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Can we assess innovative bio-based chemicals in their early development stage? A comparison between early-stage and life cycle assessments

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ABSTRACT

The chemical industry strives for the development of bio-based alternatives to prepare for the transition towards a sustainable biobasedeconomy. Key in this transition is 'safe and sustainable by design'. This entails that safety and sustainability must be taken into account at the earliest possible development stages. A remaining challenge is how to assess the sustainability and safety of a new production process while it is not yet established. Assessment methods have been developed for this purpose but they do not seem to be commonly used in Research and Development (R&D) departments.

The aim of this paper is to review and evaluate the available early-stage assessment methods (ESM) and ex-ante life cycle assessment (LCA). Using the case of lactic acid in a retrospective study, its different development stages were anticipated. The outcomes of implementing the selected ESMs and ex-ante LCA at the different development stages of lactic acid were compared with those of a full LCA of the real production at commercial scale.

Key findings are that 1) many ESMs are often not fully or clearly described and the databases suggested are outdated; 2) since most of the methods are designed to assess chemicals in general, not specifically for bio-based chemicals, the relevant environmental themes to reflect the characteristics of bio-based chemicals are often missing; 3) in terms of toxicity impacts, the reviewed methods are often crude and not accurate in the coverage of toxicity aspects.

Ex-ante LCA could play a more important role during the process design R&D phase. However, ex-ante LCA should be complemented with accessible methods to evaluate the potential toxicity impacts at the early development stage to ensure safe by design.

1. Introduction

Today's chemical industry largely relies on the use of finite fossil resources, which is a result from unsustainable consumption of non-renewable feedstock and leads to emissions of greenhouse gases (GHG). As an alternative, the shift to a bio-based economy has been recognised as an opportunity to aid sustainable development at global level (OECD, 2017). Producing bio-based materials (from renewable biological resources) entails the potential to limit the use of fossil fuels and to reduce GHG emissions compared to their conventional petrochemical counterparts (Weiss et al., 2012).

In 2016, worldwide production capacity of bio-based polymers was 6.6 million tonnes, representing a 2% share of the overall polymer production capacity (Aeschelmann and Carus, 2017). Projections indicate that worldwide production capacity of bio-based polymers will increase to 8.5 million tonnes by 2021 (Aeschelmann and Carus, 2017). The introduction of an increasing number of innovative bio-based chemicals requires novel synthesis routes and production processes. Mitigation measurements should start at the early development phase because a large share of the

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environmental impacts of a product can be influenced at the design stage (European commission, 2014). The concept of “Safe and sustainable by design” can therefore play a key role in the transition to a safe and sustainable bio-based economy.

The innovation process for (bio-based) chemicals typically moves through different research and development (R&D) stages. Design freedom decreases though the development phases but higher data quality becomes available to perform more detailed assessments (Fig. 1).

The eco-design concept is not new, being promoted by legislation in EU already in 2009 (Directive, 2009/125/EC). There are wide ranges of proposals for new methods that aim to incorporate environmental assessments into product design phases (Baumann et al., 2002; Bovea and Pérez-Belis, 2012; Rossi et al., 2016). These methods diverge on the purpose for which they were developed and their level of complexity. Some of them perform an analysis at product-level (Fitgerald et al., 2007) while others focus in influencing the user behavior (Janin, 2000). Qualitative guidelines and checklists (Nordkil, 1998; Wimmer, 1999) are fast and easy to implement but hold the risk of being oversimplified (Bovea and Pérez-Belis, 2012); more complex quantitative methods require large amounts of information (Rossi et al., 2016), the involvement of experts (Poulikidou et al., 2014) or the use of software (Rombouts, 1998; Matzke et al., 1998; Jain, 2009).

The outcomes of these assessment methods were rarely validated (Baumann et al., 2002; Bovea and Pérez-Belis, 2012; Rossi et al., 2016) and they do not seem to be commonly implemented in industrial R&D departments (Baumann et al., 2002; Pujari, 2006; Broeren et al., 2017). More importantly, the available early-stage assessment methods were not specifically designed for bio-based chemicals. Nevertheless, biomass cultivation can have a significant contribution to the environmental performance of bio-based products (Miller et al., 2007; Goedkoop et al., 2009; Weiss et al., 2012).

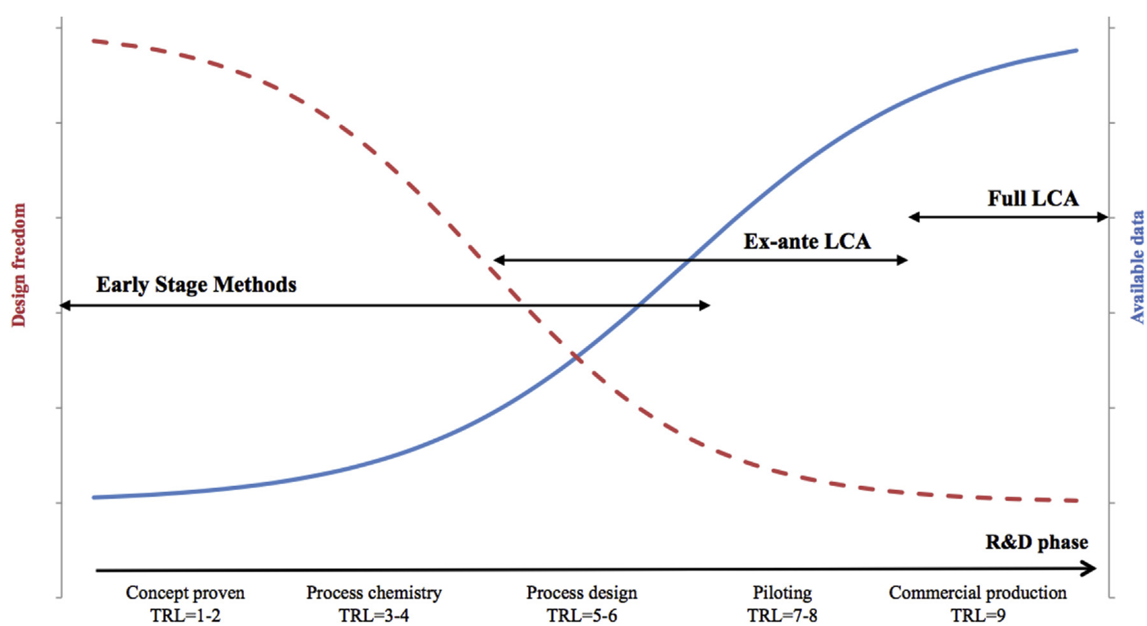
Broeren et al. (2017) conducted a thorough review of 27 publicly available early-stage assessment methods (ESMs, Technology Readiness Level (TRL, DOE, 2009; EARTO, 2014) < 6, Fig. 1) and the indicators covered by these methods. The authors evaluated the suitability of the indicators for the assessment of bio-based chemicals. Most methods reviewed include energy, climate change and material related indicators. However, only a few methods take into account the environmental indicators associated with biomass production such as land use and eutrophication. In addition, the reviewed ESMs use safety indicators that rely on available hazard information, which for newly designed chemicals is typically unknown at early development stages.

The consideration of toxicity indicators in ESMs is of high importance in the transition towards a safe and sustainable bio-based and circular economy. Currently, a lot of toxic substances are applied that can cause harm to people and/or the environment during the whole life cycle. By considering toxicity indicators at the early stage developmental process the progress of safe products/processes will be stimulated as early as possible, thereby preventing regrettable design/substitution.

When the development of a chemical enters TRL 5–6, there is usually sufficient experience and evidence to establish a process design to simulate large-scale production. The outcome of the process design (i.e. mass and energy balances of the entire processing plant) can be used as input information for an ex-ante life cycle assessment. Ex-ante LCA implements life cycle thinking to predict the potential impacts of introducing a future production process.

There is currently an unbalanced research effort between developing new methods or investigating and improving the available ones (Broeren et al., 2017). The evaluation of the applicability and accuracy of the current assessment methods can only be performed by comparing their outcomes with those of a full assessment. To our knowledge, little has been reported on such an evaluation, especially for bio-based chemicals. Having said the aforementioned knowledge gaps, the goal of this paper is to address the following research question:

How applicable are the current assessment methods for the early-stage development of bio-based chemicals and how adequate are the outcomes to ensure safe and sustainable by design?



LCA: life cycle assessment; R&D: research and development; TRL: technology readiness level, method of estimating technology maturity based on a scale from 1 to 9, being 9 the most mature technology (DOE, 2009; EARTO, 2014).

Fig. 1. Design freedom and available data at different design phases of chemical processes. Adapted from Broeren et al. (2017).

To answer this question, a team formed by academia (Utrecht University), the public sector (Dutch National Institute for Public Health and the Environment) and the private sector (Corbion Purac, a lactic acid producer) collaborated on a retrospective assessment of lactic acid, a bio-based organic acid produced by fermentation of carbohydrates since the 1880s (Groot et al., 2010) and currently produced at commercial scale.

In order to perform an early-stage assessment for a chemical that is already produced at commercial scale, different development stages of the synthesis of lactic acid were envisioned using literature information and a selection of ESMs and ex-ante LCA were implemented. The high level of maturity of the lactic acid technology allows evaluating the adequacy and limitations of the implemented ESMs and ex-ante LCA by comparing their results with those of a full LCA based on the present commercialised production. Moreover, the outcomes of the lactic acid case study can provide insights into how LCA impacts evolve from different early technology development phases to commercialisation, and how the future design tools can be improved to ensure that new bio-based chemicals are *safe and sustainable by design*.

2. Methodology

2.1. Overarching approach

The overarching approach of this study (seven steps) is shown in Fig. 2, using the development of lactic acid as an example. The first step is to identify relevant sustainability themes to be assessed, which is usually case-specific (Zijp et al., 2017). For the case of lactic acid, this is done by a workshop engaging the opinions of the relevant stakeholders, i.e. people from different business units from the lactic acid producer, academics and the public sector. The workshop resulted in six themes covering both environmental and toxicity indicators:

energy,
climate change,
eutrophication,
land use,
human toxicity, and
ecotoxicity.

The detailed procedure and outcome of the workshop are available in the supplementary information (SI.1).

In the second step, the ESMs that offer to assess the six chosen environmental and toxicity themes are identified and reviewed in detail. In this step, the results from Broeren et al. (2017), who reviewed an extensive list of publicly available ESMs, are used. Out of the reviewed 27 methods, 12 cover at least one of the six selected sustainability themes.

In the third step, the 12 selected ESMs are implemented to the case study (sections 2.2 and 3.1), i.e. the early-stage of lactic acid synthesis (TRL 1–6). The outcomes of this step serve two purposes: 1) to evaluate the *applicability* of these ESMs, and 2) to evaluate the *adequacy* of these EMs. The evaluations are conducted in the final step, after obtaining the results of ex-ante LCA and full LCA.

In the fourth step, an ex-ante LCA based on a preliminary process design of lactic acid production during its development phase (TRL 5–6) is implemented (section 2.3). The preliminary design is based on the publicly available literature data and key design assumptions. It represents what a process designer would develop as a promising route to produce lactic acid, thus it does not depicts any current technology.

The fifth step consists of the implementation of a full LCA of the

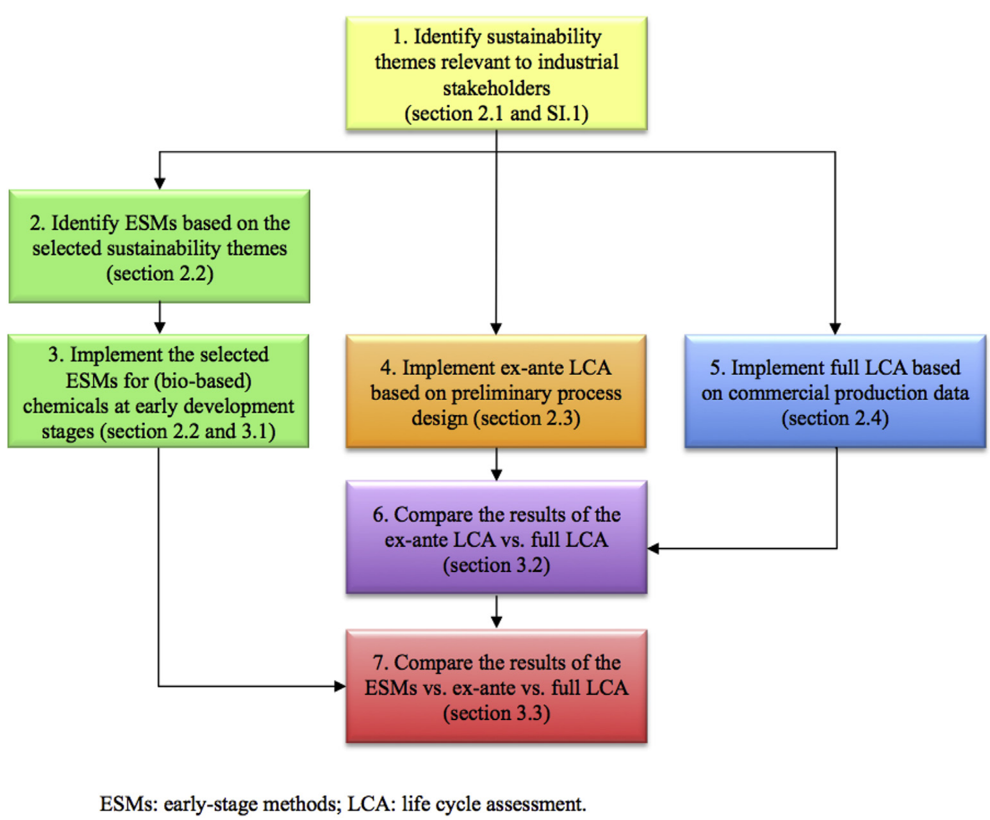


Fig. 2. Steps of the overarching approach of this study.

current commercialised production of lactic acid (TRL 9, section 2.4).

Finally, the results of the full LCA are used to be compared with the results of the ex-ante LCA (section 3.2) and the outcomes of the ESMs (section 3.3). The comparisons provide insights into the predictive power of the ESMs and ex-ante LCA, as well as how environmental and safety assessments evolve at different technology development phases until commercialisation. Thereby, the *applicability* and *adequacy* of the early-stage assessment methods can be evaluated.

2.2. Identification and implementation of the relevant early-stage methods (ESMs). Steps 2 and 3 of the lactic acid case study

The 12 selected ESMs were developed for different purposes, and just one of them was originally conceived for bio-based materials. Table 1 provides an overview of the original objectives and the assessment themes covered by the 12 ESMs. A detailed description of these 12 ESMs can be found in SI.2.

2.2.1. Themes and indicators coverage

The ESMs use *indicators* to measure the sustainability *themes*. Many ESMs define more than one indicator for the same theme (e.g. for the energy theme Sugiyama et al. (2008) use an energy loss index and the raw material cumulative energy demand as indicators, Table 1, SI2). All 12 ESMs provide energy-related and/or climate change indicators and nine ESMs also include human toxicity and ecotoxicity indicators. With respect to bio-based feedstock production, four ESMs contain eutrophication-related indicators and only two include land use-related indicators (Table 1). Only one ESM addressed all selected themes.

2.2.2. Life cycle scopes

The identified ESMs cover different scopes based on their objectives (Table 1). Six out of 12 ESMs cover a gate-to-gate scope, where the system boundary includes the single production process at the manufacturing site (i.e., a supply chain analysis is excluded). Three out of 12 ESMs cover a cradle-to-gate scope, where the system boundary is expanded including raw material extraction (or biomass cultivation for bio-based chemicals) up to the point that the product is delivered at the factory gate. Three ESMs assess mixed scopes, using different indicators for different product life cycle stages. None of the reviewed ESMs performs a cradle-to-grave assessment covering the whole life cycle of the product including the use phase and the end-of-life. This is caused by limited information at early design stages on the final application and the post-consumer waste management.

Table 1
The 12 early-stage methods and their coverage of the selected sustainability themes. The definitions of the indicators can be found in SI.2, Table S2.

R&D stage	Method	Environmental					Toxicity		Objectives as described by the method developers
		Scope of environmental themes	Energy (related)	Climate change	Eutrophication (related)	Land use	Human toxicity	Ecotoxicity	
TRL 3–4: Process chemistry	van Aken et al., 2006	GtoG	x				x	x	Post-synthesis, semi-quantitative analysis tool to evaluate quality of an organic preparation
	Patel et al. (2012)	Mixed	x	x			x	x	Method for quick preliminary assessment of chemical processes at the laboratory stage
TRL 3–6: Process chemistry; Process design	Sugiyama et al., 2008*	Mixed	x				x	x	Chemical process design framework that comprises four stages of process modelling and multiobjective evaluation characterised by the available information
TRL 5–6: Process design	Chen et al. (2002)	GtoG		x			x	x	Design procedures and guidance for optimising chemical processes including environmental aspects
	Curzons et al. (2001)	GtoG	x	x			x	x	Sustainability-based approach for chemists to quantitatively and systematically evaluate if synthetic organic reactions and processes are "greener"
	Curzons et al. (2007)	CtoG	x	x	x				Web-based tool designed to deliver metrics to determine and benchmark the "greenness" or relative sustainability of typical pharmaceutical process at an early-stage in R&D development activities
	Schwarz et al. (2002)	GtoG	x	x	x		x	x	Metrics to aid companies to begin to incorporate the goal of sustainability into management decision-making
	Sheldon and Sanders (2015)	CtoG	x			x			Set of sustainability metrics for quickly evaluating the production of commodity chemicals from renewable biomass
	Tabone et al. (2010)	Mixed	x	x	x		x	x	Evaluation of the efficacy of green design principles in polymers with respect to environmental impacts found using LCA
	Tugnoli et al. (2008)	GtoG	x	x	x	x	x	x	Procedure for quantitative assessment of key sustainability performance indicators of alternative processes, mainly at the early-stages of process design
	Voss et al. (2009)	CtoG		x					Carbon factor as a parameter to evaluate the total amount of CO_2 emitted to produce a product in chemical industrial processes
	Young and Cabezas, 1999	GtoG		x			x	x	Waste reduction (WAR) algorithm for the design of sustainable processes with simulation

2.2.3. Targeted early development stages

The selected ESMs are categorised based on the technology readiness levels (TRL) (DOE, 2009; EARTO, 2014) to understand the trade-offs between low data requirements-high uncertainty and high data requirements-low uncertainty. Based on the TRLs, four development stages can be distinguished before commercialisation (Fig. 1), corresponding to:

Concept proven (TRL 1–2): the idea of a new synthesis route for a chemical is determined by brainstorming of possible alternatives. The reaction is proven in the laboratory, the stoichiometry is gathered and a rough estimation of the required technology is generated. *None* of the 12 selected ESMs provides assessments for this stage.

Process chemistry (TRL 3–4): several synthesis routes are considered. Small amounts of purified product are obtained and data on the main reaction(s) is collected in laboratory experiments. Three of the selected ESMs are applicable at this stage (Table 1).

Process design (TRL 5–6): the synthesis route is defined and the entire production process is designed at a theoretical commercial-scale level including main reaction and separation steps. The mass and energy balance of the production process including information on process stream composition, pressure and temperature can be obtained. 10 ESMs are applicable at this stage (Table 1). In this development stage, it is also possible to carry out ex-ante LCA using the process design results.

Piloting (TRL 7–8): the process design is used to build a small-scale demonstration facility.

Commercialisation (TRL 9): the production process is in place at full commercial-scale. Real process data and testing for compliance with regulations (i.e., environmental, health and safety data) are available and therefore it is possible to perform a full assessment.

The “x” represents the themes that are included in each of the methods. GtoG: Gate-to-gate: CtoG: Cradle-to-gate. *In this method different indicators are defined for the *process chemistry* and *process design* stages, therefore it is applicable at both design phases.

2.2.4. Implementation of the selected ESMs to the case study of lactic acid for two development stages: process chemistry (TRL 3–4) and process design (TRL 5–6)

2.2.4.1. Lactic acid at process chemistry stage (TRL 3–4). Three of the selected ESMs can provide assessments at the *process chemistry* stage (Table 1, TRL 3–4). They propose semi-qualitative indicators estimated from penalty points. The method of van Aken et al. (2006) assigns penalties based on the reaction yield, safety (including toxicity), technical set-up, reaction temperature and purification. The methods of Patel et al. (2012) and Sugiyama et al. (2008) propose the use of an Energy Loss Index based on data from the reaction and separation section and an Environmental Health and Safety Index based on specific toxicity data. In order to cover the impacts of the supply chain, the methods of Sugiyama et al. (2008) and Patel et al. (2012) use the cumulative energy demand (CED) associated with raw material. As an additional indicator, the method of Patel et al. (2012) includes the GHG emissions of raw material.

The three ESMs at the *process chemistry* stage were implemented for the lactic acid case study using information from earlier literature. Input data include the reaction type and conditions (50°C, pH 6.5) and the reaction yield (95%) (Ghaffar et al., 2014). By-products are qualitatively identified (biomass and gypsum) and a conceptual technical set-up for the separation steps is developed. It should be noted that the information/technology chosen here for lactic acid represents one of the many possible routes being investigated in the *process chemistry* stage.

2.2.4.2. Lactic acid at process design stage (TRL 5–6). 10 of the selected ESMs can provide assessments at the *process design* stage (Table 1, TRL 5–6, definitions of the indicators are in SI.2, Table S2). Energy-related indicators proposed include:

total process energy, used as indicator in two methods (Curzons et al., 2001, 2007),
energy intensity (Schwarz et al., 2002),
energy efficiency (Sheldon and Sanders, 2015),
electricity and natural gas consumption (Tugnoli et al., 2008).

However, it is not specified whether the indicators quantify the final or primary energy. Climate change indicators in the selected ESMs at the *process design* stage are either defined as GHG emissions or using a different term such as “global warming potential” (GWP). All ESMs with a gate-to-gate scope also include emissions associated with energy production, even if it occurs outside process boundaries. Land use indicators included in the methods of Sheldon and Sanders (2015) and Tugnoli et al. (2008) are defined relative to a specific location. No method provides a clear definition for eutrophication-related indicators.

Ecotoxicity is covered in the form of aquatic or terrestrial toxicity. Human toxicity includes toxicity via ingestion, via inhalation and/or carcinogenicity (formulas are in SI.3). Some ESMs use a “restricted substances list” to calculate the toxicity indicators (Schwarz et al., 2002) whereas others use toxicity data, e.g. the substance concentration where 50% of the test species dies (LC50-values) or hazard classifications (Tugnoli et al., 2008; Young and Cabezas, 1999). Other methods use a risk approach combining toxicity data with exposure or fate information (Chen et al., 2002; Tabone et al., 2010). In the method of Schwarz et al. (2002) there is no specific human and ecotoxicity indicator, and one general toxicity indicator is applied.

The methods of Sugiyama et al. (2008) and Tabone et al. (2010) explicitly propose to use a cradle-to-gate ex-ante LCA for the *process design* stage, thus requiring the use of life cycle inventory databases and specific impact assessment methods.

For the estimation of the environmental indicators included in the ESMs at the *process design* stage, a preliminary process design is developed for the production of lactic acid. This preliminary process design is based on publicly available information on raw material pre-treatment, reaction and downstream process (see section 2.3).

For the estimation of the toxicity indicators, only the product itself (i.e. lactic acid) is considered. The ESMs are capable to include the impact of all substances used during lactic acid production, but here only the final product is considered because of the low quality of the toxicity assessment in the ESMs (see section 3.1.2). For the goal of this study, validation of the applicability and adequacy of the methods, assessment on the final product only is sufficient.

2.3. Ex-ante LCA implemented at process design stage. Step 4 of the lactic acid case study

This R&D stage of lactic acid was envisioned by developing a process design based on literature data in which the process steps and conditions are described. Assumptions are made when information is not available (see SI.4). Fig. 3 shows the preliminary process design developed in this study.

The preliminary process design assumes that the sugarcane is cultivated in Brazil because it is the largest producer of sugarcane in the world (FAO, 2017). Energy produced in the sugar mill covers

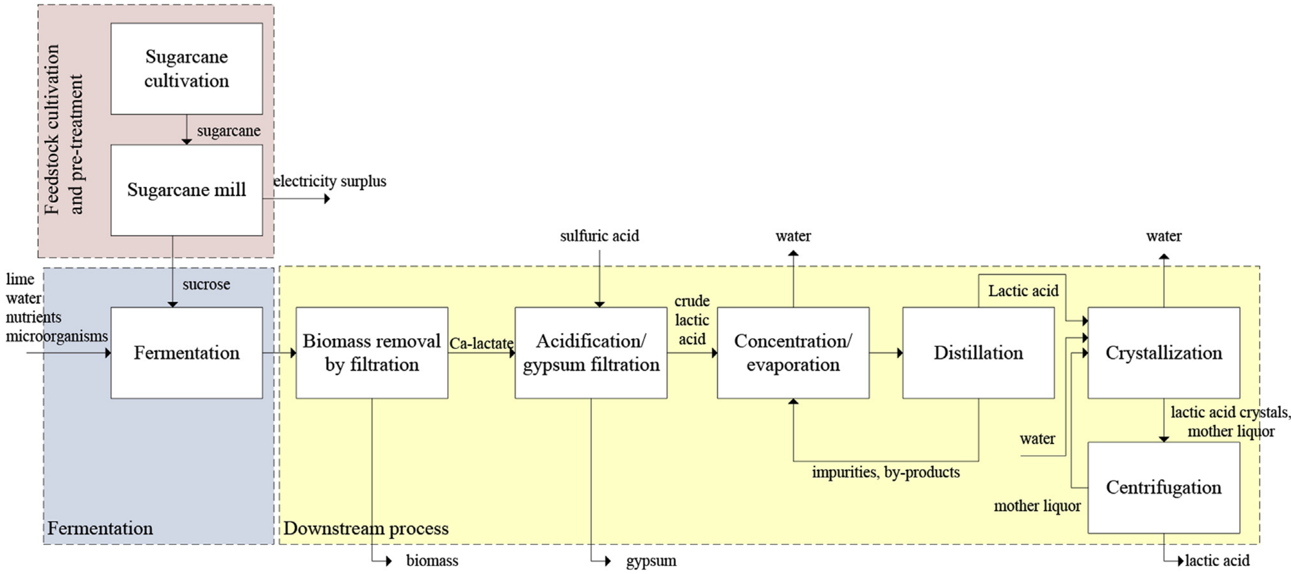


Fig. 3. Preliminary process design of lactic acid production based on published literature and several key assumptions (SI.4), envisioning that the process design occurs today and the present commercial production is unknown. It represents one of the early development possibilities and does not exemplify any specific current technology.

own energy demand at the mill and provides an electricity surplus that can be exported to the grid (Tsiropoulos et al., 2014; de Souza, 2016; Groot and Boren, 2010). Fermentation is modelled based on data reported in Ghaffar et al. (2014), Hofvendahl and Hahn–Hagerdal (2000) and Maślanka et al. (2015). To obtain pure lactic acid, the downstream process includes filtration to remove biomass (cell culture that catalyses the fermentation), acidification, lactic acid concentration prior to low-pressure distillation, adiabatic crystallisation, and centrifugation (Groot et al., 2010). Full details of the process design and a life cycle inventory including mass and energy flows are reported in SI.4. It should be noted that this preliminary process design does not depict any current technology.

The functional unit of the ex-ante LCA is 1 kg of lactic acid and the scope is from cradle-to-gate. System expansion is applied for the electricity surplus at the mill and the by-products. The use and end-of-life phases are excluded because at early R&D stages the final product application is not yet known. Transport of raw materials is not taken into account, which is often included at the later stage.

Table 2 shows the mid-point indicators and assessment methods used to provide an assessment of the selected sustainability themes (section 2.1). Background data of agricultural raw materials are taken from the Agri-footprint 2.0 database (2015). For the rest of the background data, Ecoinvent v3.3 (2016) is used. A list of the background data used is in SI.5.1.

2.4. Full LCA results compared with ESMs and ex-ante LCA results. Steps 5–7 of the lactic acid case study

The full LCA is based on the commercialised process of Corbion's existing 100 kT lactic acid plant located in Thailand (internal study from industry, confidential). The functional unit, databases and characterisation models are the same as used in the ex-ante LCA (section 2.3, Table 2). A flow diagram of the commercial production and background data used are in SI.5.2. Inevitably, ESMs, ex-ante LCA and full LCAs use different indicators, scopes, sources of data, and differ in a number of input parameters:

The ESMs and the ex-ante LCA are based on literature. The full LCA is based on the commercial production data

The preliminary process design resembles an R&D stage where little or no optimisation is made in relation to energy integration and technology choice. The commercialised production is highly optimised

The preliminary process design assumes that the sugarcane cultivation and lactic acid production both take place in Brazil because it is the largest producer of sugarcane in the world. In reality, the commercial plant location and sugarcane sourcing is in Thailand.

Therefore, comparisons between the ESMs, ex-ante and full LCAs thus should not be interpreted for the absolute differences. The focus of this retrospective study is rather on understanding the

Table 2
Mid-point indicators and characterisation models used in the ex-ante and full LCAs.

Mid-point indicator	Method	Source	Indicator
Cumulative energy demand (CED)	Cumulative energy demand v1.09	Frischknecht et al., 2007	MJ
Global warming potential (GWP)	IPCC 2013 GWP 100a	IPCC, 2013	kg CO_2 eq
Freshwater eutrophication (EU)	ILCD 2011 Midpoint+, Goedkoop et al. (2009)	Struijs et al. (2009)	kg P eq
Land use (LU) (urban + agricultural)	ReCiPe midpoint (H) v1.13	Goedkoop et al. (2009)	m^2a
Human toxicity cancer (HTc)	USEtox v1.04 (recommended + interim)	Rosenbaum et al. (2008)	CTUh
Human toxicity non-cancer (HT)	USEtox v1.04 (recommended + interim)	Rosenbaum et al. (2008)	CTUh
Freshwater ecotoxicity (ET)	USEtox v1.04 (recommended + interim)	Rosenbaum et al. (2008)	CTUe

a: area; CTUh: Comparative Toxic Unit for Human Health; CTUe: Comparative Toxic Unit for ecosystems; eq: equivalent.

evolution of impacts during the technology development of a new (bio-based) chemical and whether the trends can be predicted in the early development stages.

3. Results and discussion

3.1. Implementation of the selected ESMs. Step 3 of the lactic acid case study

A highlight of the results of the implementation of the ESMs is presented in the following sections (full details are in SI.2). The results are divided in environmental themes (3.1.1) and toxicity themes (3.1.2).

3.1.1. Environmental themes

The three ESMs implemented at the *process chemistry* stage (TRL 3–4, Table 1, complete results in SI.2.1-SI.2.3) use reaction and separation information from laboratory experiments. Following the method of van Aken et al. (2006) for the synthesis of lactic acid, two parameters receive the highest penalty points: reaction yield and purification efficiency. Four important aspects contributing to the Energy Loss Index defined by Sugiyama et al. (2008) and Patel et al. (2012) are identified: water presence at the reactor outlet, product concentration, mass loss and reaction energy. Additionally, the Energy Loss Index defined by Patel et al. (2012) takes into account whether a pre-treatment is required, which also is an important contributor in the lactic acid case study.

All three ESMs are intuitive, easy, and straightforward to use. These methods are semi-quantitative and intended for screening/comparative assessment of alternative synthesis routes of a novel chemical when they are being tested at the laboratory (TRL 3–4).

More detailed quantitative assessments are feasible when a process design is carried out. Although 10 of the selected ESMs can provide assessments at the *process design* stage (TRL 5–6, Table 1), the implementation of seven ESMs is here discussed. The methods of Sugiyama et al. (2008) and Tabone et al. (2010) follow a cradle-to-gate ex-ante LCA approach for the *process design* stage and therefore their results are discussed in section 3.2. The method of Curzons et al. (2007) is not applicable for this case study because it is designed for relative sustainability. Thus, at least two chemicals or alternative routes are required for its implementation.

Four of the seven ESMs here discussed include energy indicators (Table 1). In spite of using different definitions for the energy indicators, all four ESMs identify the process energy required in the concentration/evaporation step as the key contributor. The energy use in this concentration step accounts for 90% of the "total process energy" (Curzons et al., 2001, SI.2.5), and is a key contributor for the observed low "energy efficiency" (Sheldon and Sanders, 2015, SI.2.8), the high "energy intensity" (Schwarz et al., 2002, SI.2.7) and the high "natural gas consumption" (Tugnoli et al., 2008, SI.2.10).

Six out of the seven ESMs here discussed include a climate change indicator (Table 1). The energy needed in the concentration/evaporation step also dominates the climate change-related indicators in all the implemented methods, except in the method of Voss et al. (2009)(SI.2.11). This method assigns a credit to the biogenic CO_2 uptake. The cradle-to-gate indicator is therefore dominated by feedstock contribution and not by the process energy contribution as in the gate-to-gate indicators.

Land use assessment could not be carried out because the two methods that propose this indicator provide vague definitions and there is also insufficient data available (SI.2.8, SI.2.10, Table S2). For example, it is not possible to reproduce the information on "good agricultural soil" in France needed to grow the biomass required (Sheldon and Sanders, 2015), neither on the area that is occupied by "similar facilities" than the one of our lactic acid process design (Tugnoli et al., 2008).

It is also not possible to implement the assessment for eutrophication based on the selected ESMs (SI.2.7, SI.2.10, Table S2). The method of Schwarz et al. (2002) requires the identification of the process wastewater, which consists of mainly water removed in the concentration/evaporation step (Fig. 3). This wastewater stream barely contributes to eutrophication impact. Eutrophication in the method of Tugnoli et al. (2008) requires impact potentials derived from the literature (Pennington et al., 2000) but no further details are available on exemplifying the method neither on the background data required.

To summarise, the ESMs implemented at the *process design* stage have a good coverage of climate change and energy themes and also point to the same conclusions for these themes (i.e. process energy dominates both impacts). However, only two methods include biomass production and pre-treatment (Sheldon and Sanders, 2015; Voss et al., 2009). The important aspects for bio-based chemicals occurring in the agriculture phase, like eutrophication and land use are mostly excluded or poorly covered and therefore the relevance of the majority of the methods for the assessment of bio-based chemicals is questioned.

In terms of implementation experience, not all methods for the *process design* phase are straightforward. In some cases, assumptions are required because the descriptions of the indicators provided are not clear. For instance, gate-to-gate electricity and natural gas consumption are directly taken from the preliminary process design because no details on how to calculate these indicators are provided in the method of Tugnoli et al. (2008)(SI.2.10).

3.1.2. Toxicity themes

For most methods an extensive user-guide is provided and most of the toxicity indicators can be calculated (meaning that an outcome could be obtained; full results in SI.2). Two of the ESMs were not clear in the description of crucial aspects (Tugnoli et al., 2008; Chen et al., 2002). Without this specific information the models could not be conducted as intended and the methodologies are not repeatable.

Based on the numerical outcomes of the ecotoxicity and human toxicity indicators, it is concluded that the different indicators cannot be compared to each other. For instance, it cannot be concluded that substance 'A' has a higher concern for ecotoxicity than for human toxicity. The ESMs are better suited to compare similar indicators for different substances.

Although it was possible to apply most of the methods, the relevance of the indicators is questioned because several essential aspects were missing in these indicators. The main concerns include the focus on acute toxicity only, the coverage of a too small range of endpoints/species, or the request of information that is not available at early-stages or is too general to draw conclusions on. In more detail:

Three of the ESMs (Chen et al., 2002; Tugnoli et al., 2008; Young and Cabezas, 1999; SI.2.4; SI.2.10; SI.2.12) consider acute toxicity values only and do not include long-term (chronic) toxicity. A single acute exposure to a substance may be a good estimate for a particular situation e.g., when a substance disappears fast due to high degradation or metabolisation rates. However, when this is not the case, or when frequent exposure is expected, chronic experiments are considered to provide better estimates for toxicity. Chronic effect concentrations are usually lower than acute effect concentrations. This difference, calculated as the ratio between acute and chronic toxicity, can vary considerably between different substances, ranging from 1 to above 4000 (ECHA, 2017a; Ahlers et al., 2006). If available, it is therefore preferred to not only use acute toxicity data, but also use chronic

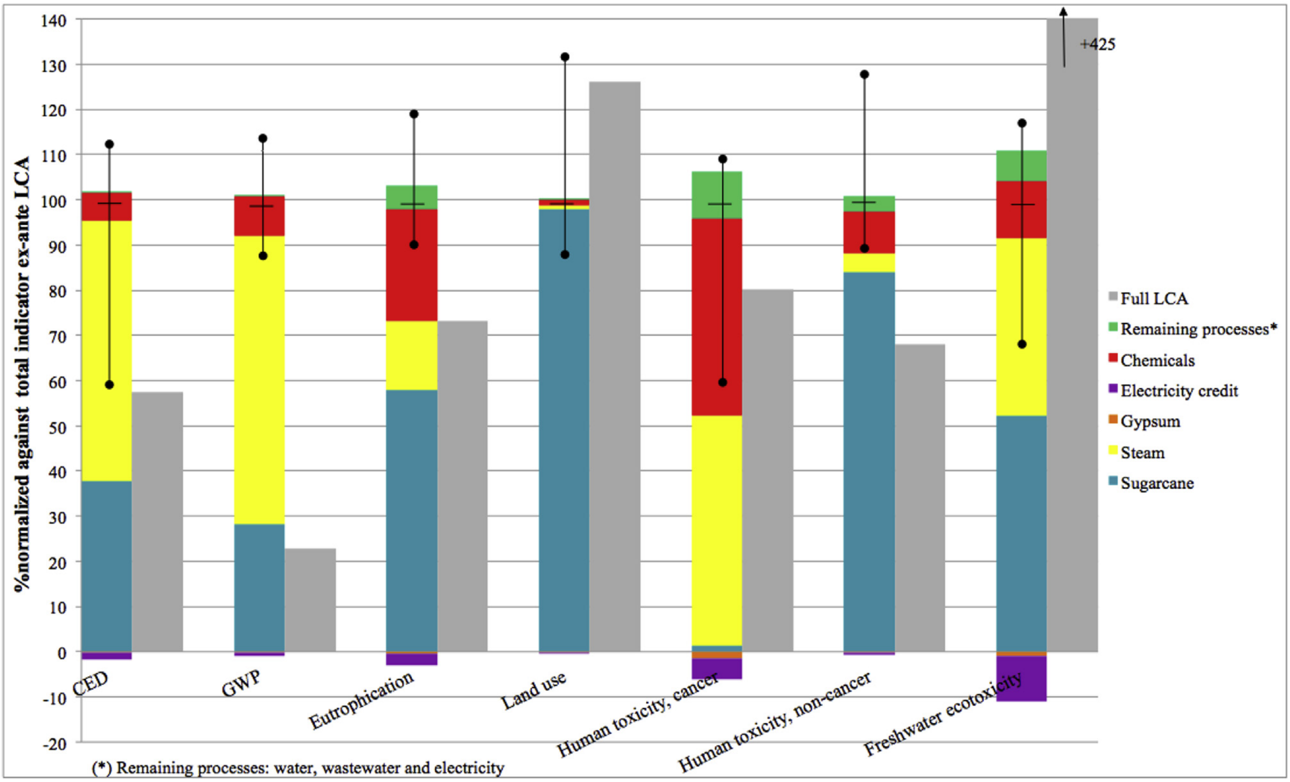


Fig. 4. Comparing cradle-to-gate environmental impacts of 1 kg of lactic acid: ex-ante LCA vs. full LCA. Lines show variation obtained from sensitivity analyses (SI.5.4).

toxicity data. These can be found for instance in the databases of ECHA (2017b) and US-EPA (2017a).

Several ESMs only consider toxicity data of one specific species, like fish toxicity data for ecotoxicity or rat toxicity data for human toxicity (Chen et al., 2002; Young and Cabezas, 1999; SI.2.4, SI.2.12), thereby ignoring species-specific differences in toxicity (e.g. invertebrates, algae, mammals)(ECHA, 2017a; Ramos et al., 2002). For standardisation and taking care that a sensitive species for the endpoint under study is used, the species to be used is prescribed in risk assessment protocols. Ideally, data on different species of different trophic levels should be used for toxicity assessment in ESMs.

Some suggested toxicity indicators are not very distinctive. For instance, the toxicity indicator as described in the method of Schwarz et al. (2002)(SI.2.7) only provides values to substances that are listed on the US Toxic Chemical Release Inventory (US-EPA, 2017b) or to substances that are marked as a criteria pollutant in the Clean Air act list (US-EPA, 2017c). Additionally, some toxicity indicators require data from tests that are normally not performed in an early-stage. An example would be the Cancer potency Slope Factors used by Tugnoli et al. (2008)(SI.2.10) which is only available for relatively few substances.[1] This type of parameters is unknown for many substances, making this ESM less applicable. In general, lack of toxicity data is especially true for new designed substances for which only limited toxicity data is available yet. On the contrary, for existing substances that are applied in new applications a lot of toxicity data may be available.

Based on these aspects, it is considered that none of the investigated ESMs covers toxicity sufficiently neither provides a reasonable estimate and comparison of the toxicity potential. Several suggestions to cope with these limitations are proposed in section 3.4.1.

3.2. Results of the ex-ante LCA (TRL 5–6) and comparison with the full LCA (TRL 9). Steps 4–6 of the lactic acid case study

3.2.1. Results of the ex-ante LCA vs. the full LCA

The results of the ex-ante LCA based on process design are shown in Fig. 4 and compared with the results of the full LCA based on the commercialised production. No detailed numerical breakdown of the full LCA results is disclosed due to data confidentiality.

Fig. 4 shows that all impact categories evaluated have a lower value for the full LCA than for the ex-ante LCA, except for land use and freshwater ecotoxicity. Based on the results of the ex-ante LCA, three main contributors to the impacts of lactic acid are identified: production of chemicals, process energy, and sugarcane production.

The contribution of chemicals is similar in both LCAs. The amount of chemicals used is not subject to major changes due to process optimisation, neither the impacts of these commodity chemicals are significantly location-dependent. Thus, the impacts associated with the production of chemicals are well captured by the ex-ante LCA.

The contribution of process energy (mainly steam) is considerably larger in the ex-ante LCA due to a non-optimised process design. This causes higher CED, GWP and HTc in the ex-ante LCA than in the full LCA. In a sensitivity analysis, an ex-ante LCA is carried out based on an improved design assuming higher fermentation concentration and that heat integration is

[1] The cancer slope factor is an estimate of the probability that an individual will develop cancer if exposed to a chemical for a lifetime.

implemented (SI.5.4). Lower amounts of steam are consumed (−70%), and therefore CED, GWP and HTc decrease by 41%, 11% and 41%, respectively (negative variability lines in Fig. 4).

Sugarcane cultivation is also an important hotspot identified by the ex-ante LCA. The preliminary process design assumes that sugarcane cultivation takes place in Brazil and the ex-ante LCA uses data obtained from background database (not primary data) (2.3 and SI.5.1). However, in the commercialised process sugarcane sourcing is in Thailand and more site-specific foreground data is used in the full LCA (section 2.4 and SI.5.2). Thai and Brazilian sugarcane have different sucrose content, and different types and quantities of fertilisers, herbicides and pesticides are used during their cultivation. As a consequence, the most important differences between the ex-ante and full LCAs are found in the sugarcane contribution:

Sugarcane contribution to the total CED is slightly higher in the full LCA than in the ex-ante LCA. More sugarcane is needed per kg of lactic acid produced in Thailand due to lower sucrose content in Thai sugarcane than in Brazilian sugarcane. The influence of sucrose content to the CED of the ex-ante LCA is investigated in the sensitivity analysis (SI.5.3). 25% lower sucrose content in the biomass leads to 13% higher CED relative to the baseline analysis, represented by the upper bound of the variability line in Fig. 4.

For GWP, sugarcane production is the second main difference (after process energy) between both studies. The large difference is caused by direct land use change, which accounts for 74% of the GWP of Brazilian sugarcane and it is negligible for Thai sugarcane.

The discrepancies between eutrophication and HT in both studies are due to different types and quantities of fertilizers, herbicides and pesticides used during sugarcane cultivation in Brazil and Thailand (SI.5.3).

Contrary to the majority of the indicators, land use is higher for the full LCA (+26%) than for the ex-ante study. Although Thailand and Brazil have similar cultivation yields, the difference lies in the sucrose content in the sugarcane from each country. The results of the sensitivity analysis (SI.5.3) indicate that 25% lower sucrose content in Brazilian biomass increases land use by 33%, and 12% higher sucrose content in the biomass reduces land use by 10%, relative to the baseline assumptions (represented by the variability lines in Fig. 4).

The value of ET in the full LCA substantially surpass (+425%) the ET value estimated in the ex-ante LCA. ET of sugarcane from Thailand is substantially higher than sugarcane from Brazil because of different types of pesticide applied which lead to direct emissions to the soil and water.

A detailed analysis of the rest of differences between the ex-ante and full LCAs per indicator is in SI.5.3.

The comparison between the results of the ex-ante and full LCAs illustrates that biomass type and sourcing play a key role in the impacts of bio-based lactic acid. The characteristics and cultivation practices of biomass are determined by the location where it grows. Knowing exactly the type of feedstock can be decisive when determining the sustainability profile of a new bio-based chemical but this knowledge will mostly not be available in the design phase.

It can thus be concluded that ex-ante LCA is a useful tool for hotspot analysis, but cannot precisely predict the impacts of the process at commercial-scale, because at this stage it is usually unknown where a potential commercial plant will be located. As such it can provide an indication for improvement and optimisation during the design stages.

3.2.2. Discussion: uncertainties in toxicity impacts

The USEtox-model (2017) is used in the ex-ante LCA and full LCA to estimate the potential toxicity impacts (Table 2). The model is recommended by the International Reference Life Cycle Data System (ILCD)(European commission, 2012) as well as The European Commission's Product Environmental Footprint (Manfredi et al., 2012). The USEtox model makes a distinction between recommended and interim characterisation factors, reflecting different robustness of background data (Rosenbaum et al., 2008; USEtox 2.0, 2017). Interim characterisation factors are temporary and intended to be used or accepted until something permanent exists. They result in high uncertainty and therefore their impact scores need to be interpreted with caution (Rosenbaum et al., 2008; USEtox 2.0, 2017).

The emissions of metals to soil from the fertilisers applied in sugarcane cultivation in the lactic acid case study are characterised only by interim characterisation factors. Therefore the USEtox "recommended + interim" model is used in the baseline of both LCAs (Table 2 and section 3.2.1). In a sensitivity analysis, only the recommended characterisation factors were used. The results of this sensitivity analysis are 70–100% lower in all toxicity categories relative to the baseline results. This indicates that there are large uncertainties in the estimation of toxicity aspects in both the ex-ante and full LCAs. It cannot be correctly answered which option is better, because "interim" does not satisfy all conditions for the determination of characterisation factors but probably toxicity is underestimated when only including "recommended" characterisation factors.

3.3. Comparison of the ESMs vs. ex-ante LCA vs. full LCA

Table 3 shows a comparative evaluation of the assessment methods included in the lactic acid case study. The evaluation considers the applicability and predictive power of the ESMs and ex-ante LCA, and the adequacy of the results in general.

Results from the ESMs and ex-ante LCA indicate that a lion's share of the energy demand and the associated carbon emissions in lactic acid production are caused by the downstream evaporation step. Next to CED and GWP, process energy in the evaporation step is also identified by the ex-ante LCA as the main contributor to the cradle-to-gate HTc impact.

Table 3
Comparing the assessment methods included in the lactic acid case study.

Type of assessment (TRL)	Environmental themes				Toxicity themes	
	energy	climate change	eutrophication	land use	human toxicity	ecotoxicity
ESMs (1–2)	No methods available					
ESMs (3–4)	+	+	No methods available		–	–
ESMs (5–6)	++	++	–	–	–	–
ex-ante LCA (5–8)	+++	+++	+++	++	–	–
full LCA (9)	+++	+++	+++	+++	–	–

Very good (+++) > Good (++) > fair (+) > poor (–) > very poor (—).

However, process energy is not identified as the most important contributor to the impacts based on the full LCA for two reasons: 1) highly optimised process energy in the commercial process; 2) sugarcane cultivation dominates many of the non-energy related impacts studied (EU, LU, HT, ET). This shows that the selected ESMs are useful to pinpoint relevant optimisation steps in the process design for later development stages. However, the lack of an assessment of biomass feedstock production can be a crucial drawback for the implementation of the studied ESMs to bio-based chemicals.

The type of feedstock, cultivation phase and location are key factors for the sustainability aspects of bio-based chemicals, as demonstrated by comparing the ex-ante LCA results against the full LCA results (section 3.2.1). The lactic acid case study shows that ex-ante LCA implemented at the *process design* phase can already identify environmental hotspots, although the variability in of ex-ante LCA should be carefully interpreted (variability lines in Fig. 4).

The toxicity indicators in the ESMs have a different scope (end product only) than the ex-ante and the full LCAs (cradle-to-gate toxicity impacts). Hence, it is not possible to compare the results of the toxicity impacts of the ESMs with those of the LCAs. It should be highlighted that the toxicity indicators in the ESMs are crude and not accurate. This emphasises that for early-stage assessment, it is urgent to improve the toxicity assessment of the product itself. In the next section suggestions to deal with these deficiencies are provided. Nonetheless, it should be borne in mind that the toxicity indicators in LCA also have latitude for improvement (section 3.2.2).

3.4. Recommendations

To address the challenge of developing new bio-based chemicals that are safe and sustainable by design, it is proposed to follow an iterative approach. Different methods are suitable for the different R&D stages, in concordance with the information available and freedom to make changes (Fig. 1). This was very well presented by Sugiyama et al. (2008), who defined different indicators for several development phases. The outcomes of the assessments carried out at each stage should be incorporated as inputs for the next development process, allowing for flexible re-design.

Comprehensive calculations at TRL <4 are not practical due to lack of data and because any new technology will experience important variations during its scale-up. Assessments should aid in the selection of the most promising ideas and synthesis routes for further development. The use of simple qualitative scoring systems or up-to-date background data that can be directly used for quick screening is therefore recommended. The method of Patel et al. (2012), which also covers the impacts of the supply chain and pretreatment, was found the most adequate at this stage. However, meaningful integration of toxicity aspects in the ESMs is still lacking. An alternative approach is presented in the next subsection.

More detailed quantitative assessments are recommended starting at TRL 5–6, when a conceptual process design and mass and heat balances of the entire production plant can be estimated. Given the amount of information available at this stage, the use of ex-ante LCA is recommended. The inherent uncertainties in ex-ante LCA results exist because it is applied to an immature technology, subject to variations through the R&D phases. However, the lactic acid case study has shown the predictive power of ex-ante LCA when estimating the environmental impacts of introducing a future technology. A cradle-to-gate scope including biomass cultivation should be implemented, especially important in the case of bio-based chemicals. As the impacts from the agricultural phase can have a large share and be very location-specific, considering the location of the manufacturing site as a strategic choice during the design procedure and as part of the sensitivity assessments of the ex-ante LCA results is recommended.

It needs to be mentioned that the toxicity impact assessment methodology in LCA (ex-ante and full) in general is still under development, limited by the uncertainty in certain groups of chemicals in the USEtox model (2017) (section 3.2.2). Currently, there is no official link between the large amount of data that is used for substance registrations within Europe (via the Registration, Evaluation, Authorisation and Restriction of Chemicals, REACH regulation, 2006) and the data used in USEtox. As a consequence, the characterisation factors might be improved when using the large amount of REACH-data if that can be made available (RIVM, 2017).

3.4.1. Recommendations of toxicity assessments in the ESMs

Regarding the limitations of the assessment of toxicity aspects in the ESMs highlighted in the lactic acid case study, it could be argued whether it is more appropriate to only focus on the most critical and essential toxicity aspects at early-stages. Within Europe, legislation (e.g. REACH) gives highest priority to substances with carcinogenic, mutagenic or reprotoxic properties (CMR), substances with persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) properties and substances with an equivalent level of concern (e.g. endocrine disruptors (ED) and sensitisers)(REACH, 2006; Schuur and Traas, 2011; United Nations, 2017). When using a comparative approach excluding substances with a low toxicity potential in general, but a relatively high toxicity compared to an alternative substance should be avoided. To illustrate: when ‘substance A’ has a toxicity on a specific endpoint of 1000 mg/kg and ‘substance B’ of 2000 mg/kg, ‘substance A’ could be judged as two times as toxic to ‘substance B’; However, as both substances have a low toxicity potential, one could decide to not make judgments based on this indicator. Similar to the toxicity classes used for classification, labelling and packaging of substances (GHS and CLP)(ECHA, 2017c; US-EPA, 1994), substances could be divided into low, medium, and high toxicity groups.

Besides focusing on CMR and PBT/vPvB properties, other specific endpoints may be considered as appropriate toxicity indicator when focusing on a specific use application. For instance, when focusing on substances for cleaning activities, irritation effects may be considered as an appropriate endpoint as well. However, in many cases the type of application may not be known at the early development stage yet. In these cases, focusing on the most critical endpoints at the early-stage is considered most appropriate.

For the CMR and ED endpoints, a similar approach may be applied as developed by the US-EPA for carcinogenicity (ECHA, 2017d). Within this method, a hazard value is provided ranging from 0 (not carcinogenic) to 5 (carcinogenic in humans). Substance classifications are considered to provide a carcinogenicity score and, when not available, quantitative structure-activity relationship (QSAR) estimations are used. Such method is also suitable for early-stage, as it makes use of estimations (QSAR data) when no classification is available based on experimental data. A similar method may also be applied for mutagenicity, reprotoxicity and/or endocrine disrupting properties. This approach on carcinogenicity is also incorporated in the ESM of Chen et al. (2002).

Another approach to improve the toxicity assessment is depicted using PBT/vPvB endpoints as an example. An adjustment of the PBT/vPvB prioritisation scheme as presented by Schuur and Traas (2011) may be useful (Fig. 5 shows an example). Within this priority scheme, the highest priority (priority 1) would indicate a high hazard and could mean no further development. Within such an approach, either experimental or estimated data could be used. Further, by comparing to certain criteria, it could be ensured that at early-stage no substances are excluded with a low toxicity potential, but with a relatively high toxicity compared to another substance.

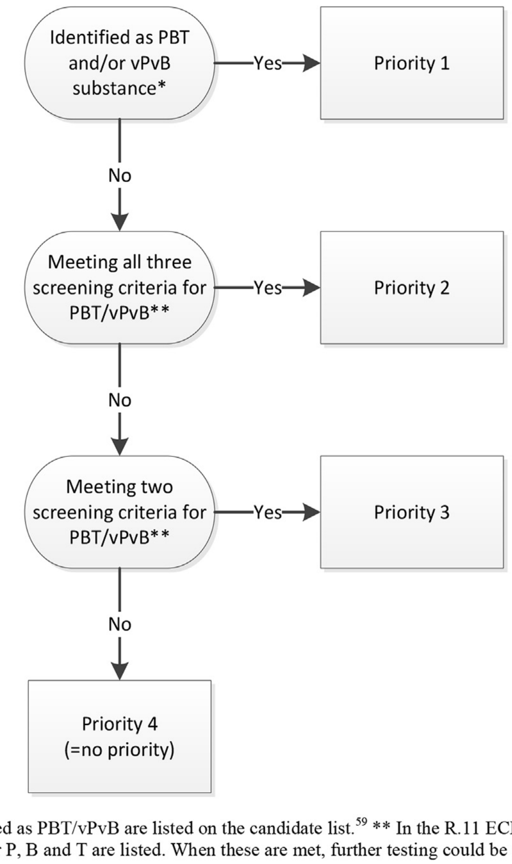


Fig. 5. Adjustment of the environmental hazard prioritisation scheme presented by Schuur and Traas (2011). A similar kind of adjustment may be applicable for early-stage toxicity screening.
* Substances that are identified as PBT/vPvB are listed on the candidate list.59 ** In the R.11 ECHA (2017e) guidance document, screening criteria for P, B and T are listed. When these are met, further testing could be considered appropriate.

4. Conclusions

This study concludes that there is a lack of methods available to assess a new technology in the *concept proven* stage (TRL 1–2) and *process chemistry* stage (TRL 3–4), which calls for more research in developing qualitative tools or more up-to-date background data that can be directly used for quick screening. At the *process design* stage (TRL 5–6), the studied ESMs are able to point to the right environmental hotspots of process energy and climate change but potential environmental impacts associated with agricultural production, such as land use and eutrophication are often overlooked.

It is also concluded that the selected ESMs show a number of limitations that hinder their application: 1) they are often not clear in the definitions of the environmental and toxicity indicators; neither transparent in background data sources nor these are up-to-date; 2) since most ESMs are designed to assess chemicals in general (not specifically for bio-based), most of them propose narrow life cycle scopes, including only the production process and excluding the feedstock production stage. Moreover, the relevant environmental themes reflecting the characteristics of bio-based chemicals are often missing; 3) in terms of toxicity impacts, the reviewed ESMs are often crude and not accurate in the coverage of toxicity aspects.

To improve the toxicity assessment in the ESMs, it is suggested to mainly focus on the most critical and essential toxicity aspects at early-stages (including CMR and PBT properties). For this purpose, experimental and/or estimated data could be used to prioritise concerns. Following this approach, substances with low toxicity potential are not excluded at early-stage, but those with a relatively high toxicity compared to another substance.

Starting at TRL 5–6, ex-ante LCA can provide a good prediction of the hotspots in new production processes of chemicals. In the lactic acid case study, ex-ante LCA successfully identified the environmental hotspots of process energy and biomass feedstock production. However, LCA should be complemented with accessible data to evaluate the potential toxicity impacts at early-stages to ensure *safe and sustainable by design*. The assessment of toxicity impacts of novel (bio-based) chemicals during the early R&D stages is a challenging task, and deserves future research efforts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclepro.2019.05.115.

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