this document complementary to the user's background and add introductory literature where needed. Two main user types are expected, LCA practitioners and safety assessment professionals, more precisely:

- LCA practitioners who will perform environmental assessments focusing on toxicity and ecotoxicity impact categories for the sustainable development of chemicals and processes within the chemical industry or academia.

- professionals who are in charge of safety assessments in the chemical industry and related value chains and are interested in learning more about assessing sustainable development in the chemical sector and its value chain.

Background and descriptions for Chemical footprints as a novel hybrid approach are intended to facilitate an integrated assessment of toxicity aspects and can therefore be beneficial for both user types and beyond.

1.2.2. What is the relationship to existing standards and guidelines?

This report complements LCA and CAA guidelines and does not cover standard procedures and issues in detail. For general LCA guidance, the ISO standards (ISO, 2006b) and (ISO, 2006c), the ILCD handbook **(JRC, 2010)** and PEF method documentation (Zampori and Pant, 2019) are recommended. For general CAA guidance the OECD Guideline for Chemicals Alternatives Assessment (OECD, 2021) and the 2014 Framework for guiding the selection of chemical alternatives by the US National Research Council (NAP, 2014) are advised.

1.2.3. Structure of this report

This report is divided into five parts. The following part, section 2, provides a brief introduction to the background of the toolbox and the assessment tiers, accompanied by recommendations for further reading. Section 3 addresses the main tools USEtox and ProScale. Section 4 provides information on case studies and specific tasks, mainly in the area of product and process innovations. Chapter 5 includes selected results from a case study; to illustrate usage of the tools, an additional example for assessing an existing product with both USEtox and ProScale is provided. In Chapter 6 conclusions regarding usability and addressing advantages, gaps and further development needs are summarized.

For further reading:

Chemical Strategy for Sustainability: **Chemicals Strategy for Sustainability (EC, 2020)**

Safe and Sustainable-by-design (SSbD) framework: **SSbD framework (EC, 2022, NAP, 2014)**

Chemical Alternatives Assessment: **OECD Guideline on Key Considerations Identification and Selection of Safer Chemicals Alternatives**, **2014 Framework for guiding the selection of chemical alternatives by the US National Research Council (OECD, 2021, NAP, 2014)**

2. Background: Toolbox and assessment tiers

The toolbox is a concept for Chemical Footprint Assessment (CFA). It is designed to be integrated in Chemical Alternatives Assessment (CAA), and new chemical design and formulations and process design, either as standalone assessment or integrated in Life Cycle Assessment (LCA).

In this chapter, the key assessment methods, Chemical Footprint Assessment (CFA), Chemical Alternatives Assessment (CAA) and Life Cycle Assessment (LCA), and the Life cycle based alternative assessment (LCAA) framework are introduced within the life cycle based toolbox.

2.1. Chemical Footprint Assessment (CFA)

CFA is used to calculate human toxicity and ecotoxicity indicators for production of chemicals, materials and products (articles), their usage and disposal. In Mistra SafeChem CFA is defined as *"an aggregated indicator of chemical pollution that enables the assessment of the potential human toxicological and ecotoxicological impacts of the entire life cycle of a product or service."*

Footprints and indicators

The overarching idea of "footprinting" is employed to assess diverse impacts of human activities and involves a significant communicative and accounting aspect. An "ecological footprint" was introduced in 1992 by Rees (Rees, 1992) and suggested to calculate a carrying capacity of countries to provide resources and accept emissions and waste (Wackernagel et al., 1999). The ecological footprint was suggested as a metric for environmental accounting and expressed as an area.

Footprinting methodologies for over 20 (isolated) environmental issues have been established subsequently, such as water footprint (Boulay et al., 2018) and carbon footprint. The latter is addressed in a global standard ISO 14067 (ISO, 2018). These footprints are used as environmental indicators and not expressed as area, but as mass or volume.

More recently, the European Commission proposed the Product Environmental Footprint (PEF) and Organisation Environmental Footprint (OEF) methods as a common way of measuring environmental performance (EC, 2013, Zampori and Pant, 2019) (EU Commission Recommendation 2021/2279). PEF and OEF are LCA based methods to quantify the environmental impacts of products (goods or services) and organisations. The PEF framework includes an option to calculate a fully aggregated score based on a set of 16 impact categories addressing toxicity, resource use, pollution and biodiversity.

The term "Chemical footprint", is suggested by different research communities with varying definitions. The non profit organization chemicalfootprint.org (CFP, 2023) characterizes the Chemical footprint as "*the total mass of chemicals of high concern used by an event, organization, service, building or product*". This definition focuses primarily on quantifying chemical usage rather than considering their impacts on human and ecosystem health. Li *et al.* found that the definition of a (Product) Chemical footprint for the textile sector depends on the study perspective (Li et al., 2021). Panko and Hitchcock suggest that a Chemical footprint serves as an indicator of potential risks posed by a product based on its chemical composition, the toxicological and ecotoxicological hazards of the ingredients, and the potential for human exposure throughout the product's life cycle (Panko and Hitchcock, 2011).

Sala and Goralczyk introduced a framework for chemical footprint assessment, integrating a life cycle assessment approach with evaluations of human and environmental risk. They defined a chemical

Footprint as: *"a quantitative measure describing the environmental space needed to dilute net chemical pollution – commonly by a mixture – due to human activities to a level below a specified boundary condition" (Sala and Goralczyk, 2013).* In a comparable approach, Bjørn, A., *et al.* defined chemical footprint for ecotoxicity impacts from anthropogenic chemical emission *"as the volume of pure water theoretically required for the dilution of chemicals that are released to aquatic environments, down to concentrations that are safe for freshwater ecosystems (Bjørn et al., 2014).* A short review and conceptual analysis of approaches suggesting to collate input from research communities on both risk assessment and life cycle assessment as a way forward was published by (Rydberg et al., 2014).

Chemical footprint assessment is used within the Mistra SafeChem research programme for toxicity and ecotoxicity indicators in a life cycle perspective. The footprint is generated for a function that could be a product or service. Relevant impacts are on human health and ecosystem integrity. Within Mistra SafeChem, the concept of chemical footprint includes the life cycle inventory and all emissions related to the function being studied. However, an absolute sustainability assessment is not included at the moment.

Within Mistra SafeChem, USEtox and ProScale are utilized as two key models for assessing the Chemical footprint of a product or service. These two models are further described in section 3 on key models. The CFA can be assessed as a standalone metric; guidance for integration in an LCA is provided.

Within the Mistra SafeChem programme, Chemical footprint assessment is defined as "an aggregated indicator of chemical pollution that enables the assessment of the potential human toxicological and ecotoxicological impacts of the entire life cycle of a product or service."

2.2. Chemical Alternatives Assessment (CAA)

CAA is a method for achieving informed substitution of harmful chemicals (OECD, 2021). The aim of informed substitution is to reduce or eliminate chemical hazards and their associated risks by replacing a chemical of concern with an alternative solution that provides a better safety and sustainability profile than the chemical being phased out based on a functional approach.
A functional approach means that the chemical of concern is not necessarily replaced by a drop-in replacement. A drop-in replacement means substituting one substance for another substance with similar properties, without changing other parameters in the product or system, and it is easier to implement compared to other approaches. Regrettable substitutions have been observed when utilizing the drop-in approach to maintain the same function. With its rather narrow focus, it is possible that the replacement can have similar or different but still harmful effects, which is referred to as regrettable substitution. One often mentioned example of this is the replacement of bisphenol A with bisphenol S (Zimmerman and Anastas, 2015). Focusing on the functional use of the chemical that will be replaced can help avoid regrettable substitution.

A functional approach means identifying the chemical function, the purpose the chemical serves, or the properties it imparts to a product or process and to evaluate the entire product and how its use may influence the assessment of alternatives. This might result in the complete discontinuation of established products or production processes, a change in the production process or an entirely new product design. Furthermore, taking a system perspective is often recommended in CAA to avoid shifting problems from one life cycle stage to another of a product life cycle. However, challenges arise from the lack of standardization in life cycle thinking within the CAA community, and the lack of data, making it difficult to assess the life cycle impacts comprehensively. The aim of CAA is to identify safer alternatives, which might include comparing and assessing one alternative against another or across multiple alternatives.

- CAA is a method for informed substitution of harmful chemicals
- Aims to reduce or eliminate hazards by replacing chemicals with safer and more sustainable alternatives
- Focuses on the functional use of chemicals to avoid “regrettable substitutions”

For further reading please see: OECD Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternatives, 2014 Framework for guiding the selection of chemical alternatives by the US National Research Council. (OECD, 2021).

2.2.1. Life cycle based alternative assessment framework (LCAA)

To address the need for the quantitative assessment of relevant life cycle impacts and exposures in CAA, Fantke et al. developed a tiered Life Cycle-based Alternatives Assessment (LCAA) framework (Fantke et al., 2020). In each tier the assessment scope is increased from use-stage risks to chemical supply chain and product life cycle impacts. The LCAA framework consists of three hierarchical assessment tiers (and one optional pre-screening tier) that increase in the assessment scope sequentially, as illustrated in Figure 2.

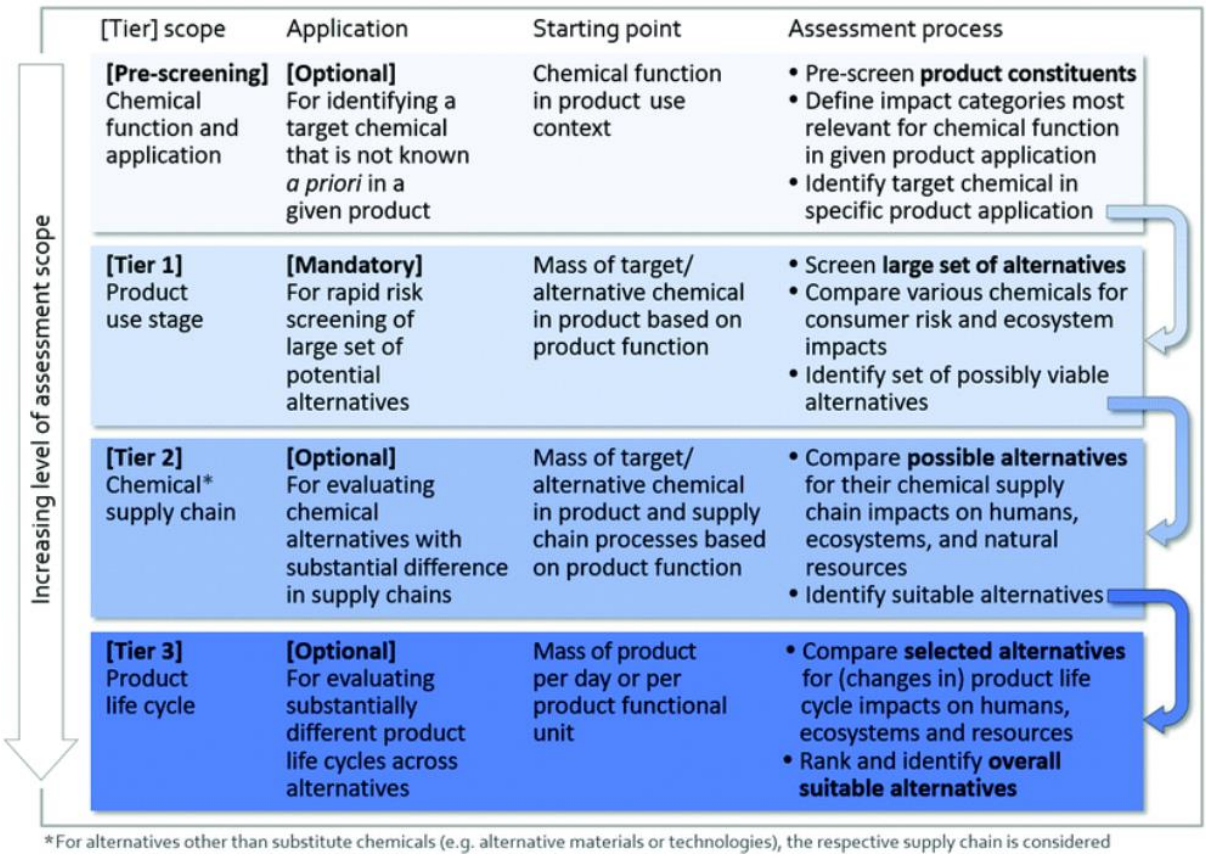


Figure 2 The diagram of LCAA framework; adopted from (Fantke et al., 2020) reused with the permission of Royal Society of Chemistry.

Scoping and the problem formulation

Scoping is an initial step and sets the stage for the process to follow. During scoping, the goals and principles that will guide the assessment are defined. It can also be used to filter whether alternative solutions are further investigated and exclude those that are unacceptable from a functional, legal, economic, market, or corporate policy standpoint. Scoping thus needs to define the performance requirements for alternative options. It involves outlining the potential effects on human health, exposure scenarios, life cycle stages, and environmental impacts of greatest concern that will be examined in the subsequent assessment. The criteria for evaluation are determined based on the characteristics of the chemical of concern and its potential substitutes in a particular product application.

Input data and models

Following the LCAA framework, USEtox 3.0 is recommended, which is based on the near-field/far-field model including exposure that a user and their immediate surroundings experience, and environmental exposure that affects the global population. Additionally the framework can be extended with other LCIA models, as an example ProScale to consider exposure in the chemical supply chain (Tier 2).

Selection of impact categories based on chemicals function and quantity used in processes and products

Following the LCAA framework, a subset of relevant impact categories are considered. The authors suggest to consider, besides toxicity and ecotoxicity, also climate change and particulate matter in air with a diameter less than 2.5 micrometre (also called fine particulate matter, PM 2.5). Climate change impacts have been shown to be strongly correlated with several other impact categories such as resource use, but to a lesser extent with chemical toxicity and ecotoxicity, which makes it complementary to this framework. Another important impact category is PM2.5 which was is identified as one of the most important contributors to human disease burden based on a systematic analysis of the Global burden of disease study (Lim et al., 2012). Therefore, these two impact categories are recommended to be included in the assessment to complement the LCAA framework. However, the selection of categories is case dependent and should consider the scoping results.

Tier 0. Optional Pre-Screening

In the LCAA framework the (optional) first step is a pre-screening and framing, where the function of the chemical is defined, and relevant impact categories is selected. Relevant impact categories are defined on a case-by-case basis. For example, when a bioactive target chemicals investigated, this potentially implies that a biocide is used for which toxicity and ecotoxicity impacts are relevant. Using this approach, it is possible to prioritize the assessment of chemicals and factors that have the most significant influence on the overall environmental impact of the product and/or processes. This pre-screening step refines the overall scope of the LCAA tiered based assessment steps.

Tier 1. Mandatory: Human risk and ecotoxicity of target chemical and alternatives

In Tier 1 chemicals of concern are identified, including reasoning for concern and identifying of potential alternatives. In this step a screening on human health risks and ecotoxicity of target chemicals and potential identified alternatives in a given product application is performed with focus on the use stage. Alternatives only pass to the next tier if they perform substantially better in the toxicity and ecotoxicity impacts than target chemical. For all other considerations and performance criteria, the performance results of alternatives could be of the same order of magnitude as long as these are not substantially worse.

Tier 2. Optional: Assessment of chemical supply chain impacts

In Tier 2 the assessment is broadened to encompass the supply chain of target chemical and alternatives. The supply chain of these chemicals needs to exhibit substantial differences to significantly impact the assessment. The proposed approach is to characterize cumulative long-term impacts related to supply chain emissions affecting workers, the general population and ecosystems. These results are then compared to the use stage scores from Tier 1. Additionally, it is proposed to evaluate relevant chemical supply chain impacts based on exposure to PM2.5 used as benchmark for toxicity-related impacts, as well as assessing impacts on climate change linked to energy consumption and various impact categories. Note that without evaluating of the supply chain options with deviating impacts beyond the use stage cannot be identified.

Tier 3. Optional: Assessment of product life cycle impacts

In Tier 3, the scope is expanded from the original chemical alternative assessment to encompass the entire product life cycle. In this tier we extend our assessment beyond the human health hazard and environmental hazard and include the alternatives with distinctly different life cycles. We proceed to characterize and compare, with the product containing the target chemical as baseline, the impacts from emissions and resources used throughout the entire product life cycle. This tier offers also an option to include normalization and ranking for a wider set of impact categories.

In summary, the LCAA framework utilises USEtox 3.0 and can be directly integrated in CAA. For further reading about the framework: Life Cycle Based Alternative Assessment Framework (LCAA).

The Life Cycle based Alternatives Assessment (LCAA) framework is a framework for quantifying human and ecosystem exposure and impacts associated with chemical supply chain and product life cycle. The framework is based on USEtox 3.0 and can be directly integrated in CAA.

For further reading about the framework: Life Cycle Based Alternative Assessment Framework (LCAA).

2.3. Life cycle assessment (LCA)

LCA considers the entire life cycle from raw material extraction to end-of-life, called cradle to the grave. The purpose of including the entire life cycle aims to avoid sub-optimization and burden-shifting between different life cycle stages. Moreover, considering a set of impact categories is intended to avoid shifting of burden between different environmental issues. LCA studies are designed with different goals and scopes and serve to identify hotspots and to compare products and product options. Cradle-to-gate studies, which only consider material sourcing and production, and a combination of cradle to gate and end-of-life perspectives are a often selected if the intention is to support manufacturing and process industries in reducing their environmental impact.

LCA is based on an inventory of elementary flows that cross from ecosphere to technosphere (resources) and from technosphere to ecosphere (emissions to air, water and soil) and therefore addresses impacts on the environment and a general or average population, increased impacts on users and workforce that are exposed to increased emissions due to their proximity to a source are usually not considered. Adding a chemical footprint assessment is thus an approach to populate the technosphere and consider both direct exposure for users and workforce. Note that datasets in LCA databases in current form do address elementary flows.

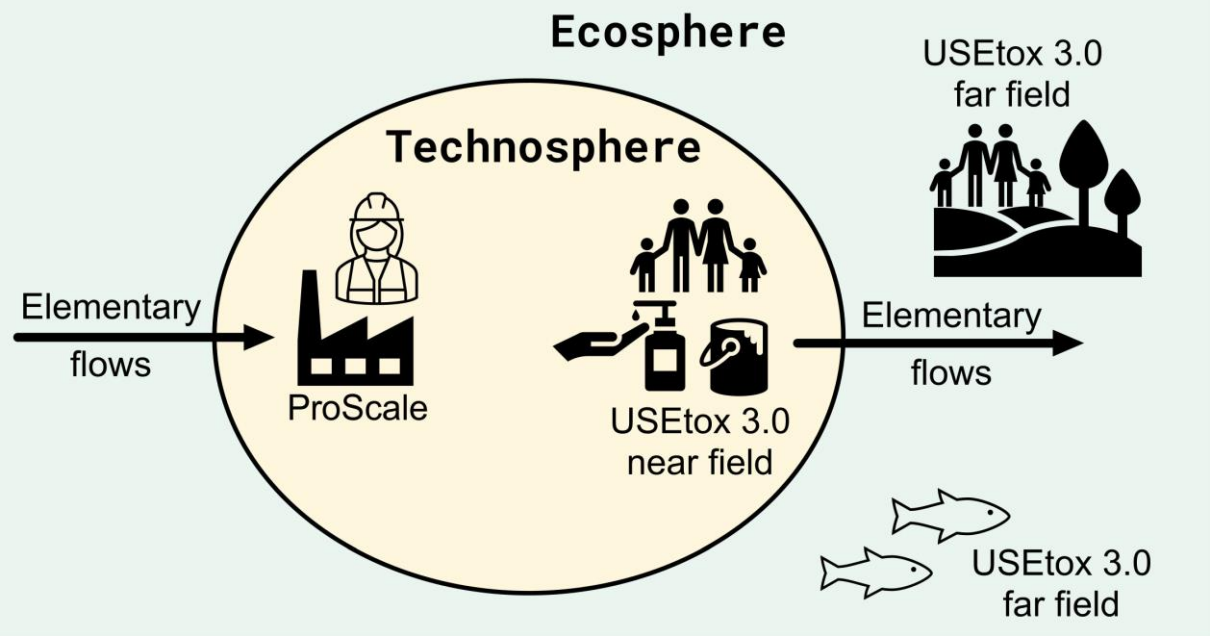


Figure 3: Illustration of the conceptual connection between life cycle assessment considering elementary flows crossing the border between ecosphere and technosphere and tools included in the Mistra SafeChem LCBA toolbox considering direct exposure in a life cycle context

Global standards ISO 14040 and 14044 illustrate the procedure on an LCA with four iterative phases: (1) definition of goal and scope; (2) life cycle inventory analysis (LCI); (3) life cycle impact assessment (LCIA); and (4) interpretation of results (See Figure 3). The following short descriptions are representative for the procedure according to the ISO standards, unless otherwise mentioned.

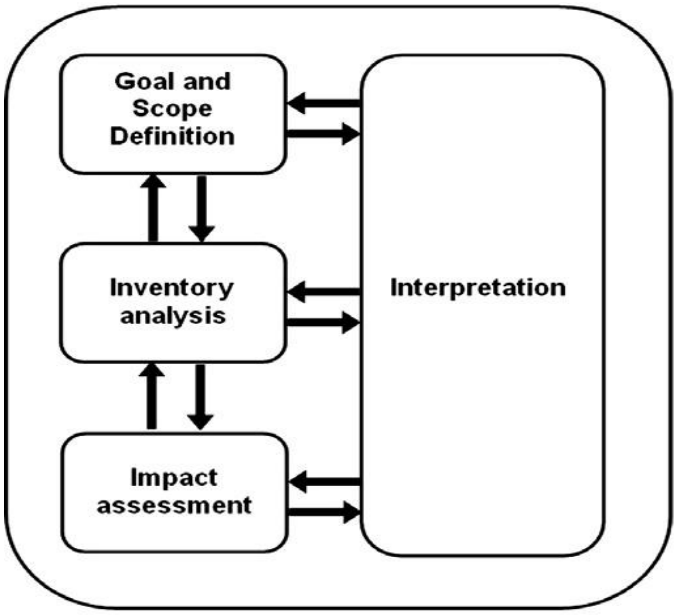


Figure 4 The four iterative phases of a life cycle assessment according to ISO 14044 (SS-EN ISO 14044:2006, 2006)

Goal and scope definition

The goal and scope definition is the first stage of an LCA, where the purpose of the study and the intended audience is described. Also, the boundaries of the product system are defined according to factors such as time constraints, data availability and depth of study required. At this point a 'functional unit' is defined, which provides a reference to which the inputs and outputs of the analysis are related.

Inventory analysis

Inventory analysis involves data collection related to the inputs and outputs of the system described in the 'goal scope and definition'. It inventories quantities of raw materials, waste flows and emissions attributed to the products life cycle. Flows are followed up to the boundary of the technosphere to identify elementary flows that contribute to the inventory.

Life cycle impact assessment

Life cycle impact assessment involves associating inventory data with specific environmental impact categories and category indicators, thereby attempting to condense information and illustrate these impacts. Emissions are linked to areas of protection, natural environment, human health, and natural resources. Emissions and resource use are linked to areas of protection via cause effect chains. Two main strategies are applied, defining characterisation factors on a midpoint level of the cause effect chain (e.g. carbon dioxide equivalents for climate change impacts) and on an endpoint level (disability adjusted life years for human health).

LCIA provides mandatory and optional steps to carry out this task. Mandatory steps are classification, this is a grouping of individual substances to impact categories, and characterisation, converting the amounts within an impact category to a reference substance or a common unit.

Optional steps are normalisation, which means that results for an individual study are compared to global (or European, national) emissions. Normalised results are either dimensionless or expressed per capita, thus the magnitude of different impact categories can be compared. Ranking of normalised results is possible. Weighting requires that results are converted, and weighted results can then be aggregated into a single score. The use of weighting can be based on distance to target (DtT) approaches, with targets defined by policies or planetary boundaries. Use of single score results is restricted according to the global standards, the PEF framework foresees a weighting step and also provides weighting factors for implementation.

Interpretation

Here results are interpreted, summarised, and discussed, conclusions are drawn, and recommendations made against the initial goals. Figure 3 shows that that there are possible interactions between all stages of an LCA, indicated as arrows. This includes interpretation, as the study is constantly measured against its initial goals and scope and refined during its duration. The phase does also include as a mandatory part sensitivity and uncertainty analysis to test the robustness of the result and consider data and model uncertainty. As LCA is an iterative method, the interpretation of results may involve corrections of other phases, for example in cases where data gaps are discovered ISO (2006b).

2.3.1. Methodological choices in LCA

The inventory analysis requires a number of methodological choices, such as partitioning burdens between different products and by-products for multi-output processes and also for multi-input processes, which are very common for disposal. Collected data thus need to be allocated to the studied product. Another choice is related to the defined goal of the study and addresses whether the study is intended to sum up the complete impacts related to a specific product (attributional LCA) or the expected changes when a specific product replaces other options (consequential LCA). Consequential LCA aims to describe how environmentally relevant flows will change in response to possible decisions (Finnveden et al., 2009) This choice affects also the data collection stage. Cases in the Mistra SafeChem research project address the development of novel processes and chemicals and it can therefore be argued for both attributional or consequential modelling principles.

Another aspect of modelling novel processes and products is that data for flows, yields and other parameters are available for laboratory scale and pilot scale and modelling impacts based on these inputs can lead to overestimation if future process optimisation is not considered, or to underestimation if laboratory conditions cannot be implemented on a larger scale. A scale-up framework was suggested by Piccino et al. (Piccinno et al., 2016). Beyond up-scaling, systematic consideration of scenarios for both novel technologies and a benchmark scenario for business as usual is required. Prospective LCA is suggested for assessing emerging technologies (Arvidsson et al., 2018). A technical report by JRC addressed various aspects of prospective LCA for biobased product systems (Cucurachi et al., 2022).

Within the Mistra SafeChem research programme a systematic literature review on approaches for prospective LCA was carried out related to one case study (Appiah-Twum, 2022), furthermore different scale-up approaches have been used, among others using attributional LCA based on a theoretical process model of a future system but within current societal and technological settings and in a modelled future setting, with adjusted parameters.

- LCA is a standardized method for quantifying the environmental impacts of products and services
- Considers the entire life cycle from raw material extraction to disposal (cradle to grave)
- Identifies hotspots and compares products and services for environmental performance

For further reading see: ISO 14040 and 14044

2.3.2. Life cycle inventory (LCI) for chemicals

Data gaps in life cycle inventories significantly impact their quality and reliability of results. The life cycle inventory (LCI) phase becomes less certain when mostly average and proxy sources are used. The quality and completeness of the LCI is crucial as it directly affects the overall quality of the LCA. The reasons for data scarcity in LCI are multifaceted. Confidentiality concerns surrounding industrial processes and products can restrict availability, this is true even for suppliers of chemicals and products. Where suppliers are frequently changed for bulk inputs, efforts to collect specific data are not always justified. Additionally, the complexity of production systems often hinders comprehensive data gathering. Reviewed data from case studies and databases can have limitations if it was collected to be used in a specific context, as an example if data has been collected and reviewed for use in carbon footprint assessments the use in environmental footprint assessments might be limited. This is especially the case for aggregated data (system processes).

Within the Mistra SafeChem case studies, different approaches for handling lack of data have been applied, see case study examples. Beyond the use of adapted database data, some of the case studies applied an approach developed for generating gate-to-gate life cycle information of chemical substances based on chemical engineering process design (Jiménez-González et al., 2000). Available databases for chemicals will be evaluated in phase II of the Mistra SafeChem research programme, a preliminary overview follows here.

Databases

Databases (for example, Ecoinvent, LCA for experts (GaBi), carbon minds), are commercially available and used by companies, academia, and organizations to model inventories. Background systems for which own data collections are not feasible or seen as tedious are often modelled with such modules. Free open access datasets are made available in academic publications, but specific databases have not reached a sufficient level of completeness and oftentimes need to be complemented with background modules from the aforementioned providers.

A limitation with commercial databases is that they at least partially contain aggregated data for systems. Elementary flows from aggregated processes can be entered into impact assessment models, but it is not possible for the user to review (and adjust) modelling assumptions, if a comparable but not similar process is required in a model. Selecting data from databases adds uncertainty, and cannot be reviewed independently, but only based on information supplied by providers. Review processes are in place, it is however not clear whether they are suitable to cover a wide range of impact categories or focus on specific applications in carbon footprint calculations, for which a high market demand is established.

Environmental genome of industrial products EGIP

In the LCAA framework (Fantke et al., 2020) the Environmental Genome of Industrial Processes (EGIP) is recommended as a starting point to link chemical supply chain impacts to inventory data. The database is not publicly available. It uses information on resources and a sequence of synthesis processes to create gate to gate unallocated LCI modules that can then be used to generate LCIs. Production locations for synthesis processes and more metainformation can be considered. (Overcash, 2016). This concept can potentially benefit from AI and digitalisation of process data and add transparency.

Data prediction tools

The life cycle impact assessment models in focus within the Mistra SafeChem research programme also require effect values (USEtox) and hazards (ProScale). When experimental data is missing, predictive models can be employed to derive relevant information. The Mistra SafeChem in silico toolbox focuses on chemical hazard prediction and is based on machine learning. It includes 67 newly trained hazard prediction models, including traditional machine-learning models with chemical descriptors and descriptor-free deep-learning models. The hazard endpoints are not compatible with data used in USEtox.

2.3.3. Evaluation procedure for LCA scores in the SSbD framework

The procedure to evaluate LCIA results for the SSbD framework is under development. In spring 2024 it foresees application of the environmental footprint impact categories and further processing. Aggregating individual impact categories into four groups toxicity, climate change, pollution and resource use is suggested as initial step (Caldeira et al., 2022). After that, normalisation based on factors derived from planetary boundaries ((Sala et al., 2020) as published in a report about case studies (Caldeira et al., 2023) are applied. Normalised results can then be compared to assess changes, with the reference product or substance set to 1 (Abbate et al., 2024). Improvements of less than 5% are considered as fail for step 4 of the SSbD framework (score 0 and 1). A failed score indicates increased or stagnating environmental impacts, identifying contributing processes and chemicals in the supply chain is recommended.

3. Key models

In this chapter the key models USEtox and ProScale within the toolbox are further described. Note that both models have been developed elsewhere and are still continuously further advanced, by contribution from the Mistra SafeChem programme among several other initiatives. Applying them in case studies is a contribution of this research programme to support this development as new research needs are identified. In addition, by showcasing how the tools can be used for different assessment contexts such as substitution, process development for green chemistry and product evaluation, the aim is also to provide guidance for use of the tools by other actors.

3.1. USEtox

USEtox was developed under the auspices of the joint United Nations Environment Program (UNEP) and the Society for Environmental Toxicology and Chemistry (SETAC) Life Cycle Initiative. The initial release provided characterization factors (CF) for human toxicological and freshwater ecotoxicological impacts of chemical emissions in LCA (Rosenbaum et al., 2008, Hauschild et al., 2008, Fantke, 2018). Consideration on indoor air compartments was implemented in USEtox starting with version 2.

This model provides midpoint and endpoint chemical toxicity CFs for usage in LCA. The model derives aggregated effects across different exposure routes, see also the scope illustrated in Figure 5.

The current published version of USEtox is 2.13. This version is implemented as ready-made LCIA method in LCA software. Note that datasets that are directly extracted from databases such as Ecoinvent usually do not include inventory data for indoor air emissions, even if CFs are available for USEtox 2.13. To include toxicity impacts in LCA software, both inventory data and characterisation factors need be added.

The upcoming version USEtox 3.0 is in beta status and based on an integrated near-field (indoor and product-related pathway, user exposure) and far-field (outdoor pathways, general population) model that considers impacts from chemical emissions and products applications. It is aligned with the CFA approach as additional relevant exposure pathways are considered. Separate evaluation of chemical emissions to the environment (far field, based on elementary flows) is possible.

Note – toxicity assessment in the EF and subsequently the SSbD framework is based on USEtox (2.1) and expanded to include information collected via European authorities (ECHA, EFSA) and other sources (PPDB) to increase the number of available CFs for modelling (Saouter et al., 2020, Sala et al., 2022). Deviations between CFs in USEtox® and EF have been observed. When choosing a ready made set of characterisation factors, users are advised to double check the origin, the method explored in Mistra SafeChem refers to USEtox®.

For further details about the background and development, see the USEtox documentation and manual (Fantke, 2018).

CFs derived with USEtox reflect the contribution of chemical substances to a potential environmental impact. Impacts scores are calculated as shown in Figure 5, similar to other impact categories.

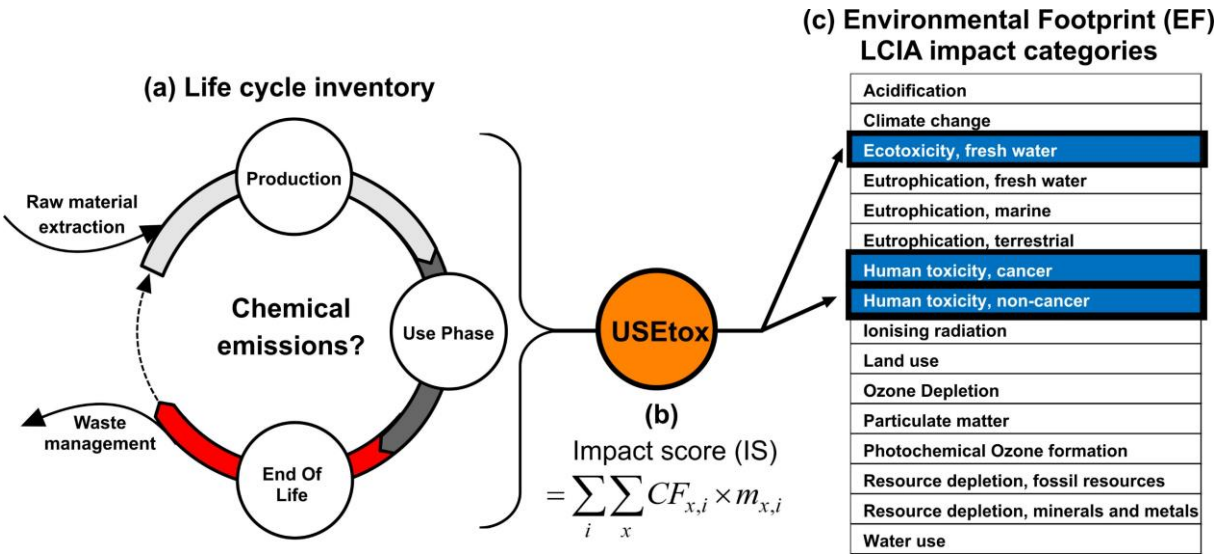


Figure 5 A simplified workflow of the application of USEtox in Life cycle impact assessment.

3.1.1. Human toxicity characterization factors

CFs are derived from the product of three matrices containing fate factors (**FF**), human exposure factors (**XF**), and human toxicological effect factors (**EF**):

$$CF = FF * XF * EF$$

The product of **FF** and **XF** results in a matrix containing human intake fractions (**iF**). The intake fraction represents the fraction of the mass emitted into a specific compartment that is taken in by the human population:

$$iF = FF * XF$$

Intake through inhalation and ingestion routes are considered in iF calculations. FFs link the quantity released into the environment to the chemical masses (or concentrations) in a given compartment and are the same for ecotoxicity and human toxicity.

Multimedia fate models are used for predicting environmental FF and XF. The study area is represented by a number of homogeneously mixed compartments, each representing a specific part of the environment (i.e. air, water, soil).

Effect factors reflect the change in lifetime disease probability due to change in life time intake of a pollutant (cases/kg). To arrive at endpoint level, midpoint characterization factors for human toxicity are multiplied with a severity factor (DALY/case).

Units CF Human toxicity	
Midpoint	cases/kg Comparative Toxic Units (CTU)
Endpoint	DALY/kg (Disability-adjusted life years) Comparative Damage Unit (CDU)

Figure 6 calculation principle for midpoint and endpoint human toxicity assessment in USEtox

3.1.2. Ecotoxicity characterization factors

Ecotoxicological CFs for freshwater ecosystems are derived from the product of three matrices similar to human toxicological factors:

$$CF = FF * XF * EF$$

Multimedia fate models are commonly used for predicting environmental FF and ecosystem XF. The fate factor is calculated similar as for human toxicity, but for freshwater ecotoxicity the transfer of a chemical to freshwater is of interest. The FF can be interpreted as the product of the fraction of an emission that reaches freshwater (dimensionless) times its persistence in freshwater.

The XF represents the bioavailability of a substance, i.e. the fraction of the chemical dissolved in freshwater. Apart from FF and XF, freshwater aquatic ecotoxicity EF are required in the calculation of ecotoxicological CFs. The ecotoxicological EF reflects the change in the potentially affected fraction (PAF) of species at midpoint level and the change in the potentially disappeared fraction (PDF) of species at endpoint level due to change in substance concentration in freshwater, integrated over the freshwater volume (m3) per substance mass emitted to freshwater (kg), see Figure 7.

Similar to human health, CFs for freshwater aquatic ecotoxicity are reported for different initial release compartments: emissions to household indoor air, occupational indoor air, urban air, continental rural air, continental freshwater, and/or continental agricultural soil.

Both midpoint and endpoint CFs can be calculated, the midpoint CFs for freshwater aquatic ecosystem toxicity are multiplied with a severity factor (PDF/PAF) to calculate endpoint CFs.

Units CF aquatic ecotoxicity	
Midpoint	PAF.m^3/kg potentially affected fraction of species exposed in a freshwater volume per unit mass emitted. Comparative Toxic Units (CTU)
Endpoint	PDF m^3.d/kg Potentially disappeared fraction (PDF) of ecosystem species exposed over a given time and freshwater volume per unit mass emitted. Comparative Damage Unit (CDU)

Figure 7 units for midpoint and endpoint ecotoxicity assessment in USEtox

3.1.3. USEtox 3.0 near-/far-field model

USEtox 3.0 (currently available as beta version at usetox.org) includes the emissions and exposure of products during the use phase of consumer products.

The new USEtox version includes a near-field model that considers the chemical mass in product application. The extended framework addresses human exposure pathways during and after product use. This acknowledges that the concentration of chemicals emitted from consumer products to near-field environments (e.g. a room) can be much higher than exposure to environmental concentrations (Wambaugh et al., 2013). For non-users or non frequent users the far-field exposure

is still relevant. Ecotoxicity calculations in USEtox 3.0 are based on other EF compared to versions 2.x; instead of extrapolated chronic EC50 HC20 values are used. This is aligned with global recommendations (Owsianiak et al., 2023).

3.1.4. Applying USEtox 3.0 in the context of CAA

The application of USEtox 3.0 in a life cycle based alternative assessment is suggested by (Fantke et al., 2020) and briefly described in section 2.2.1 above. The framework includes chemical emissions during the use-phase and calculation of detailed exposure pathways for humans with the near field model (e.g. inhalations, ingestion, or dermal uptake of chemicals). The hazard quotient (HQ) can be taken as a measure of the exposure risk for specific use-stage scenarios (Equation 2). The Hazard quotient measures whether the exposure is higher or lower compared to a reference concentration or dose. The reference dose (RfD) or concentration (RfC) is an estimate (with uncertainty spanning roughly an order of magnitude) of a continuous exposure to the human population (e.g. via inhalation) that is likely to be without an appreciable risk of deleterious effects during a lifetime (equation 1).

$$Rfd\ or\ RfC = \frac{NOAEL}{UF}$$

Equation 1:

NOAEL: no observable adverse effect level [mg/kg bodyweight-day]
UF: Uncertainty factor
1 to 10 for animal to human extrapolation.
1 to 10 inter individual variation within human.
(an additional factor of 10 can be selected for specific effects)
1 to 10 depending on data quality.

Equation 2: $Hazard\ quotient = \frac{Exposure\ level\ (measured\ or\ predicted)}{RfD\ orRfC}$

An HQ of < 1 indicates that exposures are unlikely to result in any adverse health effect. HQs of > 1 suggests that there may be concern for potential non-cancer effects.

For cancer effects the incremental lifetime cancer risk (ILCR) predicted in USEtox 3.0 can be taken as a measure to estimate the risk for cancer due to chemicals exposure. The ILCR sums up risks probability for cancer via ingestion, dermal contact, and inhalation over the lifetime of a human population and is calculated by multiplying the daily exposure dose by a route specific cancer slope factor (CSF). This risk probability can then be compared to the defined acceptable lifetime cancer risk of 10^{-5} for the general population and 10^{-4} for workers, depending on the jurisdiction.

In the mandatory Tier 1 of the LCAA HQ and ILCR are calculated and compared for the use stage of a reference chemical and potential substitutes and displayed together with the ecotoxicity impact score.

3.1.5. **Human toxicity characterization factors (USEtox 3.0)**

USEtox 3.0 considers two types of chemical inventory masses. The first one which is considered in LCA is the mass [in kg] of a chemical transferred to the environment (e.g. air, water, soil) per functional unit as elementary flow. The second mass is the chemical mass in a product application (in

kg per functional unit). These inventories are used to calculate the chemical masses transferred to the near-field (product transfer fraction) and far-field (emission transfer fraction) environment. To account for the fate and exposure processes the intake fraction and the product intake fraction for the chemicals (kg intake per kg emitted) are calculated, which both enter the cumulative mass for the human product and population exposure. Via dose-response factors (incidence risk per kg intake) the chemical exposure can be used to calculate the disease incidence per functional unit for humans. With the help of an effect severity factor (DALY per incidence) the toxicity-related damage (DALY per functional unit) can be calculated as well as the human toxicity characterization factor (DALY/kg inventory mass, endpoint CF).

USEtox 3 is thus designed to consider direct exposure in addition to the background exposure for the general population. Note that this requires modelling of additional inventory flows and is usually not done for other life cycle impact categories.

Health and safety for workers and consumers are included among the subcategories in the Guidelines for social Life Cycle assessment of products and organisations (Benoît Norris et al., 2020). For health assessment, this document refers to using DALY without detailing implementation.

3.2. ProScale

ProScale has been developed as an industry initiative and as a simpler-to-use approach for use in toxicity and ecotoxicity assessment, when compared to other more complex approaches, and can now be considered an industrial consensus model. The rationale for a simplified approach to toxicity and eco-toxicity assessment of

ProScale is a life cycle oriented method designed to assess toxicological potentials of product systems (Lexén et al., 2017). The method was first published in 2017 and is available as a guidance document and associated Excel calculation sheet, and a webtool with a database of processes under development. At the time of this report (spring 2024), the tool is operational for direct exposure assessment with comprehensive guidance for the assessment in relation to worker, professional and do-it-yourself application related exposure, and more general guidance for service life and end-of-life related exposures.

Rooted in life cycle thinking, the ProScale method allows for the calculation of scores at different levels of aggregation, such as for an entire life cycle, part of a life cycle or for a specific unit process. Within each unit process, considerations include substances used alone as ingredients, the substances supply chains, production of the substance and its inclusion in a product. For details see the guidance document (Lexén et al., 2017)**.**

The ProScale method utilizes publicly available hazard and exposure data reported to the European chemicals agency (ECHA) based on REACH legislation, making use of established and agreed procedures. Resources for data generation are required for inventory data such a mass flows and can be shared with LCA. If ProScale is applied in parallel with a full-scale LCA and uses the same bill of materials for modelling upstream supply chains results are first available during the sustainability assessment stage. This was done in the Mistra SafeChem research programme.

The calculaton of a ProScale score is based on four parameters:

- **Hazard factor**, based on hazard statements and acceptable concentration levels as Occupational Exposure Limit (OEL) or Derived No-Effect Level (DNEL). OEL is the maximum allowable concentration of a hazardous substance in a workplace. It is defined as the upper

limit of concentration in the air. In ProScale, OELs reflect the potency of a substance, which allows establishing distinctions between substances with low threshold level and with high thresholds, the lower the threshold, the higher the potency. So, a low threshold value of a substance will generate a higher ProScale Hazard factor and vice versa. When OEL is missing, the substance will be assigned a worst case assumption and be assigned the highest HF of the class it belongs to. Hazard factors are substance specific.

- **Exposure concentration factor** (ECF) provides an estimate of the exposure levels related to a process and the substances occurring in a process. defines the potential concentration to which an individual may be exposed during a specific process or activity. It functions as a conservative factor and enabling the differentiation between various exposure scenarios and does not mirror the actual exposure and cannot serve as a foundation for a risk assessment. Direct Eexposure spans the entire life cycle of a product, affecting diverse groups of people. For instance, workers may encoun-ter exposure throughout the production, use and end-of-life while consumers may face exposure during the use phase and service life. The ECF is based on the exposure modelling. The ECETOC Targeted Risk Assessment (TRA) Tier 1 approach (ECETOC 2012) is used to estimate potential ex-posure concentrations for all life cycle stages except service life, as service life is not included in the Tier 1 approach. To obtain the Exposure Concentration Factor, the modelled potential exposure con-centration is transformed into a dimensionless factor via a route-specific transformation function. A high value means high exposure potential while a low value means low exposure potential.

- **Person-hours factor** describe the person-hours of exposure per mass unit of produced product, service or process. Process specific.

- **Mass flow** describes the amount of substance needed to produce a product (per functional unit). Product system specific.

The four parameters are calculated for each chemical and each unit process and are then combined to calculate the ProScale score (PSS). ProScale scores are derived separately for inhalative and dermal exposure routes. The method allows for inclusion of oral exposure, but this is not included in the standard setting.

$$PSS = \sum_{\substack{substances \\ unit\ processes}} HF * ECF * PHF * MF$$

Hazard factor (HF)

The HF is based on the substance hazard statement (H-phrase) and the OEL or DNEL when OELs are not available.

The hazard statement comes from a classification according to the Globally Harmonised System (GHS). GHS is an internationally agreed-upon system, created by the United Nations, defining and classifying hazards and communicating information on labels and safety data sheets. The GHS is implemented in the EU with the regulation on classification, labelling and packaging (CLP). Criteria for the hazard classification, resulting in hazard statements given as H-phrases, under CLP is available in the report Guidance on the application of the CLP criteria (ECHA, 2024). Currently only EU specific H-phrases are included in ProScale.

In ProScale the H-phrases are divided into five ProScale hazard classes. The hazard class is complemented to account for potency by use of the OEL or DNEL. The transformation into a numeric factor involves a combination of the H-phrase class and the OEL, resulting in a dimensionless number. For each exposure route (dermal or inhalation), the HF of a substance is determined independently, resulting in distinct hazard factors for each route.

Grouping of H-phrases

In ProScale, H-phrases are assigned to 5 hazard classes, where class A corresponds to the lowest hazard and class E corresponds to the highest hazard. Each class spans a bandwidth of one order of magnitude, starting from 10^0... 10^1 to 10^5 … 10^6. This is done to group substances that need the same level of control to protect against health risks arising from hazardous substances used in the workplace. A substance may have several H-phrases. In that case, the H-phrase that corresponds to the highest hazard class determines the hazard class for that substance in that exposure route.

Exposure concentration factor

ProScale's Exposure Concentration Factor (ECF) provides an estimate of the exposure levels related to a process and the substances occurring in a process. It functions as a conservative factor enabling the differentiation between exposure scenarios and does not mirror the actual exposure and cannot serve as a foundation for a risk assessment. Direct exposure spans the entire life cycle of a product, affecting diverse groups of people. For instance, workers may encounter exposure throughout the production, use and end-of-life while consumers may face exposure during the use phase and service life. The ECF is based on exposure modelling. The ECETOC Targeted Risk Assessment (TRA) Tier 1 approach (ECETOC, 2012) is used to estimate potential exposure concentrations for all life cycle stages except service life, as service life is not included in the Tier 1 approach. To obtain the ECF, the modelled potential exposure concentration is transformed into a dimensionless factor via a route-specific transformation function. A high value means high exposure potential while a low value means low exposure potential.

Person-hour factor

The person-hour factor converts a concentration into a dose by accounting for the duration of exposure and the throughput of a unit process, establishing a link between the ProScale score and the functional unit.

3.2.1. Webtool and associated databases

The ProScale webtool and associated databases is available to ProScale consortium members (see www.proscale.org). Membership is available upon a fee, based on a business proposal from the host organisation IVL Swedish Environmental Research Institute. Part of the databases are built on LCA-databases by Sphera and ecoinvent and are hence only available to users with appropriate licenses. The guidance to the tool is open access and available to the public for manual modelling of a system for ProScale assessment.

3.2.2. ProScale-E

Ecosystem impacts and exposure of humans via the environment is not yet implemented but under development. The concept of ProScaleE, i.e. ProScale ecotoxicity assessment, is presented by (Rydberg et al., 2024). The Mistra SafeChem programme has contributed to method development for ProScaleE by testing ProScale for a product (indoor wall paint) that was investigated in a PEF pilot case study (Neuwirth et al., 2022), investigating requirements on a ProScaleE method, developing instruction material to facilitate implementation of ProScale assessment in product and service evaluations.

ProScale-E is developed in analogy with ProScale on human health (ProScale-H). Hazard factors are based on H-phrases from the 400-series on environmental hazards, and potency adjustment with a so called “M factor” based on EC50 values. Fate is considered via classification of persistence (P), and biodegradation. Environmental emissions are accounted based on environmental release categories (ERC), in case emissions are not available otherwise.

- ProScaleE covers ecotoxicity impacts and could therefore in principle be applied for ecotoxicity impacts in PEF, as an alternative. In any case, ProScale appears currently to be useful for life-cycle based toxicity screening in the SSbD context. ProScaleE characterization factors are derived from hazard banding based on H4XX hazard phrases, M-factors, and degradability. The hazard banding is similar to the hazard levels outlined in the SSbD framework. ProScale contains also a parallel approach for human health risks, ProScaleH.

4. Understanding user perspectives in toolbox applications

Within the Mistra SafeChem research programme an important contribution is to support collaboration between academia and industry partners, to increase the understanding and ultimately usage of Mistra SafeChem tools and methods in process and product development. The LCBA toolbox offers options to address different user needs. Ultimately a consistent application for CAA, CFA and LCA is the goal, and this will need further development of tools and methods. This also needs to be supported by clarifying user needs, and identifying barriers to application of tools and methods based on the current state of development.

This was approached by performing several case studies in collaboration according to a case study catalog, analysis of reports to collect results and guided discussions with case study participants to gather their experiences. Different generic user types have been identified, depending on their position in a productife cycle from cradle to grave. For all user types it is assumed that they focus on innovations, however the maturity of the innovation can range from basic research to pre-commercial development. Due to the limited sample size, conclusions are tentative.

4.1. The life cycle of chemicals in products and processes

The life cycle begins with the extraction of raw materials such as crude oil, minerals or harvesting of biobased raw materials. These raw materials are processed to create a chemical substance. This sequence of stages usually involves various chemical reactions and purification processes. In the next stage the chemical substance can be used as it is or formulated (blended) with other chemicals to create the desired product. Chemicals or chemical-containing products are then distributed to various markets. Applications range from being a component in a larger product, usage in industrial processes or direct consumption by end-users. After its use, the chemical reaches its end-of-life stage. This could involve various disposal methods, including incineration, landfill, or recycling (transition to another use phase).

4.1.1. Information along the chemicals supply chain

Complex end-consumer products contain many different chemicals, for the example of a car the number is estimated as 10.000 (Samuel, 2018). Each stage of the life cycle adds complexity regarding the chemical content of products and parts, while reducing transparency of chemical information available for downstream actors. The need for information varies depending on the sector, the application and type of actor involved.

Chemical supply chains usually involve a large number of suppliers, intermediate users and stakeholders within the chemical industry. In these supply chains often a multitude of material streams are interlinked to create consumer products. Supply chains are dynamic entities, and can change over time evolving with new product models and spanning across international borders with varying chemical regulations (Negev et al., 2018). This adaptability poses challenges for efficient communication within supply chains.

Trade secrets and undisclosed proprietary information restrict the transfer of chemical information at each transaction point, or “Handover” in Figure 8. Publicly disclosed information, such as patents intended to protect intellectual property, typically lack detailed composition data, making it challenging to correlate chemical trade names with identifiable CAS numbers. Material Safety Data Sheets (MSDS) which are used as transfer documents, provide limited information, generally covering substances with known hazard potential without revealing the full composition. The Ecodesign for Sustainable Products Regulation (ESPR), approved in May 2024, will implement the concept of Digital product Passports (DPPs) for a wide range of product categories. Here, chemical

content and material composition will be integrated data points which will over time have a positive effect on the transfer of chemical information.

4.1.2. Challenges for a complex (end-)product manufacturer

One of the challenges faced by manufacturers of complex products is maintaining an accurate and comprehensive understanding of the chemical content in their products. Some industries have established tracking systems for main materials in their product (e.g. International Material Data System for the automotive industry) or are obligated by law to disclose a substance ingredient list (e.g. the cosmetics industry). This information is provided for specific purposes and therefore limited; for the case of IMDS access and usage is restricted to selected purposes. Many other industry sectors do not have a good overview of the chemical content of their products (Scruggs, 2013). This lack of detailed chemical information poses significant challenges in ensuring safety and sustainability, a problem that intensifies along the supply chain and retailers often have only a limited knowledge regarding the chemical compositions of the products that they sell to their customers (Becker et al., 2010).

For a user of the LCBA toolbox this creates a challenges as the chemical information for complex products and how they were produced is often very limited. Information about the (intended) use-phase and the end of life is on the other hand in general more accessible for manufacturers and retailers of complex products. Even if a complete declaration of chemical content is available, upstream supply chains are not well documented, in many cases because this is considered as confidential.

4.1.3. From a chemical manufacturer perspective

In contrast, companies involved in the production of chemical raw materials and the development of new chemicals typically have access to more comprehensive information about the chemical and their production routes. However, they often lack detailed knowledge about how these chemicals are used in complex end-product applications.

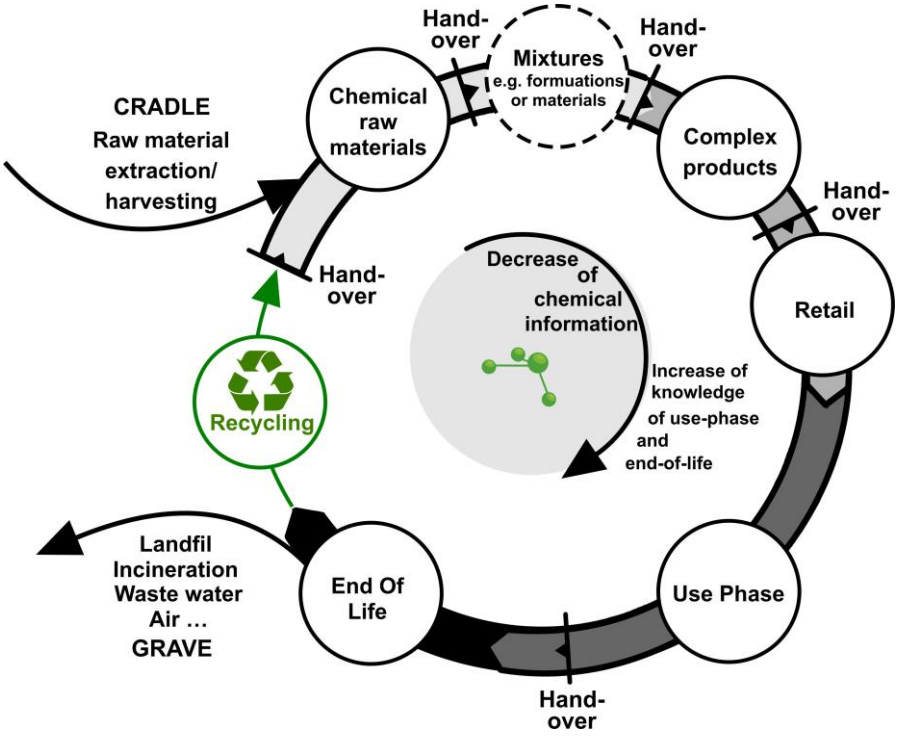


Figure 8 A simplified representation of the chemical life cycle

In summary, this highlights the network of stages and actors involved in the chemical life cycle, underscoring the challenges in information flow and transparency. It stresses the need for enhanced communication and data-sharing practices to enable effective chemical management and utilization of assessment tools like the LCBA toolbox.

4.2. Technology Readiness Level (TRL) as orientation guide

Tools in the LCBA toolbox are intended for different stages of product and process development from initial ideas till pre-commercialisation. To better understand different constraints and requirements, TRLs are used as orientation guide.

4.2.1. TRL spectrum and Toolbox Application

TRLs are suggested for estimating the maturity of technologies (EC, 2014) in research and innovation projects. They are scaled from 1 to 9 where 9 is the most mature technology. In this guideline the TRL levels are used to distinguish cases according to their status in technological development and innovation. The assignment to a specific TRL is to some extent flexible.

Table 1 Technology Readiness Levels extract from Part 19 – Commission Decision (2014) 4995.

TRL	**Definition**
1	Basic principles observed
2	Technology concept formulated
3	Experimental proof of concept
4	Technology validated in lab
5	Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies
6	Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies
7	System prototype demonstration in operational environment
8	System complete and qualified
9	Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)

Within Mistra SafeChem, the LCBA toolbox has been employed across a spectrum of TRLs in different case studies. They include early-stage fundamental research (low TRLs, approximately 1-3), validation and process upscaling in the chemical industry (mid to high TRLs, approximately 4-6) to pre commercial development, substitution in cosmetic formulation and complex products (TRL 7-9).

Fundamental research at low TRLs (1-3)

The toolbox has been explored for early-stage development at lab scale. The degree of freedom (e.g. the choice of raw materials or process conditions) is high due to the exploratory nature of the work, and challenges arise for life cycle-based assessments due to limited data availability and the inherent uncertainties in early-stage research, including lack of optimisation and integration that are addressed during upscaling. Note that this stage was addressed in the research programme with academic partners, and is potentially challenging to address for industrial partners in a collaboration since it is difficult to protect IPR at this stage. This stage is crucial for laying the groundwork for future applied research and development. Read more about how life cycle assessment at low TRL has been handled in Mistra SafeChem case studies in the case study reports.

Validation and Upscaling in the Chemical Industry at medium TRL (4-6)

For projects that advance into the phase of process upscaling within the chemical industry, the toolbox has been applied in settings where parameters are more precisely defined compared to the earlier, low TRLs. In this stage, the degree of freedom decreases compared to fundamental research but there is an increase in data availability (e.g. about potential raw materials and process conditions after the scale-up in production) which reduces uncertainties for life cycle-based assessments and decision-making. This increased data availability together with reduced uncertainty, facilitates more precise evaluation and decision-making. (Appiah-Twum, 2022). Read more about how life cycle assessment at medium TRL has been handled in Mistra SafeChem case studies in the separate reports on the programme website.

Complex products and Consumer formulations at high TRL (7-9)

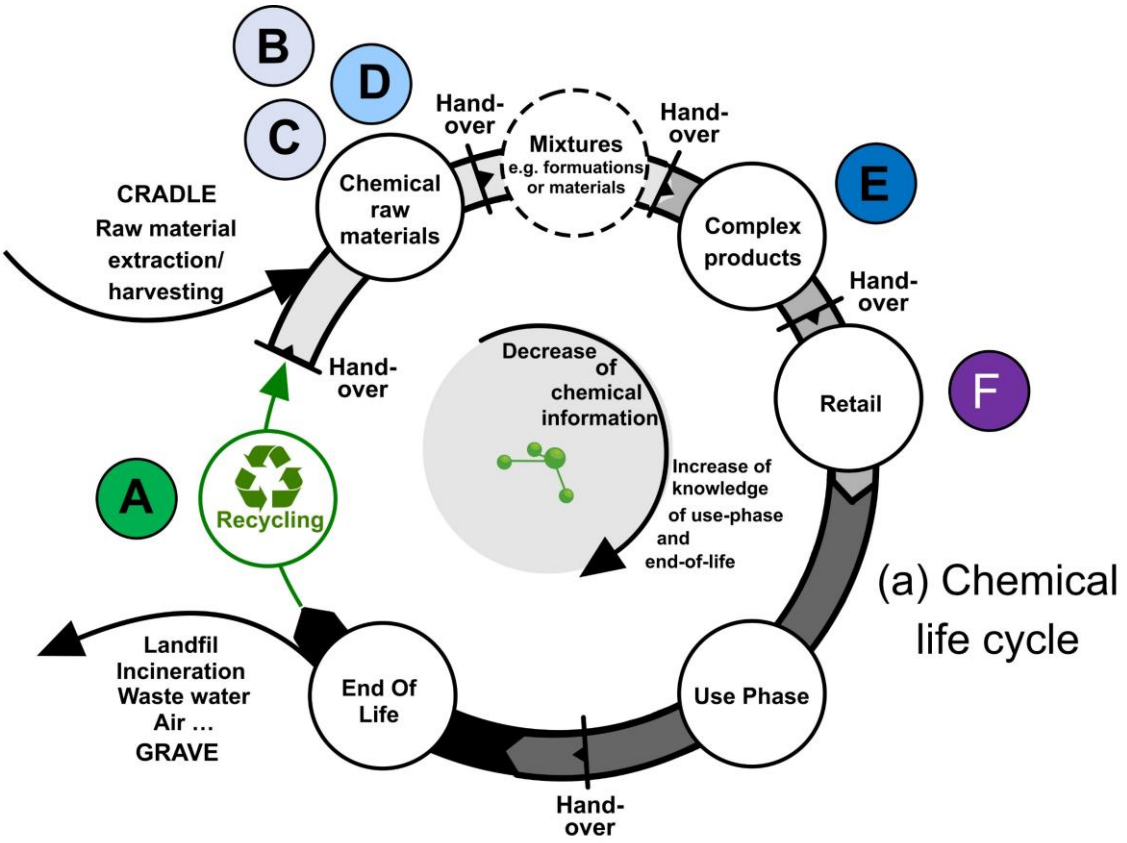
In the development of complex products or formulations, such as a car-part or cosmetics, the toolbox is applied in contexts where detailed chemical information often is challenging to manage. Manufacturers in these stages need to consider many different parts from several sources, and systematic data availability regarding the chemical content. Read more about how life cycle assessment at high TRL has been handled in Mistra SafeChem case studies in separate reports on the programme website.

For commercially available products high TRL and also high market readiness is assumed. This implies availability of data for industrially implemented processes. In the research programme the case of indoor paint has been considered to test the application of the tools, not to further develop a commercial product.

4.3. Mistra SafeChem case studies

The following section illustrates Mistra SafeChem case studies and provides an overview how the LCBA toolbox was applied to investigate sustainability aspects.

Figure 9 shows an overview of selected case studies from the Mistra SafeChem program, their positions along the product life cycle and their (approximated) Technology Readiness Level (TRL). The case study topics and the context in relation to the LCBA toolbox is also provided.



Case	Case study topics	Case context/TRL
A	Textile recycling: Optimizing sustainability	Recycling to new chemical/material (Academia)/ **Low TRL**
B	Sustainability assessment of a novel hydrogenation reaction process	Early-stage development (Academia)/ **Low TRL**
C	Safer and more sustainable by design in discovery chemistry	Early-stage development (Academia)/ **Low TRL**

Case	Case study topics	Case context/TRL
D	Production of a low-risk building block chemical for surfactants	Scale-up and market introduction of a new chemical (Industry)/ **Medium TRL**
E	Indoor air quality –materials inside the car that do not cause health effects	Manufacture of complex products (Industry)/ **High TRL**
F	Cyclosiloxanes and silicones in cosmetics	Retailer of complex products (Industry)/ **High TRL**

Figure 9 (a) A simplified representation of the chemical supply chain and (b) selected cases studies within of the Mistra SafeChem program for which different user categories are suggested as well as their position in the product life cycle. TRL ranges of case studies are also included to show the maturity level each chemical, process, or product development.

The following tables contain short summaries of cases studies in context of LCBA toolbox application. This overview is a simplification of complex processes in the chemical life cycle where sharp separation user categories might not be possible for all cases. However, to start integrating life cycle thinking into the design and optimization of chemicals and processes these suggestions can still provide a useful orientation for the toolbox user. These short summaries are based on the work experience with the LCBA toolbox within the cases studies. For case studies C and E information is available from separate reports.

Case	Case study topic	TRL	Toolbox user in MSC	Aim of assessment
A	Conversion of post-consumer cotton-based textiles into cellulose nanocrystals (CNC)	Low	Academia	Screening LCA of an early-stage development based on lab scale data.

Case study summary

Position in the chemical life cycle: Recycling to new chemical/material

Type of assessment: Screening and mapping cradle to gate analysis of an early stage development of secondary raw materials based on the framework of Piccinno et al (Piccinno et al., 2016).

Time capacity for LC-based assessments: LCA work has not been considered in previous projects. It should be an integral part of future research projects. If projects and capacities (funding) are planned in advance, LCA work can be conducted throughout the process development (e.g. 3-4 years) and contribute to better decision making.

Application of the LCBA toolbox:

- Cradle to gate LCA for CNC (application not defined, no knowledge about use phase and End of life);
- To assess the environmental impact of the of lab-scale processes, the life cycle impact assessment (LCIA) method used was EF3.0

Comment: Use of recycled feedstock with unknown chemical content, additional risk assessment required. Publication with details available (Ruiz-Caldas et al., 2023).

Case	Case study topic	TRL	Toolbox user in MSC	Aim of assessment
B	Sustainability assessment of a novel hydrogenation reaction process	Medium	Academia	Screening LCA of an early-stage development based on lab scale data.

Case study summary

Position in the chemical life cycle: Manufacturing of raw materials

Type of assessment: Screening life cycle assessment of an electrochemical hydrogenation reaction process using a novel catalyst instead of the conventional option (Pd/C). To be used as guidance in early process development for evaluating and improving the environmental performance of the novel reaction.

Time capacity for LC-based assessments: The technology developer or problem owner spent approx. 16 man months focussed on technology development. Additional approx. 2 man months for LCA related work (scale up, recyclability, LCI for two substrates). LCA operator had approximately 200 hrs for this task (approx. 1 man month), this included data collection, meetings, modelling and reporting and quality checks. The time available was determined with a top-down approach, i.e. it was not based on how much time is needed for the assessment but rather on how much resources the project could allocate to the case study.

Application of the LCBA toolbox:

- To assess the environmental impact, the life cycle impact assessment (LCIA) method used was EF3.0 for all impact categories except for human- and ecotoxicity. For those indicators, USEtox 2.12 was used.

Comment: working paper accessible as preprint published in November 2023 (Tortajada Palmero et al., 2023), 10.26434/chemrxiv-2023-p4q71 .

Case	Case study topic	TRL	Toolbox user in MSC	Aim of assessment
C	Safer and more sustainable by design in discovery chemistry	Low	Academia	Evaluate a biocatalysis route for synthesizing molecules with amide functionality

Case study summary

Position in the chemical life cycle: Chemical raw material (low TRL), screening for low hazard and risk in substrates and products for biocatalysis of amides and comparison between the biocatalysis route with the conventional chemical catalysis route.

Type of assessment: The case study is executed in two steps. Step 1 is a screening assessment where the LCBA toolbox is used via USEtox 2.12 to include fate and exposure parameters in the screening of substrates and products. In step 2 one product (amide) from the filtering is selected and the biocatalytic route is compared to a conventional chem-catalytic route with LCA, including (eco)toxicity and other relevant impact categories.

Time capacity for LC-based assessments: -

Application of the LCBA toolbox:

In step 1 a screening assessment was based on hazard information as generated by the Mistra SafeChem *in silico* predictions toolbox and characterization factors as calculated with USEtox 2.12. Missing values (human toxicity) were conservatively imputed by using in-domain predictions.

In step 2 (on-going) a screening of amide synthesis reactions from a list of acids and amines was conducted, resulting in the selection of one amide to be studied by LCA. The synthesis of the selected amide via biocatalysis is explored at laboratory and pilot scale, and life cycle inventory (LCI) data are collected. At the same time, LCI data are collected for the synthesis of the selected amide via a traditional chemical synthesis route. Finally, LCA will be conducted, comparing the two synthesis routes. The results will be interpreted and discussed aiming to evaluate the potential of biocatalysis in the specific context of the case study.

Comment: Step 1 of this case study was reported by Söderberg et al. (2023) in the pre-print 10.26434/chemrxiv-2023-x8f25. Step 2, the LCA, will be reported in a programme internal deliverable and in part incorporated in the external case study report.

Case	Case study topic	TRL	Toolbox user category	Aim of assessment
D	Production of a low-risk building block chemical for surfactants	5	Industry	Optimization of production phase by assessing the environmental impacts. Consideration of use-phase emissions by prediction of degradation products and their potential ecotoxicity.

Case study summary

Position in the chemical life cycle: Raw material manufacture

Type of assessment: LCA for a new chemical raw material before market introduction including chemical footprints

Time capacity for LC-based assessments: not assessed

Application of the LCBA toolbox: For the process optimization of new building block chemicals for surfactants ProScale, USEtox 2.13 and a cradle to gate LCA (in combination with Aspen process simulation) were used.

Comment: see separate case study reports

Case	Case study topic	TRL	Toolbox user category	Aim of assessment
E	Indoor air quality – materials inside the car that do not cause health effects	High	Industry	Identification of hazardous of safe and sustainable alternatives as substitutes in an existing product

Case study summary

Position in the chemical life cycle: Manufacture of complex products

Type of assessment: Alternative assessment in the context of chemical substitution.

Time capacity for LC-based assessments: not assessed

Application of the LCBA toolbox:

Support in decision-making to find better chemical alternatives to plasticisers found in indoor air. USEtox 3.0 was used in the context of the LCAA framework adopted from (Fantke et al., 2020) to assess the risk and (eco)toxicity impacts. Data collection was complemented with the CAS Scifinder Reaction database.

Comment: Modelling approach and framework is appreciated, demand for input data seen as (too) high. Interface for the current beta status is a barrier for implementation, feedback for further development was provided.

User category: Retailer of complex products (high TRL)

Case	Case study topic	TRL	Toolbox user category	Aim of assessment
F	Substitution of cyclic siloxanes and silicones in cosmetics	9	Retailer of complex products (Industry)/	Chemical Alternatives Assessment: Identification of safe and sustainable alternatives as substitutes to siloxanes in cosmetic formulation

Case study summary

Position in the chemical life cycle: Retailer, own brand

Type of assessment: Alternative assessment in context of chemical substitution. Support in decision-making to find better chemical alternatives to regulated/hazardous chemicals in cosmetic formulations.

Time capacity for LC-based assessments: Ca. 1 year parallel to the functional testing of alternatives

Application of the LCBA toolbox:

In this case study the LCBA toolbox was used to conduct a CAA. The workflow was mirroring the new SSbD framework with the aim to identify safe and sustainable alternatives to cyclic siloxanes in cosmetic formulations.

After a first prioritization of alternatives (STEP 1 of the SSbD) with low toxicity by means of a hazards assessment (not part of the LCBA toolbox) a comparison of selected alternatives was conducted with the help of the USEtox model to estimate their risks of exposure during the use phase (STEP 3 in the SSbD). For this purpose, the USEtox near field model was used to estimate the risk for the consumer with the example of a face makeup that is applied every day and that can contain high amounts of cyclic siloxanes (e.g. D5) as solvents/emollient. The goal was to find alternatives with low exposure risk and the Hazard Quotient (HQ, further explained in was taken as a measure to compare cyclic siloxanes with alternatives in relevant use-phase scenarios.

Moreover, USEtox was used to calculate human and ecotoxicity characterization factors to estimate the chemical footprint for D5 and potential alternatives. For selected alternatives with available data a screening. LCA (STEP 4 of the SSbD) was conducted to consider different raw material sources for the production of alternatives (e.g. petroleum vs biobased) to also consider other life cycle impacts in a broader sustainability assessment. Work environment exposure for the baseline option and all alternatives was evaluated with ProScale.

Comment: This case study is described in a separate report in detail, see the programme website.

Additional case study -solvent borne paints

For the case studies described above, process and product innovations contributed by research partners were investigated. This means that processes, substances and applications were only partially defined, and data gaps in inventories and impact assessments affect interpretation of results and applicability.

An additional case study is introduced to illustrate how the toolbox can be used when data are available for established products. Starting point is a published case for the application of the USEtox 3.0 far-field and near-field model and selected results were thus chosen to illustrate the application of USEtox in context of the LCBA toolbox. The case study context was also used to complement with an application of ProScale for production processes and a screening LCA (cradle to gate).

To provide some context, the case study is illustrated in the Mistra SafeChem format.

Case	Case study topic	TRL	Toolbox user category	Aim of assessment
	Substitution of solvent in paint for interior applications	Market	Retailer of complex products (Industry)/	Chemical Alternatives Assessment: Identification of safe and sustainable alternatives as substitutes to xylene in paint formulations

Case study summary

Position in chemical life cycle: comparable to manufacturer/retailer - own brand (Figure 6)

Type of assessment: Alternative assessment in context of chemical substitution. Support in decision-making to find better chemical alternatives to regulated/hazardous chemicals in paint formulations.

Time capacity for LC-based assessments: -

In this case study the LCBA toolbox was used to explore USEtox and ProScale for a limited number of chemicals in indoor wall paints. A CAA was conducted based on the procedure for Tier 1 of the LCAA suggested by (Fantke et al., 2020)(see 2.2.1. Life Cycle-based Alternatives Assessment). Exposure risks and ecotoxicity impact scores for xylene and potential alternatives were estimated and compared in relevant use-stage scenarios. Moreover, human and ecotoxicity CFs were calculated and discussed. As a complement ProScale was used to identify direct toxicity hotspots from cradle to the application stage of the wall paint.

The results related to USEtox are an extract of a more comprehensive study by (Huang et al., 2024) to assess the chemical exposure of paint ingredients and were kindly by the authors.

5. Results – fact sheets

Separate case study reports are available and will be updated further on the programme website.

Additionally to the case studies conducted within the research programme, a published case of commercially available indoor wall paint options with different solvents was used to test the integrated use of tools. An important aim with this pilot test is that data are available. Note that this case is not intended to develop new paint.

Selected findings of a study by Huang et al. (Huang et al., 2024) on indoor wall paints were used to illustrate application of USEtox, the indoor wall paints topic was also chosen to apply the ProScale model to estimate direct toxicity hotspots during production and application stage of the wall paint phase (Neuwirth et al., 2022).

USEtox 3.0 was here used in the context of CAA focusing on replacing xylene in a solvent borne paint. A selection of other hazardous chemicals in paints were also included to show how the exposure risk during the use-phase can be assessed with the USEtox near-field model. Moreover, characterization factors suitable for LCA models were calculated.

Case Nr	Case study topic	TRL	Toolbox user	Aim of assessment
-	Substitution of xylene in solventborne paint	Market	n/a	Substitution of solvent xylene – test of tools

Case study summary

In this case study example, the LCBA toolbox was applied in a simplified CAA to evaluate the substitution of xylene in solvent-borne paints to illustrate the application of the different models (Figure x). USEtox 3.0 was used to estimate the risk during paint application for do-it-yourself and professional painters. Aggregated near field and far field characterization factors were calculated for the use phase-related impacts of solvents on humans and the environment (toxicity-related impact score per chemical). These results are based on a more comprehensive study of (Huang et al., 2024) and were kindly contributed by the authors.

Direct toxicity impacts for the supply chain of paint were calculated using ProScale. Additionally, a screening LCA (cradle to gate) was conducted to consider environmental impacts of the paint production based on the Environmental Footprint 3.1 category set. The toxicity impacts were calculated with USEtox 2.13 as implemented in existing LCA software. All result estimates were used to compare human exposure risks and sustainability parameters of paint solvents in different life cycle stages.

Background

This case study was selected as an example to explore how the LCBA toolbox can be used for a chemical substitution project. Paint solvents and other paint ingredients are well characterized regarding their toxicity, physicochemical properties and inventory data for LCA are available.

The solvent xylene has nearly been phased out in Europe due to hazardous properties, but is used elsewhere globally. Solvents like xylene in paint contribute to the evaporation of volatile organic compounds (VOCs).

Background and input data for this case study were kindly provided by Huang *et al.(Huang et al., 2024)*. The evaluated paint formulation is for interior application (solventborne alkyd paints) in Sri Lanka. Note that residential houses are frequently repainted due to hot and humid climate, which is considered in the model.

Two scenarios in residential houses are assessed. For professional painters ("Pro-Painter"), a daily application of of 4.77 kg of paint on a 42 m^2 wall area painted in 5.6 hours, equalling 2 hours needed for painting an area of 15 m^2. The painter works for 200 working days per year and 40 years per lifetime of 70 years. For household residents ("DIY painter"), annual use of 17.3 kg of paint over 241 m^2 wall area is assumed with a year between paint applications. This considers exposure over one year, with residents present during application and residing in the house thereafter.

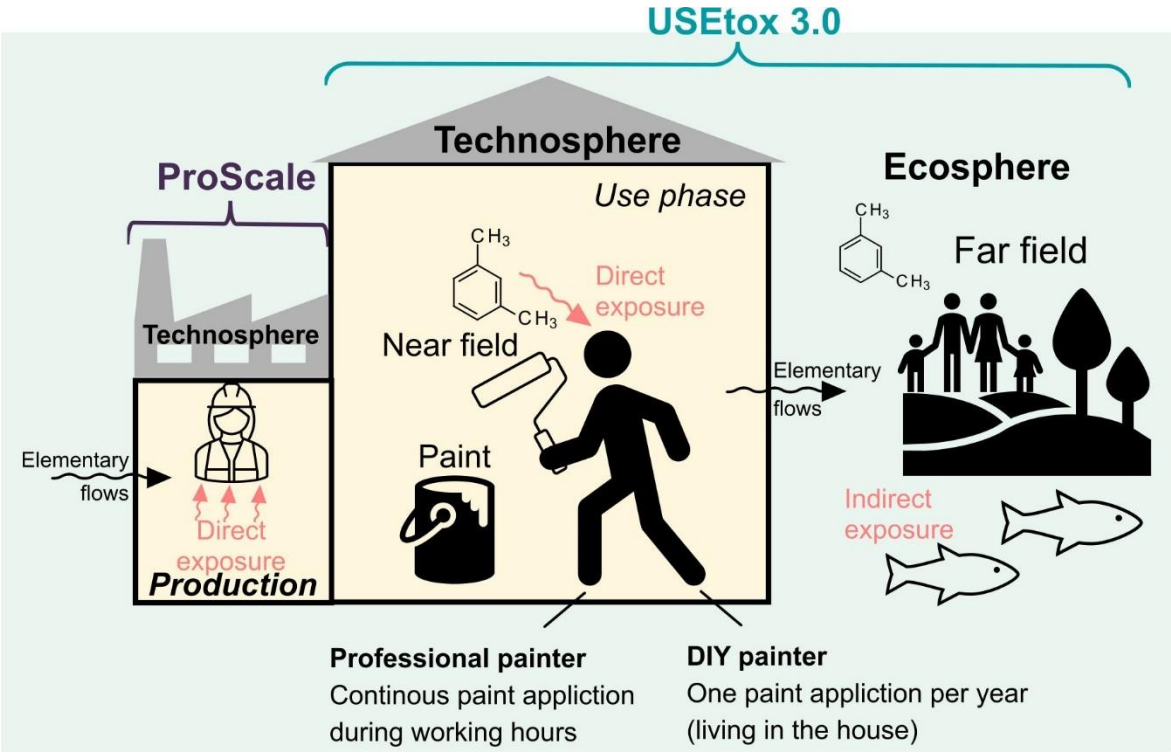


Figure 10 Paint application for professional and do-it-yourself painters and the application domains of the impact assessment models ProScale and USEtox 3.0

Research questions related to the LCBA toolbox application:

- What are the risks of chemical exposure to xylene and potential alternatives in solvent-borne paints during the use phase? (model applied: USEtox 3.0 near-field)?
- What are use phase related human- and ecotoxicity characterization factors and impact scores for the solvents during the use phase (toxicity-related impact score per chemical) (model applied: USEtox 3.0 near-/far-field model)
- What is the direct toxicity potential for upstream production processes of the paint (model applied: ProScale).

- What are other environmental impacts of paint ingredients during the production process (model applied: cradle-to-gate screening LCA results)
- How can USEtox 3.0, ProScale and LCA results support a decision-making in a chemical substitution cases

5.1. Application of the LCBA toolbox within the case study

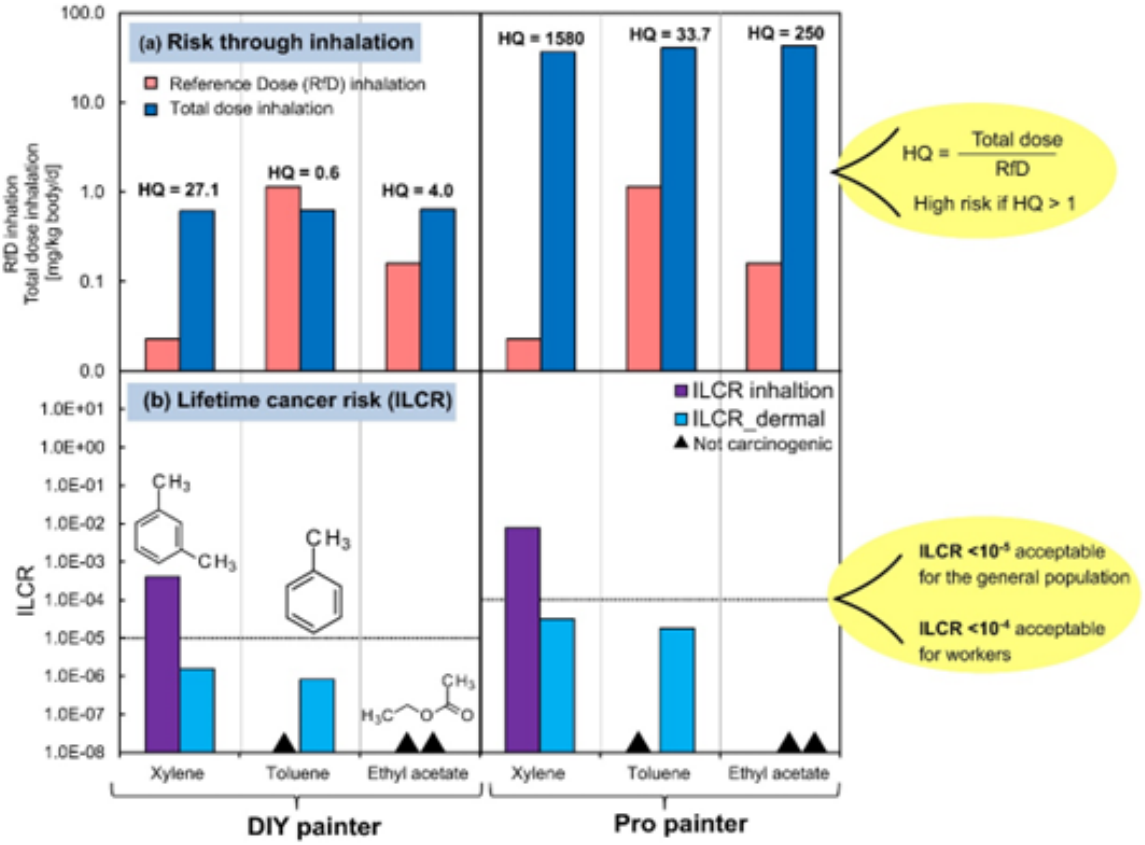
USEtox 3.0 was used to assess xylene and potential alternatives. A combined near-field and far-field model (Figure x (above)) is used to assess the exposure risk during paint application and to derive characterization factors for human and ecotoxicity. For human toxicity characterization factors, impacts on the user of the paint product and the population that is exposed via emissions to the environment are considered. Furthermore, ProScale was used to determine direct toxicity potentials (workers' exposure) of the upstream processes of the paint production process considering xylene, potential substitutes, and other paint ingredients in a simplified formulation. Finally, a cradle-to-gate screening LCA was performed for the paint formulations to also include other enviromentla impacts in the comparison.

5.1.1. USEtox 3 (near-field/ far-field) for the use phase

The use phase related cancer and non-cancer risks for DIY- and professional painters due to exposure to xylene and two alternative solvents (toluene and ethyl acetate) are summarized in Figure 3. The modelling results show that the inhalation of solvents is the main exposure pathway during paint applications and minor amounts are taken up via the skin. Figure 3a displays the reference dose (RfD) which is the “safe dose” for chemical exposure and the total dose of solvents that are estimated to be inhaled during paint application in this case example.

The results show that xylene has a high non-cancer exposure risk (HQ >1) for the DIY painter while toluene has a HQ value below 1. The HQ was lower for ethyl acetate in comparison to xylene for the DIY painter, but above 1. For the Pro painters who apply the paint on a daily basis the inhaled dose for the solvent was higher by a factor of ~60 to 67. This led to significantly higher HQ values, indicating that the work related solvent exposure is of very high risk. The dermal exposure to solvents was lower resulting in HQ values of <1 for DIY and pro painter, except for toluene with an HQ value above 1 for the pro painter, which suggests a considerable risk.

For cancer effects the incremental lifetime cancer risk (ILCR) due to dermal exposure and inhalation was estimated. For xylene the recommended ILCR of 10^{-5} for DIY painters and 10^{-4} for the pro painters are exceeded. Xylene and also toluene have also elevated ILCR values for dermal exposure, but those are below recommended limits. Ethyl acetate is not cancerogenic. The results of the exposure risks evaluation show differences between the chemicals, but none of the alternative solvents are substances of low risk. Especially for professional painters who work under continuous exposure the risks are very high.



(a2) HQ dermal DIY painter			HQ dermal PRO painter		
Xylene	Toluene	Ethyl acetate	Xylene	Toluene	Ethyl acetate
0.012	0.015	0.003	0.760	1.060	0.173

Figure 11 Paint use-related exposure risks to solvents for the DIY and professional painter. Non-cancer hazard quotients (HQ) are shown for (a1) inhalation and (a2) dermal exposure. ILCR are shown for cancer risks.

The paint use related freshwater ecotoxicity and human toxicity impact scores (IS) are summarized in Figure 12. These can be interpreted as impacts per chemical for 1kg of paint applied in the use stage and were in general higher for the professional painter than for the DIY painter.

Comparing the total human toxicity impact scores in Figure 12 the results reveal that xylene and toluene have comparable impacts while the IS of ethyl acetate is lower. When looking at the different contributions to the human toxicity factors, the noncancer general effects had the highest contributions for the paint solvents followed by noncancer reproductive/developmental effects. Cancer effects were higher for xylene than for toluene while ethyl acetate is not cancerogenic. Moreover, the results show that the ecotoxicity impacts were higher for toluene than for xylene and highest for ethyl acetate.

In summary, it can be concluded toluene and ethyl acetate should not be considered as recommended alternatives to xylene. Although these solvents showed some advantages regarding lower HQ values and reduced cancer effects, the risk is still high, especially during continuous application for professional painters. While the human toxicity ISs were lower, the ecotoxicity ISs associated with the emissions during use (Figure 10) were higher. Thus, further alternatives need to be assessed using the USEtox 3.0 near-field/ far-field model. Related work has been conducted in the study by (Huang et al., 2024) that also included a water-based paint formulation as a product alternative for indoor wall paints.

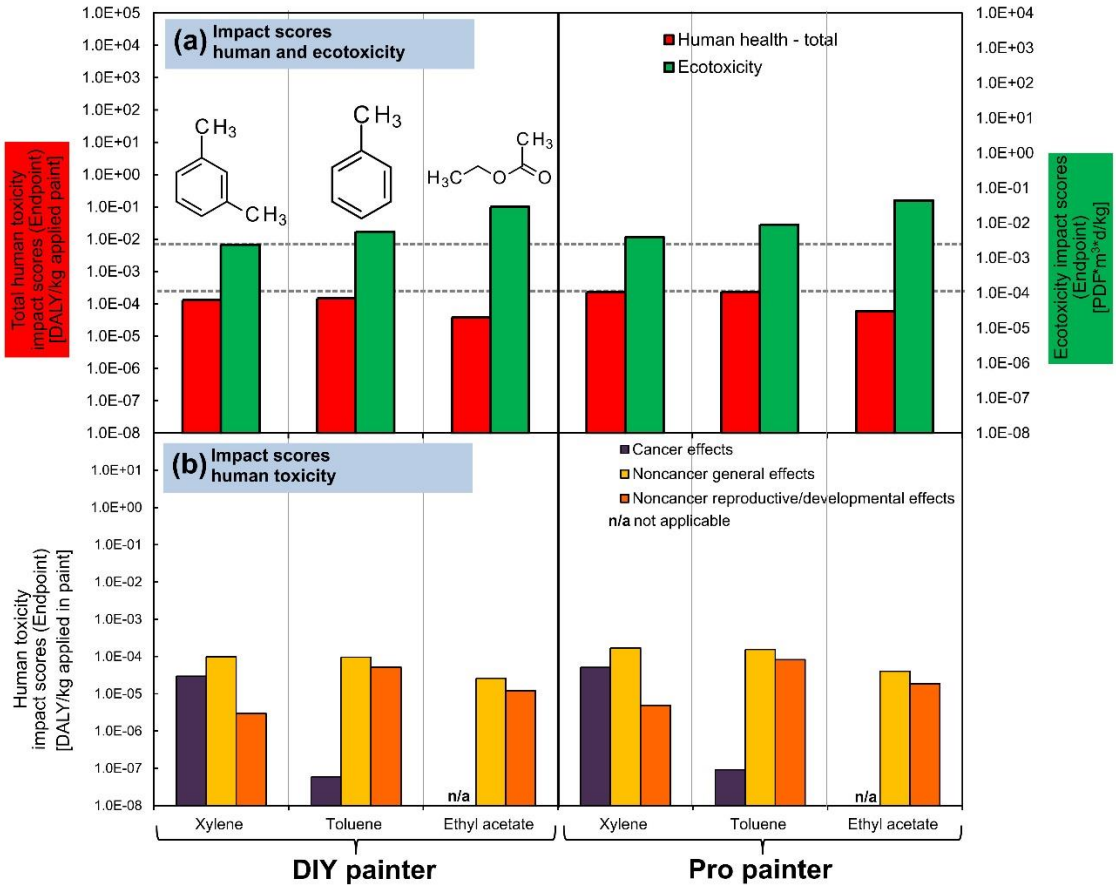


Figure 12 Use phases related impact scores for paint solvent; (a)shows total human toxicity and freshwater ecotoxicity ISs (b) shows the different contributions of cancer, noncancer general effects and noncancer reproductive/developmental effects

5.1.2. **ProScale** for assessing the direct toxicity potential of the upstream processes

ProScale was used to identify the most dominating process contributors to the direct toxicity potentials of the paint based on ethyl acetate. In ProScale non-cancer and cancer hazards are combined into one hazard score and emissions from energy sources and transport are not considered. A generic result for the production of paint based on xylene has been used as a reference. The two paint formulations are presented in Table 2 Paint formulations assessed with ProScaleTable 2 and the system boundaries are presented in

Figure 13. The functional unit is to protect and decorate 42 m^2 indoor wall area for 40 years in Sri Lanka.

Table 2 Paint formulations assessed with ProScale

Substances	**Paint based on xylene (case 1) (%)**	**Paint based on ethyl acetate (case 2) (%)**
Solvent	19.4	19.4
TiO_2	13.8	13.8
Alkyd resin	66.8	66.8

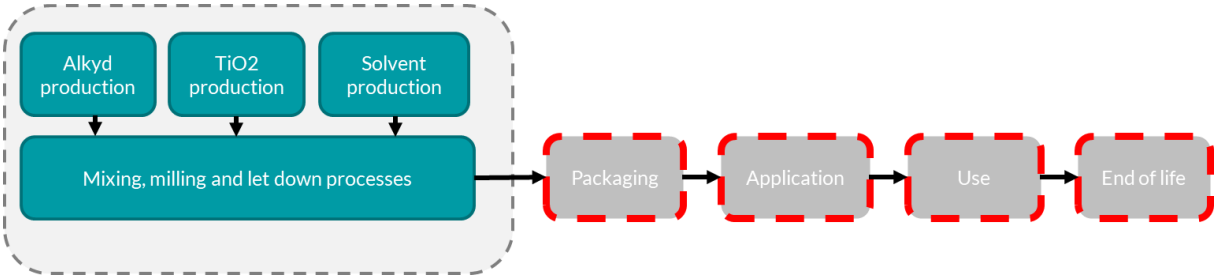


Figure 13. System boundaries of the studied system. The green boxes are processes that are included in the assessment while the grey boxes with red dotted lines are not in the assessment.

Data for the manufacturing of the ingredients were based on both generic and proxy data, collected from Ecoinvent 3.9.1 as implemented in SimaPro and the ProScale process database. Mass flows were extracted from existing datasets without modifications, except for the dataset for alkyd resin production. This dataset includes a small amount of xylene to reduce the viscosity of the alkyd resin. In the paint containing ethyl acetate, the alkyd resin data set was adjusted to contain ethyl acetate instead of xylene to adjust the entire paint formulation based on ethyl acetate as solvent.

The datasets used from Ecoinvent were:

Titanium dioxide: Titanium dioxide RoW| titanium dioxide production, chloride process | Cut-off, U was used without any modification.
Alkyd resin: Alkyd resin, long oil, without solvent, in 70% white spirit solution state RoW| alkyd resin production, long oil, product in 70% white spirit solution state | Cut-off, U was used r the paint containing xylene as solvent. Xylene was replaced with ethyl acetate in the paint formulation containing ethyl acetate as a solvent.
Xylene: Xylene RoW| xylene production | Cut-off, U was used without any modification.
Ethyl acetate: Ethyl acetate RoW| ethyl acetate production | Cut-off, U was used without any modification.
The titanium dioxide production is based on the chloride process with rutile as input. Alkyd resin is produced from soybean oil, by alcoholysis of soybean oil with pentaerythritol followed by esterification with phthalic anhydride and pentaerythritol. Xylene is produced from the catalytic reforming process to convert petroleum refinery naphtha into high-octane liquid products (reformates). It is assumed that 1 kg of naphtha/pygas results in 1 kg of a mixture of toluene, xylenes, and benzene. The xylene contents in the reformate stream largely depends on the composition of the feedstock, the type of reformer, the operating conditions, and the catalysts. Therefore, this data should be considered a rough approximation. Ethyl acetate is produced by esterification of ethanol with acetic acid.

The result of the ProScale assessment for the paint based on xylene is presented to the left (case 1) and the paint based on ethyl acetate is presented to the right (case 2) in Figure 14. For the paint formulation containing xylene (case 1), xylene has the highest contribution to the direct toxicity for inhalation. On the other hand alkyd resin has the highest contribution to the paint containing ethyl acetate (case 2).

Furthermore, two scenario analyses were performed based on varying parameter of dustiness for titanium dioxide in the milling process. The scenario analysis showed expected trends. The PSU score increased as the dustiness of the titanium dioxide data set varied from not dusty to very dusty. The PSU score also increased as the PROC number changed from a closed looped system to open system for the mixing processing step.

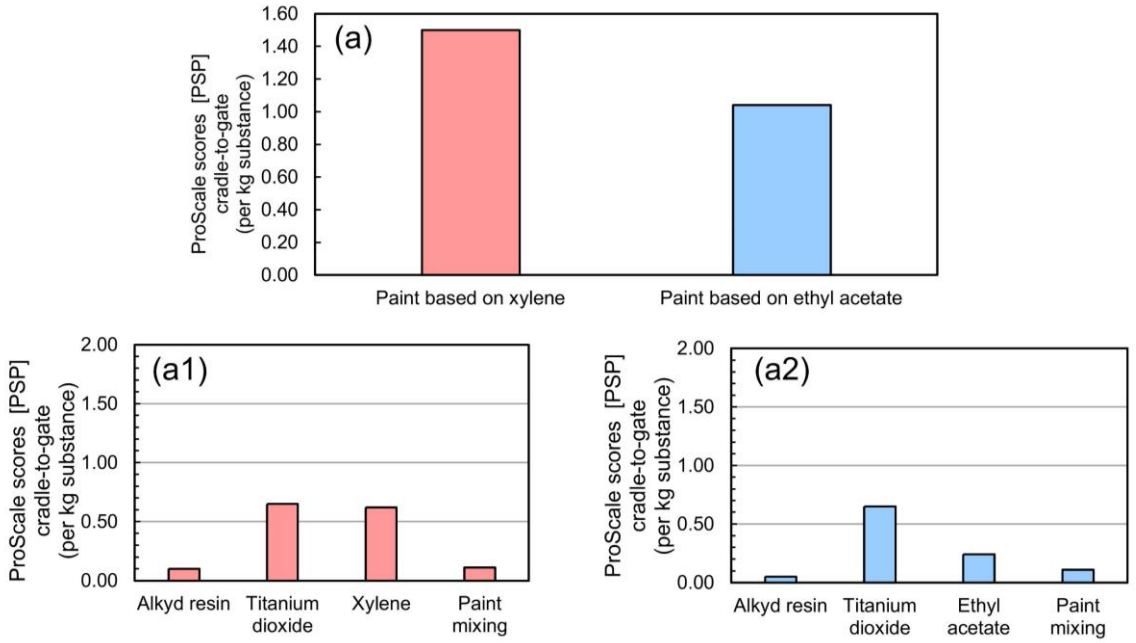


Figure 14 Visualization of the direct toxicity potential (PSP scores) for inhalation during cradle-to-gate production steps. (a) shows cumulative PSP scores during production of the paint formulations while (a1) shows then contributions of the selected paint ingredients for the formulations based on xylene and (a3) based on ehtylacetate as the main solvent.

5.1.3. Cradle-to-gate screening LCA

A cradle to gate screening LCA was performed to identify hotspots of the solventborne paint formulation based on ethyl acetate. The goal and scope, functional unit, system boundaries, and datasets used are the same as in the ProScale assessment. The results are not intended to be used in comparative assertions but a generic result for the production of paint based on xylene has been used as a reference.

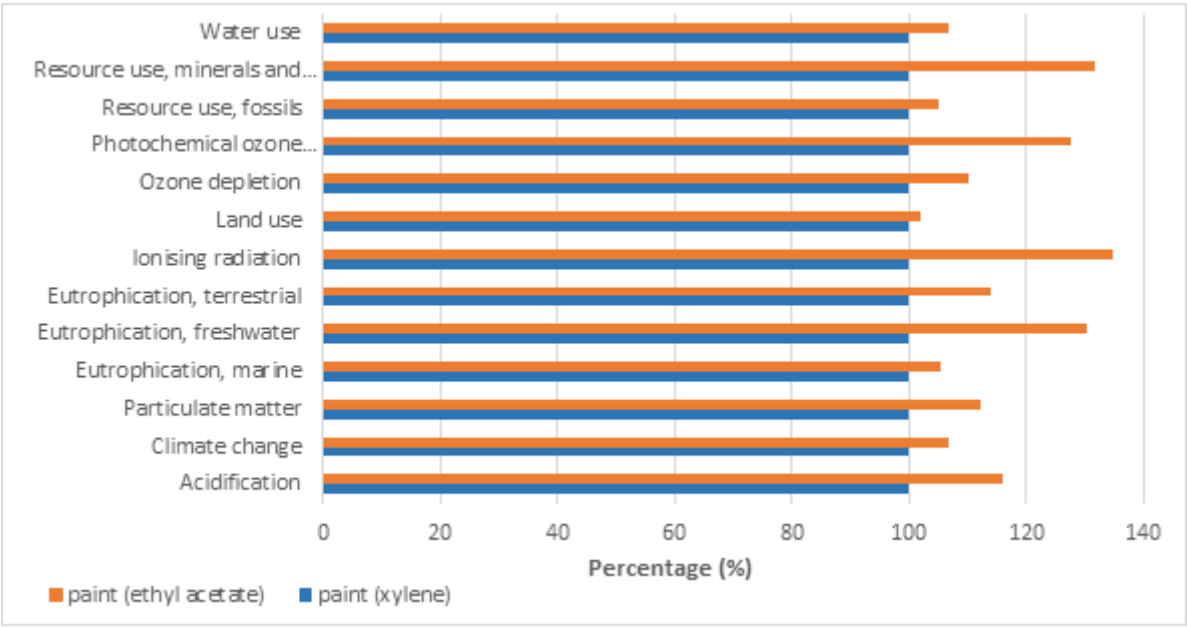
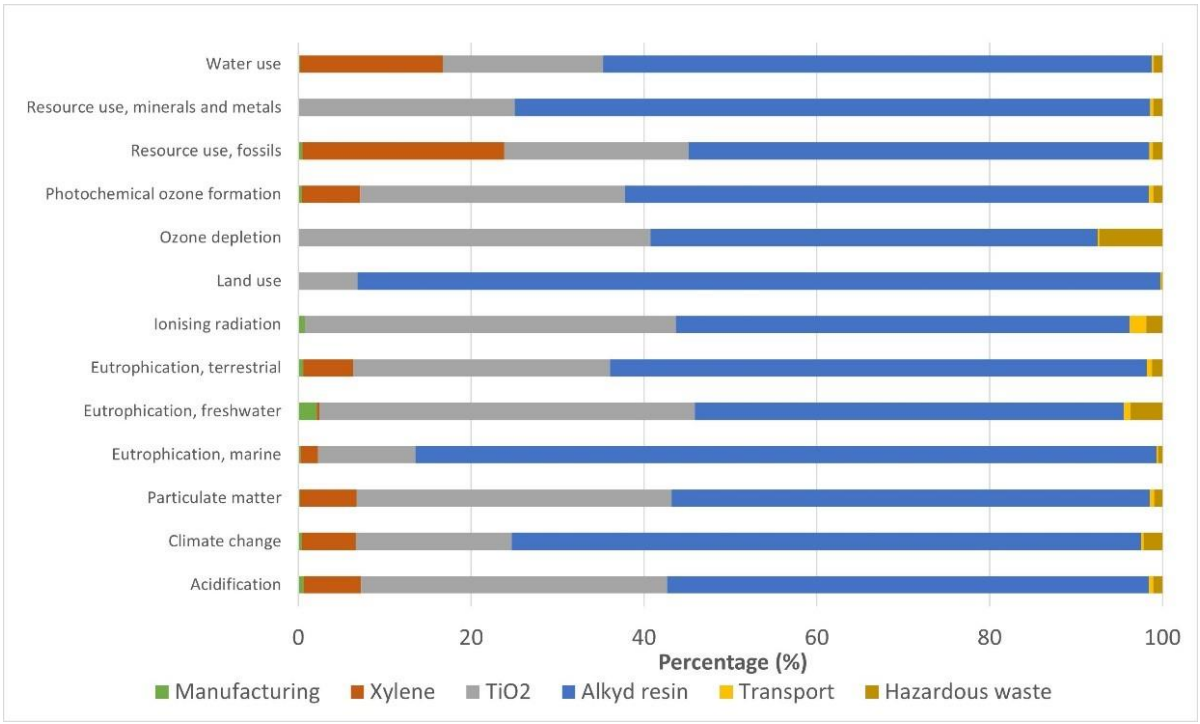
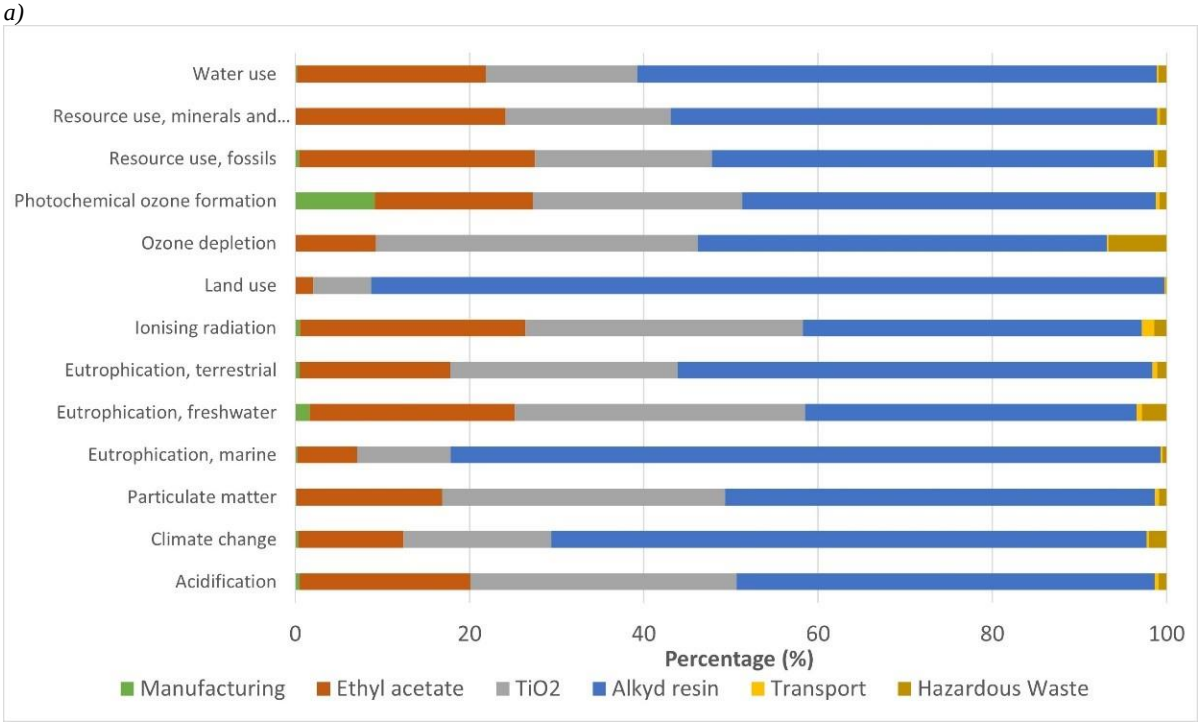


Figure 15 EF 3.1 results for the paint based on xylene (case 1) and the paint based on ethyl acetate (case 2). (Eco) toxicity impact categories are excluded. Impacts are normalized to the paint based on xylene (case 1)

Impact assessment results for Environmental Footprint 3.1 categories (without toxicity) are shown in Figure 15. USEtox 2.13 results are shown in Figure 16. The paint based on xylene is set to 100% for each impact category. The paint based on ethyl acetate (case 2) shows higher environmental impact in all the impact categories both for the EF 3.1 method and USEtox 2.13. The contribution analysis shows that the production of the alkyd resin is the most dominating contributor in almost all impact categories and the most dominating environmental impact from the production of alkyd resin is land use due to the cultivation of soybean.



a)



b).

Figure 16 Contribution analysis of a) paint based on xylene (case 1) and b) paint based on ethyl acetate (case 2)

USEtox 2.13 recommended and interim results (Figure 17) show higher contributions for the paint based on ethyl acetate for both human cancer, non-cancer and ecotoxicity (case 2).

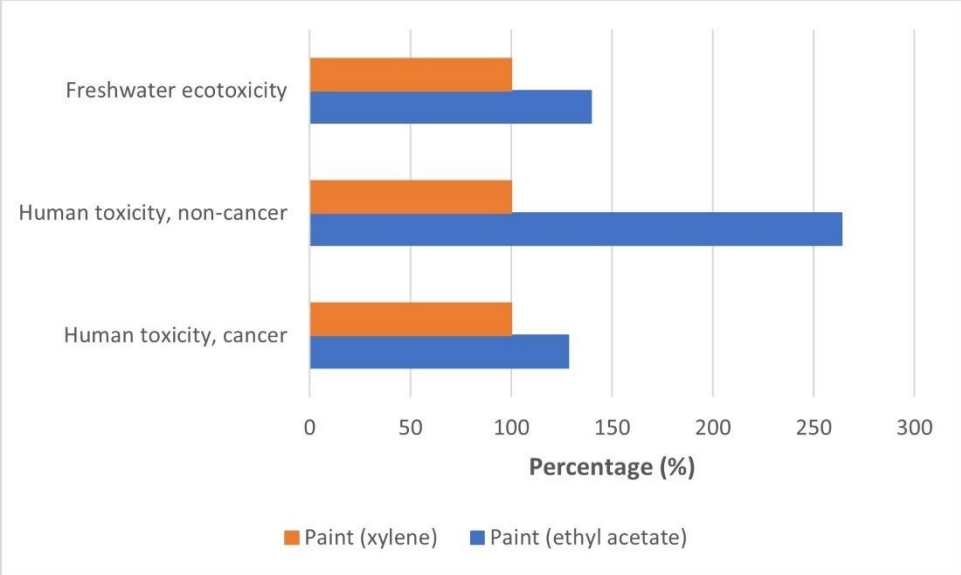


Figure 17 Cradle to gate human toxicity and ecotoxicity impacts of paint based on xylene (case 1) and paint based on ethyl acetate (case 2) (USEtox 2.13 recommended and interim).

Table 3 values calculated with USEtox 2.13; cases are the unit provided in SimaPro for midpoint characterization results (CTU).

Impact category	**Unit**	**Paint based on xylene (case 1)**	**Paint based on ethyl acetate (case 2)**
Human toxicity, cancer	cases	1.9E-07	2.5E-07
Human toxicity, non-cancer	cases	8.7E-08	2.3E-07
Freshwater ecotoxicity	PAF.m3.day	1.0E+04	1.5E+04

5.1.4.Summary

The initial research questions regarding exposure risks and impacts could be addressed with the LCBA toolbox. A simplified result summary shows that advantages for individual aspects can be identified, though the overall result indicates that none of the options can be recommended. This simplified case study showcases how the LCBA toolbox can be used to assess alternatives with multiple criteria and to get an improved understanding of the chemical footprint and other life cycle impacts in chemical substitution cases.

Table 4 aims to summarize the results of the paint cases study in a simplified overview. Xylene and the potential alternative solvent ethyl acetate were assessed with a variety of LCBA toolbox models. The results show no clear improvement in using ethyl acetate instead of Xylene in interior paints. Ethyl acetate showed high risks of chemical exposure during the use phase, especially for professional painters. In addition, increased ecotoxicity effects were predicted for ethyl acetate due to the use phase related emissions. For the production, ethyl acetate had advantages for the direct toxicity potential but has higher impact for all LCA-related impact categories including human and ecotoxicity impacts. The overall results that ethyl acetate is not a preferable alternative to Xylene in interior wall paints.

Table 4 Simplified result summary of all LCBa toolbox models applied for solvents in interior wall paints (a) the paint application during the use phase and (b) the upstream production of paint ingredients (a simplified rankings applied to provide an overview).

(a) Use phase (paint application)	DIY Painter			Pro Painter			
	Xylene	Toluene	Ethyl acetate	Xylene	Toluene	Ethyl acetate	Models
Risks of chemical exposure (inhalation)	😞	😐	😞	😞😞😞	😞	😞😞	USEtox 3.0
Lifetime cancer risk (inhalation)	😞	🙂	🙂	😞	🙂	🙂	
Lifetime cancer risk (dermal)	😐	😐	🙂	😐	😐	🙂	
Characterization factors human toxicity	😐	😐	🙂	😐	😐	🙂	
Characterization factors Ecotoxicity	😐	😞	😞	😐	😞	😞	

(b) Paint production	Xylene	Toluene	Ethyl acetate	Models
Direct toxicity potential (inhalation)	😞	-	🙂	ProScale
LCA impacts Environmental Footprint	😐	-	😞😞😞*	EF 3.1
Human toxicity impacts, non cancer	😐	-	😞	USEtox 2.13
Human toxicity impacts, cancer	😐		😞😞	USEtox 2.13
Ecotoxicity impacts, feshwater	😐	-	😞	USEtox 2.13

* higher impacts in all EF categories

Simplied ranking	
🙂	Low risk/impacts
😐	Medium risk/impacts
😞	High risk/impacts
😞😞😞	Very high risk/impacts

5.1.5. Challenges and data gaps

This case was foremost used to illustrate usage of the toolbox and is thus not intended to support implementation of a substitution in a realistic setting. Given the setup based on generic data for identifying mass flows to calculate the ProScale scores, results need to be considered with caution. An expected premise for this case was that data are available for established chemicals, facilitating the application of the toolbox.

The quality of the life cycle inventory (LCI) is important for both the ProScale assessment and the screening LCA. For this study, predominantly generic data from Ecoinvent have been used and one data set was slightly modified. However, the datasets from the unit processes used in this study have been checked and their quality, relevance, and representativeness have been evaluated and identified as suitable for use. Another challenge is to identify a suitable PROC for the ProScale assessment. In this case, expert judgment and information from exposure scenarios in the MSDS have been used. Furthermore, different scenario analyses have been performed for the ProScale assessment.

5.2. Fact sheets for selected case studies

Results from Mistra Safe Chem case studies are published in separate reports. The LCBA toolbox has been used to support the development of processes and products on different TRLs, guiding a dialogue between research communities. The following short summaries of selected case study approaches and results provide insights.

5.2.1. CASE A: Textile recycling: Optimizing sustainability

Case study background

Due to their excellent mechanical properties crystalline nanocellulose (CNC) are materials of significant interest as reinforcement agents and building blocks for functional materials. While wood serves as the primary source for CNC extractions, isolating pure cellulose from wood requires multiple steps due to its low cellulose content (40-50%) (Krässig et al., 2004) This case study supported the process development of CNC production from post-consumer cotton textiles and their blends with polyester and acrylics by implementing life cycle assessment (LCA). In addition human health and safety aspects during the production were also considered with a first estimate of direct toxicity potentials for different CNC production routes. Cotton represents a purer form of cellulose with a high crystallinity compared to other plant-based cellulose sources (Thomas et al., 2018, Vanderfleet and Cranston, 2021) and is thus a promising alternative to utilize an upcycling of post-consumer waste materials as CNC source materials.
This work was published in Journal of Materials Chemistry A in 2023, Vol 11, pages 6854–6868 (DOI: 10.1039/d2ta09456h).

Application of the LCBA toolbox

By implementing a life cycle assessment (LCA) study based on laboratory-scale data, the environmental impact of using post-consumer cotton as CNC source could be compared to the use of wood pulp. The environmental burden of each process stage could be identified through a hotspot analysis. The upscaling process was simulated at lab scale to provide data for the LCI. Furthermore, the framework developed by Piccinno et. al. was used to estimate the scale up the chemical process from the laboratory data.

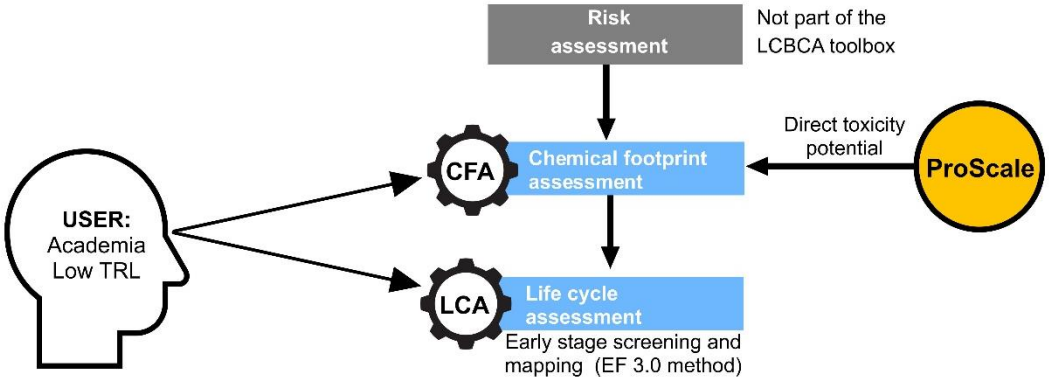


Figure 18 application of the LCBA toolbox in the cases study

The process for CNC extraction from real post-consumer textiles was developed within MSC by using sulphuric acid hydrolysis as described by Ruiz-Caldas et. al.(Ruiz-Caldas et al., 2022). The LCA delivered further insight into the use of citric acid hydrolysis for CNC extraction instead of sulfuric acid. Moreover, the LCA processed models were used as a basis to estimate direct toxicity potentials during production for the different CNC extraction routes using the software SimaPro by using lab scale data provided by the process developers. For ProScale assessment the mass flows for the citric acid production were based on proxy data, based on a study by (Wang et al., 2020)

Result highlights

The LCA results in Figure Xa indicate that CNC production from wood pulp had a higher environmental impact across all 16 categories (EF 3.0) compared to CNCs from post-consumer cotton using sulphuric acid for extraction (SCNC). However, cotton fabrics may contain unwanted impurities from both their production and use, which can potentially limit the field of applications of the extracted CNCs. Concerning citric acid extraction route (Figure 19b), the hydrolysis step was the most dominant contributor due to the usage of citric acid, whose production contributes to all 16 impact categories. The high impact of citric acid can be reduced by decreasing the input amount and improving the acid recovery.

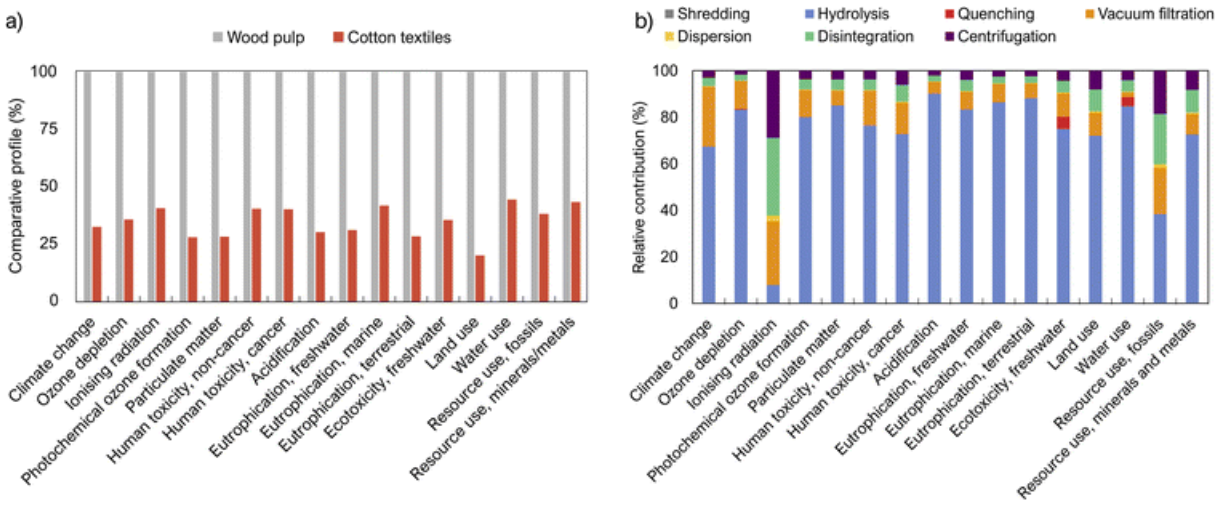


Figure 19 (a) Comparative environmental profiles for CNC preparation from wood pulp and post-consumer cotton textiles using sulphuric acid hydrolysis (Impacts are normalized to the wood pulp process) (b) Environmental profile of hydrolysis with citric acid (CitCNC)

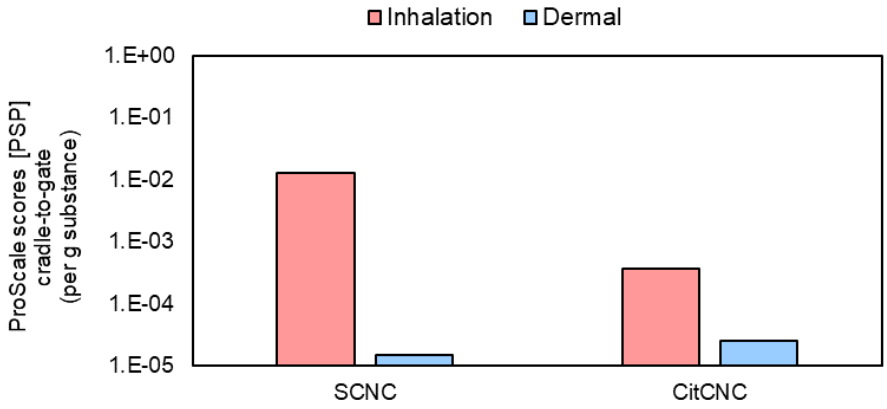


Figure 20 ProScale scores for inhalation and dermal exposure comparing the CNC production with the conventional sulfuric acid process (SCNC) and hydrolysis with citric acid (CitCNC)

Figure 20 shows first estimations of direct toxicity potentials to account for human health and safety aspects during CNC production. In comparison, the sulfuric acid process had higher Pro Scale Scores (a measure for the direct toxicity potentials) for the exposure via inhalation than using citric acid route while the PSP score was lower for the dermal exposure.

This case study showcases how the LCBA toolbox can inform process developers in an early stage (Low TRL) about safety and environmental impacts to make better decisions in process upscaling processes.

Challenges and data gaps.

A challenge that remains is to find data for biobased chemicals and materials, both in LCI and LCIA data, and in this case, particularly for the chemical footprint assessment of citric acid production. Another challenge in this case study was the identification of relevant hotspots along the entire lifecycle due to the undefined use phase. Furthermore, the production facility and process design were unknown. These limitations hinder the possibility of performing an in-depth assessment of the entire lifecycle, including the setup of a relevant inventory model and data selection for both foreground and background systems. Therefore, the generation of a relevant LCI inventory for the foreground system in the screening cradle-to-gate model was based on assumptions as the production process was not defined.

5.2.2. CASE B: Sustainability assessment of a novel hydrogenation reaction process

Background

The traditional reaction process for hydrogenation of carbon-carbon double and triple bonds is using a metal catalyst. These metals, such as palladium and platinum, are often rare and the reactions often involved hydrogen gas (H2) which is derived from fossil resouces as well as presenting a physical hazard during its use. Nickel, in the form of Raney Nickel, presents both similar activity and physical hazard. For that reason, we explored the use of a less reactive nickel foam and electricity as a more sustainabile alternative, since nickel is a more abundant metal and hydrogen is taken from the water instead of from fossil resources. To assess the reaction process, a screening LCA was used to evaluate the environmental performance of the reaction and to identify options for improvement.

The study was reported by Tortajada Palmero et al. (2023) in the pre-print 10.26434/chemrxiv-2023-p4q71.

Application of the LCBCA toolbox within the case study

To answer the first research question the nickel foam system was modelled in the LCA software GaBi by the use of first hand data from WP4, in a cradle-to-gate model. The process of collecting life cycle inventory (LCI) data was interative with a close dialogue between the LCA operator and the technology developer. The LCIA method used for evaluating the environmental performace of the nickel foam reaction process was EF3.0 and USEtox 2.12. Characterization factors were calculated by the use of USEtox 2.12 for two substances to further complete the chemical footprint. The (eco)toxicity indicators applied covered environmentally mediated exposures.

The second research question was firstly addressed via a literature review to check the availability of LCA studies of hydrogenations using Pd/C as catalyst that could be used for comparision between the two alternatives. Thereafter the conventional system, though executed in lab-scale, was modelled in GaBi. Also here WP4 provided the LCA operator with first-hand data for the lab set up.

In both models, upstream processes used data from existing datasets in the professional database in GaBi and ecoinvent (version 3.7.1) as far as possible. When there were no dataset available, assumptions were made based on structural similarities.

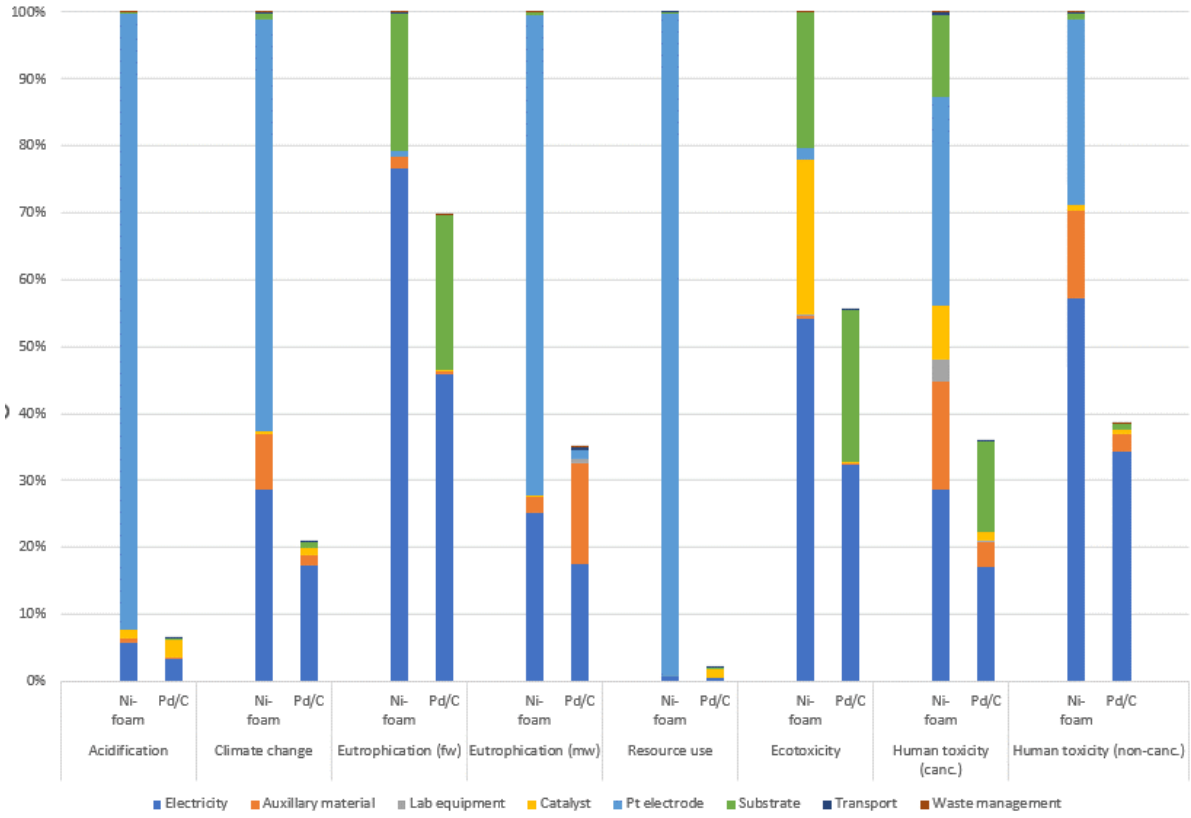


Figure 21 Normalized contribution for the different impact categories. Catalyst stands for Pd for the Pd/C system and and Ni foam for the Ni foam systems, Plot adopted from (Tortajada Palmero et al., 2023)

The LCA screening assessment in Figure 21 showed a in summary higher impacts for the nickel foam system in comparison to the using Pd/C as catalyst. For both systems platinum (Pt) electrode production and electricity production were the main contributors. The screening LCA conducted herein indicates that the Ni foam reduction method is hampered by the high potential impact of the platinum electrode, and further investigation of the possibilities for the substitution of this electrode is advisable.

Challenges and data gaps

Data gaps were observed both in LCI and LCIA. Some of the gaps were possible to adress and other were out of scope in this screening LCA.

One of the substances for which characterization factors were calculated was palladium. Data gaps were observed for all parameters in USEtox for exposure and fate. All those parameters were assumed to be equal to those of Ag(I), being the closest substance (in the periodic table), using data from the USEtox 2.12 database. Furthermore, ecotoxicological data from only one species was included (*Hyalella Azteca*), available via the Ecotox knowledgebase. For quality control, in a second stage, the CF of palladium was recalculated using Cr(VI) as proxy because of its high (eco)toxicological impact. Impact on the results was only observed in the human toxicity (cancer) indicator and the preliminary characterization factor calculated for palladium was assessed sufficiently relevant for this screening LCA.

Challenges were of course many and are here listed in selection:

- To find a common language in dialouge between technology developers, hazard/risk asessors and LCA-experts.
- The generation of a relevant inventory for the foreground system, i.e. experimental work to derive first hand data, at an appropriate scale.
- The identification of key processes to focus modelling on as a screening LCA does not allow for in depth assessment of the full system. This includes the set-up of a relevant inventory model and data selction for the background system.
- To find appropriate data for calculation of characterization factors and to correctly derive input data for USEtox 2.

5.2.3. CASE C: Safer and more sustainable by design in discovery chemistry

Background (short)

Amide synthesis is of great interest in the chemical and pharmaceutical industry. However, the production of amides using traditional chemical synthesis routes involves several drawbacks. The traditional chemical synthesis routes rely on the use of stoichiometric quantities of activating agents (such as thionyl chloride, carbonyldiimidazole (CDI) and oxalyl chloride), which results in large quantities of waste. Furthermore, some of these activating agents are considered problematic from an environmental point of view. An alternative route for synthesizing amides is biocatalysis, relying on the use of enzymes as catalysts. Researchers have previously reported that biocatalytic reactions would be highly competitive for the large scale production of pharmaceuticals when considering efficiency and sustainability (Sabatini et al., 2019). To explore this further, life cycle assessment is conducted within the case study.

Comment: Additional relevant background is available in (Söderberg et al., 2023), pre-print 10.26434/chemrxiv-2023-x8f25.

Application of the LCBA toolbox:

In step 1 a screening of amines, acids and amides to be investigated within this case study was based on hazard information as generated by the Mistra SafeChem in silico toolbox and characterization factors as calculated with USEtox 2.12, with input generated by publicly available in silico models, OPEn structure-activity/property Relationship App (OPERA), Ecological Structure Activity Relationships Program (ECOSAR) and Conditional Toxicity Value (CTV). Uncertainties were propagated from the prediction models by Monte Carlo analysis, considering reliability of results in relation to the models' applicability domain. Missing values (human toxicity) were conservatively imputed by using in-domain predictions. The hazard screening covered 15,374 amines and 5,994 acids of which 347 were selected for USEtox assessment (30 acids, 62 amines, and 255 amides). The subsequent ranking, based on characterization factors calculated with USEtox, extended the screening of substances beyond their intrinsic hazard properties to a quantitative impact assessment based on fate, exposure and effect.
In step 2, a screening of amide synthesis reactions starting from the previously selected acids and amines was conducted, based on computational predictions of the efficiency of biocatalytic reactions. This screening resulted in the selection of one amide synthesis to be explored at laboratory scale and assessed by LCA. First hand life cycle inventory (LCI) data for modelling the biocatalytic synthesis were collected. At the same time, first hand LCI data were collected for the synthesis of the selected amide via a representative traditional chemical synthesis route, which was also performed at laboratory scale. Finally,

LCA was conducted on the two synthesis routes with the aim to highlight hotspots in the processes and evaluate the potential of biocatalysis in the specific context of the case study.

Result highlights

Step 1: Screening assessment

For each of the substrates (starting substances on which an enzyme acts) and products as filtered out in the hazard screening carried out by computational predictions (30 acids, 62 amines, and 255 amides) human toxicity and ecotoxicity impact potentials expressed as characterization factors were calculated using USEtox 2.12. Potential impacts for emissions to continental freshwater and rural air were included, most applicable for a potential industrial synthesis setting. Characterization results were compared based on the characterization factors, assuming equal emissions. Input parameters were predicted using in silico methods, OPERA for basic chemical and fate-related properties, ECOSAR for ecotoxicity effects and for human toxicity effects. Median values for characterization factors per substance were derived by Monte Carlo analysis, accounting for uncertainty in the underlying prediction models, in relation to their respective applicability domain. Missing values (applied for human toxicity) were conservatively estimated by taking the 95th percentile of the given effect parameter data across the dataset within each chemical class. The characterization factors across chemicals were used for the further risk ranking of the large dataset of acids, amines and amides, i.e. building blocks and products.

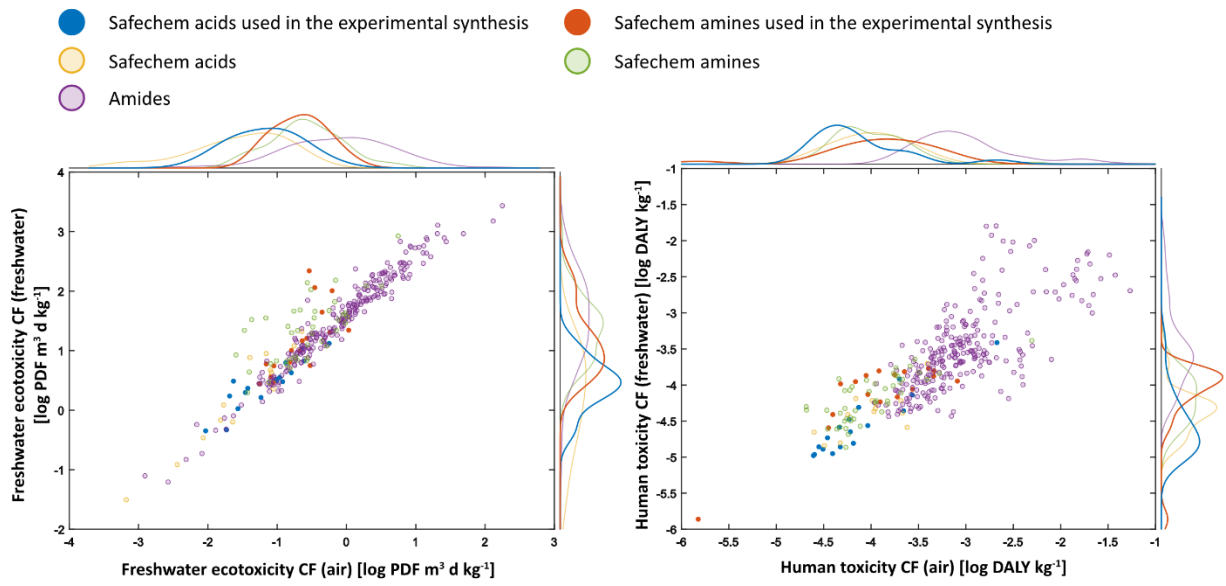


Figure 22 Example for uncertainty in CFs; further details in {Söderberg, 2023 #240}

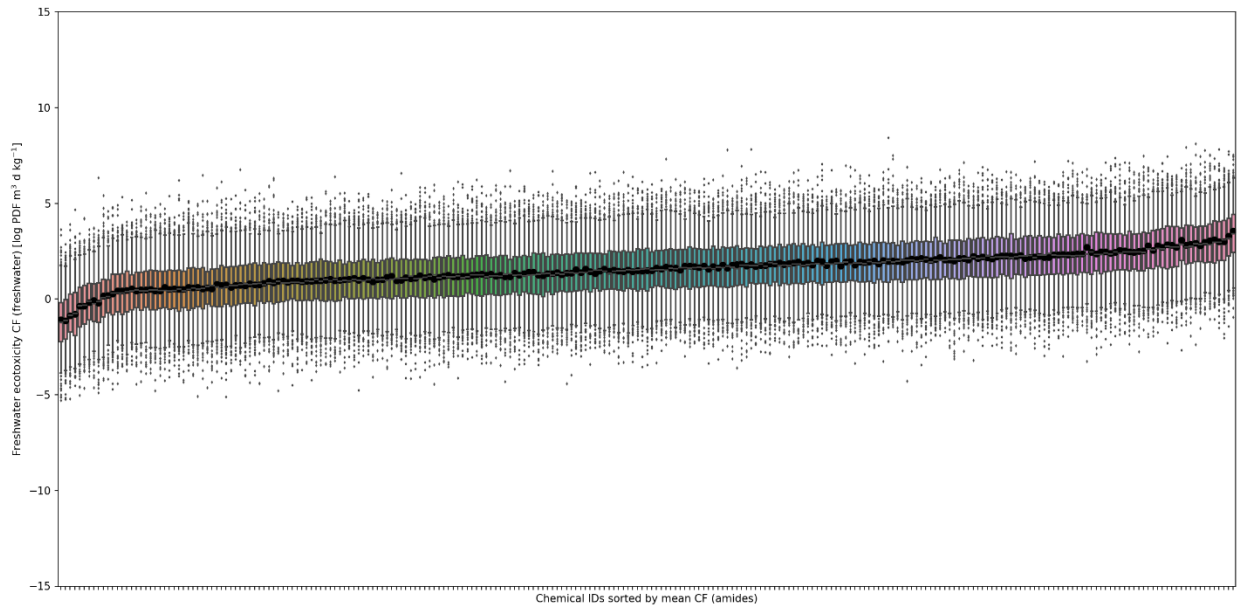


Figure 23 Characterization results obtained from Monte Carlo analysis in USEtox showing boxplot distributions of freshwater ecotoxicity characterization factors (CF) for emissions to freshwater for all amines selected as "safechems" sorted by increasing median CFs with the deterministic CFs indicated in black.

Step 2: LCA

Models of the cradle-to-gate systems of the selected amide synthesis processes at laboratory scale (via biocatalytic and traditional chemical synthesis route) were set up in the LCA for Experts (GaBi) software, by using available LCI databases for the background system and first hand data from academic and industry partners for the final synthesis steps, corresponding to the foreground system. Life cycle impact assessment was conducted by using Environmental Footprint (EF3.1) characterization factors for a broad scope assessment covering 16 impact categories. The results of the LCA pointed at the amide purification step as a hotspot in both synthesis routes at laboratory scale, as it involves the use of relatively large amounts of organic solvents. This aspect was significantly affected by the small scale of the reactions. Ongoing work is being conducted with the aim of publishing the results of the amide syntheses screening and LCA in a scientific journal.

Challenges and data gaps

In step 1 one of the major challenges was that the current version of the Mistra SafeChem toolbox for in silico hazard prediction does not cover all input parameters needed for USEtox. Other models available had to be used to generate a complete dataset. These models vary in applicability across chemicals. However, applicability is reported differently across different approaches and none of them reports individual confidence intervals per prediction. We assigned semi-quantitative confidence intervals based on validated prediction errors and available applicability domain values. However, due to difference in methodology, this does not guarantee consistency and coverage of confidence intervals across parameters and chemicals. Current work is ongoing in Kerstin von Borries' PhD project to fill this gap.

In step 2 a major challenge lied in ensuring a fair comparison of the biocatalytic and traditional synthesis routes within LCA, as data sources for the background system differ in terms of inventory practice as they cover very different fields, and due to difference in maturity of the technologies.

FACT SHEET CASE E: Substitution of cyclic siloxanes and silicones in cosmetics

Background (short)

Silicones have unique properties such as excellent spreadability, a smooth, soft, dry and non-tacky feel and are thus widely used in cosmetic products (Bletsou et al., 2013). Cyclic siloxanes are a subgroup of silicones, listed as substances of very high concern (SVHC) in REACH, since their properties fulfill 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.
Comment: This case study is described in a separate report in detail, for further information see the programme website.

Application of the Life Cycle-Based Assessment (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 EU (see Figure 24 a). The workflow was also inspired by life cycle based alternatives assessment (LCAA) for chemical substitution approach suggested by Fantke et.al. (Fantke et al., 2020) (see section 2.2.1).

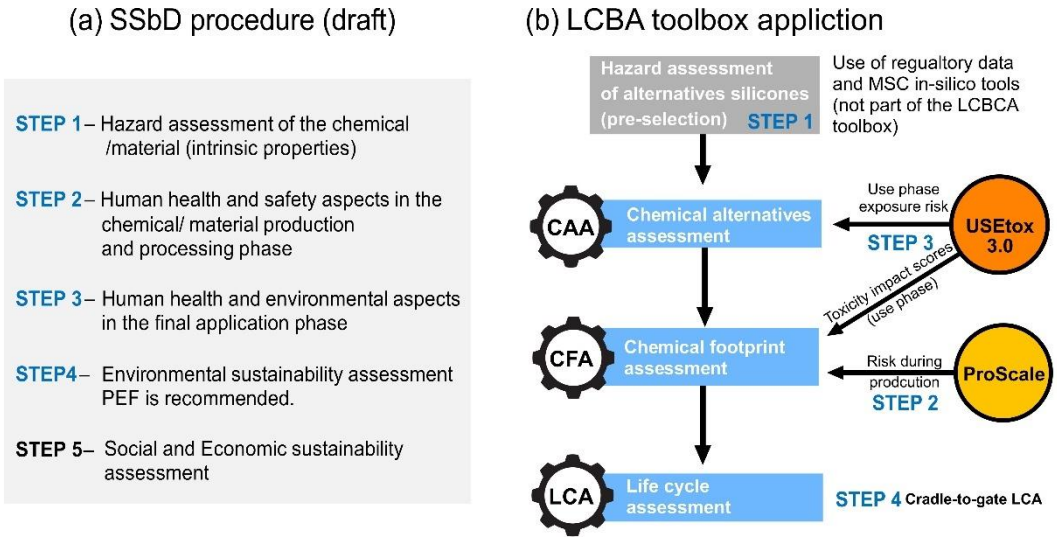


Figure 24 Workflow for the case study about substitution of cyclic siloxane in cosmetics with (a) the draft of the SSbD procedure and (b) the workflow of the cased study and application of the LCBA toolbox in orientation the SSbD

After an initial prioritization of alternatives (STEP 1 of the SSbD) with low toxicity by means of a hazards assessment (not part of the LCBA toolbox), D5 and selected alternatives were further assessed for their use phase exposure risk (STEP 3 in the SSbD) using the USEtox 3.0 near-field model in a typical cosmetic product application scenario of makeup formulation. Moreover, the USEtox (near-/far-field) model was used to calculate human and ecotoxicity impact scores for the use phase for D5 and potential alternatives.

A cradle-to-gate LCA with environmental footprint 3.1 impact categories (SimaPro 9.5, adapted) was conducted to consider different production routes and raw material sources (e.g. petroleum vs biobased) in a broader environmental sustainability assessment (STEP 4 of the SSbD). Data were selected from the Ecoinvent data base 3.9.1 (unit processes) and adjusted where necessary to represent the benchmark and alternatives. All alternatives are based on an esterification process as inventoried in Ecoinvent:

- Benchmark Polydimethylsiloxane (GLO), unit process
- Alternative Diisopropyl adipate based on diisooctyl adipate, added isopranol as input flow, removed isooctanol related input, masses adjusted according to stochiometry/molar mass
- Alternative diethylhexyl sebacate based on diisooctyl adipate, added sebacic acid proxy (fatty acid (coconut oil based and sodium hydroxide as input materials), removed adipic acid related input, masses adjusted to stochiometry/molar mass
- Alternative decyl oleate based on diisooctyl adipate, added stearic acid (plant oil based, C18) and fatty alcohol based on coconut oil (C12), masses adjusted according to stochiometry/molar mass.

Toxicity impacts for upstream processes were calculated with the USEtox 2.13 characterization factors. Human health and safety aspects in the chemical production phase (STEP 2 of the SSbD) were considered by applying the ProScale model for the identified upstream processes. Basis for the assessment were production processes investigated in the cradle-to-gate LCA. Assessment of work place exposure was thus postponed compared to the the original SSbD sequence.

Selected results

The use phase related hazard quotient (HQ) and ecotoxicity impact scores of D5 and selected alternatives are displayed in Figure 25 (STEP 3) The results show that D5 had low exposure risk during their use in the makeup formation (HQ> 1 are considered as high risk). For the selected alternatives Diisopropyl adipate had showed a high exposure risk (HQ ~11) while decyl oleate had a lower value in comparison to D5. decyl oleate also then only alternatives which showed improved ecotoxicity scores caused by emissions during product use.

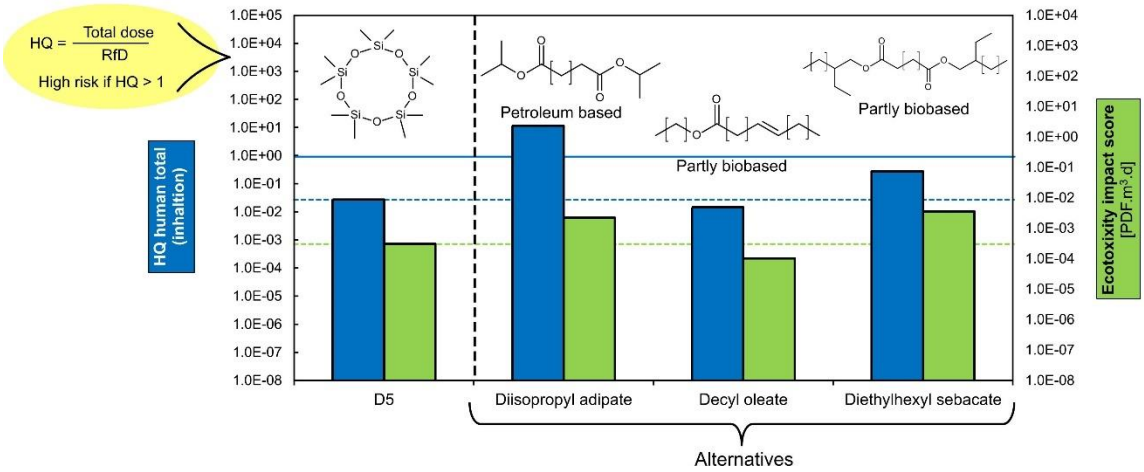


Figure 25 HQs estimations for D5 and alternative esters that are exposed via inhalation (main exposure pathway) and the ecotoxicity impacts scores caused by emissions during the use of the make up formulation

The ProScale modeling (Figure 26) to assess safety aspects during chemical production (STEP 2) showed significantly higher scores for Diisopropyl adipate and Diethylhexyl sebacate in comparison to D5 while Decyl oleate was of lower risk. The high risk was mainly caused by the use of naphtha from oil refining which was

used as an input material in production of adipic acid and isopropanol. Decyl oleate is modelled as completely biobased option.'

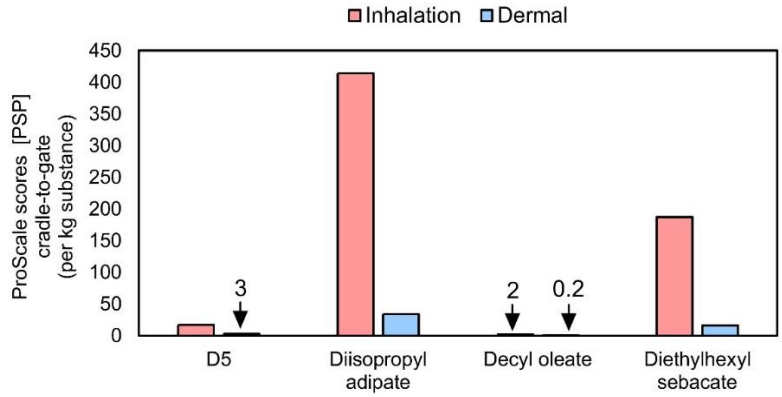


Figure 26 ProScale scores for inhalation and dermal exposure for the cradle-to-gate production systems (PSP) for D5 and alternatives.

The cradle-to-gate LCA results of the broader environmental sustainability assessment (STEP4) showed lower impacts for the alternatives esters in the majority of impact categories.
The alternatives showed lower toxicity impacts compared to the reference polydimethyl siloxane based on the USEtox 2.13 impact categories (Figure 27). In this figure, the result for polydimethyl siloxane is set to 100% as a reference substance, and the values for ester alternatives are compared to that. Diisopropyl adipate shows lower results for human toxicity non cancer effects compared to the two other alternatives, but higher results for human toxicity cancer effects and freshwater ecotoxicity.

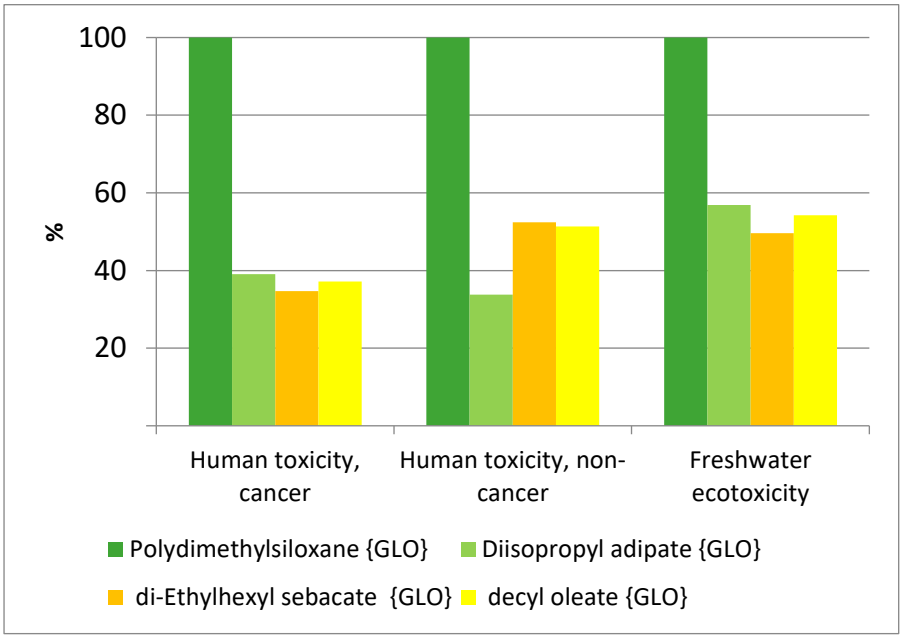


Figure 27 Toxicity impacts results the production of Polydimethyl siloxane and alternatives (USEtox 2.13); D5 originates from the same production process as polydimethylsiloxane (Muller–Rochow reaction) The dataset for the polydimethylsiloxane was thus taken as a proxy for D5.

The Environmental Footprint 3.1 impacts in Figure 28 LCA results of the production of D5 (Polydimethylsiloxane) alternatives according to the Environmental Footprint 3.1 categories (without toxicity) show that the partly biobased esters (decyl oleate and Diethylhexyl sebacate) had higher impacts for land- and water use, while decyl oleate had also higher impacts for marine eutrophication. These higher impacts can be explained with the cultivation biobased raw materials (e.g. palm fruit) which is used production of the partly biobased esters. However, following the guidelines published in spring 2024, only diisopropyl adipate showed sufficient improvement compared to the reference polydimethyl siloxane to pass the score for all impact categories. Diethylhexylsebacate has a score of 0 for land use and water use, and decyl oleate has a score of 0 for land use, water use amd marine eutrophication. Low scores were observed for bio-based raw materials. As a consequence suggested by the SSbD framework, alternative options to source raw materials should be checked, for example using by-products from food industry that are not suitable for human consumption, or utilizing more side streams in biorefineries. Note that the scoring was only done for the impact categories that were calculated according to the EF 3.1 approach.

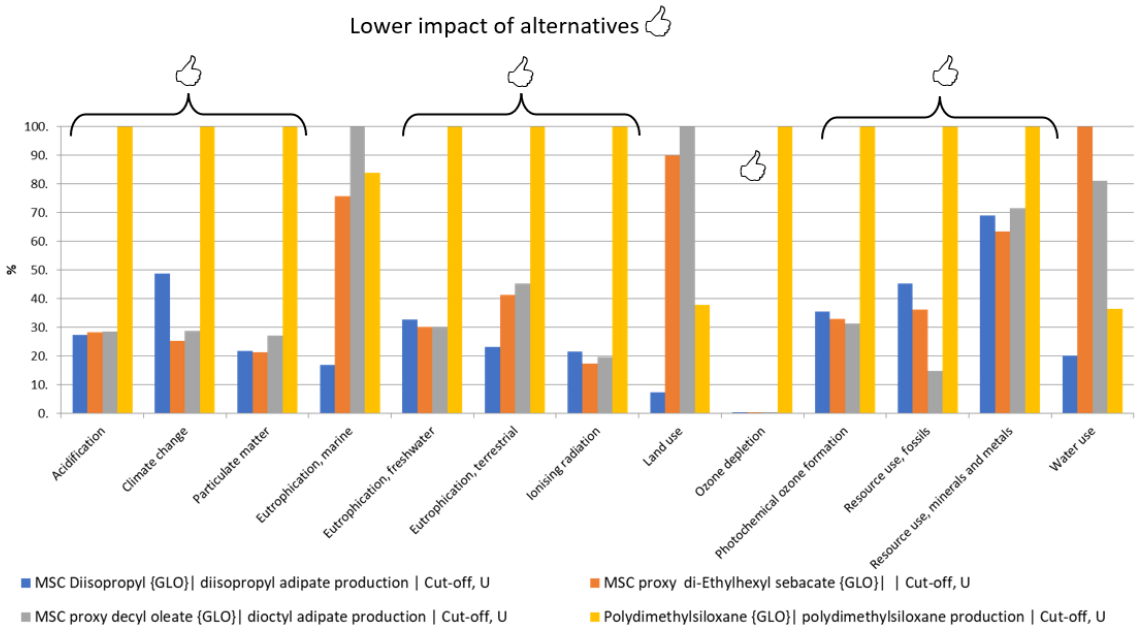


Figure 28 LCA results of the production of D5 (Polydimethylsiloxane) alternatives according to the Environmental Footprint 3.1 categories (without toxicity)

Our case study and workflow is a first attempt to apply the MSC lifecycle-based assessment tools in a SSbD context. While the application and workflow needs to be further developed the first results of this case study points out trade-offs between safety for users and environmental impacts. The combination of lifecycle-based chemical assessment tools can contribute to an improved understanding of the chemical footprint and other life cycle impacts in chemical substitution cases to find better alternatives.

5.x.4. Challenges and data gaps.

Challenges that occurred during our work in this case study was the availability of input data (especially toxicity date) to run USEtox 3.0 model. None of these chemicals had complete data sets for all categories and it was necessary to extrapolate toxicity data (e.g. oral to dermal) which increases the uncertainty of the results. Predicted toxicity input data (e.g. EC10 and RfD) using the in silico tool using Conditional Toxicity Value Predictor (CTV) showed high deviations from data that were already present in USEtox input data tables. Substances with data caps for all toxicity input data were thus not included. Moreover, a lack of data for inventory and impact assessment made a comprehensive assessment of with the SSdD framework not possible so far.

6. Conclusions and outlook

Benefits, gaps, current developments

Assessment frameworks to consider health and safety and environmental impacts of substances used in products and processes are established and have been found to address a range of aspects, however they are rarely used simultaneously and thus results are not intended for use in parallel, but rather address complex and multifaceted challenges within their respective domains safety and sustainability. Adding a requirement to simultaneously address both domains adds a layer of complexity and is needed to address potential conflicts of aims, e.g. when secondary raw materials need to be used and exposure to contaminations is increased or when novel processes with lower exposure risks are initially less efficient. The workpackage on sustainability assessment was therefore designed to expand the scope and consider impacts due to exposure to chemicals during production and use in a life cycle context by applying the tools ProScale and USEtox 3.0 with both near field and far field modules. Both tools are under development, thus libraries and databases to collect factors and scores are sparsely populated. Adding information from digital models and related areas is a promising approach here and has been tested in case studies. The iterative workflow that was tested within case studies also helped to understand information demand and user needs. To support decision making in applications for newly developed safe and sustainable products and processes frameworks for providing and evaluating information will be further tested in phase 2 of the research programme, which will include more case studies and address specific methodological challenges related to upscaling and integration of information.

7. References

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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
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