Green Chemistry

CRITICAL REVIEW

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From qualitative analysis to quantitative insights: a systematic review of early phase sustainability assessments of chemical processes

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Sustainability assessment from the beginning of the process design phase is crucial to ensure the development of a sustainable chemical process. Hence, a myriad of different methods for sustainability assessment of chemical process designs are reported in the literature. These methods differ significantly in terms of the sustainability dimensions they cover, their applicability in different phases of process design, their methodological approach and data needs. While there are several reviews existing on this topic, there is a lack of reviews focusing on sustainability assessment methods for chemical process design applicable in the early stages. Therefore, we perform a systematic literature review focusing exclusively on early-phase sustainability assessment methods. For this purpose, we use a mixed-method approach combining qualitative analysis and quantitative bibliometric analysis. From the complete literature dataset (n = 565), the analysis uncovered a diverse array of 53 methods well-suited for early-phase sustainability assessment of chemical processes. Through qualitative analysis, the reviewed literature was organised into distinct categories, including assessment methods, decision-making procedures and result characteristics. Additionally, quantitative analysis *via* bibliometric techniques revealed five distinct research clusters and several trends within the field, highlighting areas for potential future exploration. As a synthesis of the review, we visualised and structured the identified assessment tools in a sustainability target graphic and developed a decision tree to support the identification of an appropriate sustainability assessment method. With this review, we aim to offer a comprehensive and informative overview and guidance for researchers seeking to assess the sustainability of chemical processes during the early design phase.

Green foundation

1. This study reviews and analyses various methods for conducting early-phase sustainability assessments of chemical processes, encompassing elements of green and sustainable chemistry, using both qualitative and quantitative approaches.
2. As most of the sustainability impacts of a chemical process are determined in the early stages of process development, it is imperative to integrate sustainability assessment into the initial phases of chemical process design. Our review specifically focuses on sustainability assessment methods applicable during the early design phase of chemical processes.
3. Our review seeks to provide researchers with a comprehensive overview of the available methods for early-phase sustainability assessment of chemical processes, along with guidance for selecting the most appropriate tools. Future studies should focus on addressing data uncertainty, enhancing social sustainability, and integrating the concepts of circularity and absolute sustainability.

1. Introduction

The pursuit of sustainability has become a pressing global concern, affecting various sectors, including production,[1] mobility[2] and consumerism.[3] The chemical industry, as a significant consumer of resources and energy, contributes substantially to worldwide carbon emissions.[4] In response, industry and academia are reevaluating traditional operational models, striving for more sustainable chemical product and process design.[5] This shift has led to an extensive body of research aimed at developing assessment methods to guide

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early-phase process design toward environmental, economic and social sustainability. The integration of sustainability considerations at every stage of the development process is fundamental to sustainable chemical process design. It is widely recognised that a chemical's sustainability impacts are largely determined during the early phases of process development.[6] Consequently, despite the challenges associated with data availability and quality during early process design, conducting sustainability assessments during the research and development phase is essential for achieving a sustainable process.

Certainly, the 12 principles of green chemistry, as outlined by Anastas and Warner in 1998,[7] have significantly influenced the discipline of sustainable chemical process design. These principles centre on redesigning chemical products and processes to minimise or eliminate the use and generation of hazardous substances, aiming to achieve sustainability at a molecular level. The impact of the green chemistry approach extends across various industries, including pharmaceuticals, cosmetics and agriculture,[8,9] addressing all stages of the chemical life cycle and emphasising the reduction of inherent hazards in products and processes, with potential economic benefits.[8] Numerous metrics have been developed to assess the sustainability of processes in the context of green chemistry. For instance, Calvo-Flores[10] reviewed key parameters for analysing chemical reactions and processes, including material and energy efficiency metrics like the *E*-factor, atom economy and process mass intensity. The translation of principles into user-friendly green chemistry metrics has facilitated the increased consideration of sustainability during the development of new reactions and processes. However, to achieve a comprehensive, multidimensional sustainability assessment, it is essential to integrate green chemistry metrics with other tools and methodologies such as life cycle assessment (LCA), toxicity assessments and broader sustainability indicators.[11]

When our research group sought to conduct an early-phase sustainability assessment of a newly developed lab process in the past, it was overwhelmed by the multitude of methods documented in the literature. Despite the abundance of reviews on sustainability assessment for chemical processes, a lack of focus on those relevant to the early development phase was found. Hence, to complement existing reviews on sustainability assessment of chemical processes, this study focuses on assessment methods relevant to the initial stages of chemical process design. The primary aim was to gain insight into appropriate methods, compare their distinguishing features, and identify their respective opportunities and limitations. The research was guided by three key questions:

RQ1: Which sustainability assessment methods are suitable for early-phase chemical process design?

RQ2: Which categories can be used for comparing sustainability assessment methods for early-stage chemical process design and how do they differ?

RQ3: What are trends and topics in the field of early-phase sustainability assessment and which sustainability indicators are frequently considered?

To address these research questions, the review is structured as follows: section 2 provides an overview of existing reviews on early-stage sustainability assessment of chemical processes. In section 3, the principles of the qualitative analysis and bibliometric methods for document and conceptual structure analysis are detailed, including factorial analysis and thematic mapping. Section 4 presents the research results, focusing on the analysis of themes and clusters in early-stage sustainability assessment research, with an emphasis on sustainability dimension coverage, indicator usage, data requirements, handling of data limitations and uncertainty and overall methodological approach. In this study, classical bibliographic analysis such as (co-)citation analysis, co-author analysis and bibliographic coupling was not performed, as it was

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not considered relevant for answering the research questions. The key findings of the analysis and answers to the research questions formulated are presented in section 5, while section 6 encompasses conclusions, final remarks and limitations.

2. Overview and delimitation with respect to previous reviews on that topic

Upon reviewing the literature thematising early-stage sustainability assessments of chemical processes, we noticed that the interpretation of "early-stage assessment" varied among authors and considered different phases of process development. We define early-phase sustainability assessment as encompassing chemical route selection, which involves evaluating chemical pathways, stoichiometry, yield and related factors, and process synthesis, where multiple potential solutions are generated and screened to identify a small set of promising options.[6] These solutions are then assessed in greater detail based on criteria such as product yields, energy efficiency, raw material consumption and environmental impact. In the literature, this early design phase is also referred to as the "process chemistry" phase.[12,13] When considering "technology readiness levels", our focus is on the "applied research phase" (TRL 1–4), which involves modifying inherent natural phenomena to achieve specific outcomes.[14] In our understanding, early assessment is clearly distinct from conceptual design, which involves developing process flow diagrams (PFDs), determining the required equipment, defining process conditions and identifying key unit operations.[6]

Existing reviews on sustainability assessments of (chemical) processes address a variety of critical aspects, not focusing on early process design but covering different stages of development. The references provided below are illustrative rather than exhaustive. The inherent properties of chemical materials and processes, such as safety[15–17] or occupational health hazards,[18] are frequently discussed but environmental sustainability and particularly green chemistry[11,19–23] are also topics of great interest. Apart from that, several reviews give an overview of different sustainability assessment tools available for different phases of process design.[24–27] Additionally, selected literature reports delve into sustainable manufacturing,[28] the comprehensive concept of sustainable development,[29] comparative analyses between early phase assessment and LCA,[30] the application of multi-criteria decision analysis methods[31] and the sustainability of flow and microreaction technology.[32]

From published reviews it becomes clear that achieving sustainability is a complex challenge that cannot be addressed by individuals or countries alone; it requires collective effort and teamwork. In this respect, the Joint Research Centre (JRC) of the European Commission approached the assessment of sustainability in chemical processes in different ways; these are outlined in more detail in the following. Firstly, the EU's safe and sustainable by design (SSbD) concept[33] brought early-phase sustainability assessment into focus, emphasising the need to evaluate the sustainability of chemical processes from the very beginning. As part of this concept, a general five-step methodological framework was proposed, which could be adapted to specific cases as needed.[34] Before developing the concept, a literature review was conducted.[35] This search identified 119 relevant documents, covering (i) sustainability dimensions and aspects considered in various frameworks, (ii) assessment methods, models and tools, (iii) indicators (both quantitative and qualitative) and (iv) evaluation procedures, including scoring systems.[35] While this review provided insights into sustainability assessments at different stages of chemical process design, it did not specifically focus on early-phase assessment. Secondly, in 2024 Caldeira *et al.*, the same lead author behind the SSbD concept, published a review on sustainability assessment frameworks for safe and sustainable chemicals and materials.[36] This review analysed the application of such frameworks in the early stages of chemical process design, with a search focused on "solvent selection", "life cycle" considerations and "multicriteria assessment". While their work highlighted tools relevant to early-phase assessments, their definition of "early phase" appeared to be broader than ours, as it included the conceptual design stage. In contrast, we focus specifically on "chemical route selection" and "process synthesis". Consequently, our review serves as an extension to Caldeira *et al.*'s work[36] and provides a detailed analysis of early sustainability assessment methods. Our focus is on evaluating process sustainability primarily using laboratory and theoretical data rather than (pilot) plant data. We conduct a thorough examination of the available tools and application examples from a sustainability standpoint, which also includes bibliometric analysis. In contrast to Caldeira *et al.*,[36] we have chosen to omit solvent selection guides, as these have been thoroughly examined and published elsewhere.[37–39] While

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acknowledging the undeniable significance of solvent selection in sustainable process design, our focus is directed towards analysing more comprehensive assessment approaches that encompass various design parameters.

3. Methods

For this systematic review focusing on the early-stage sustainability assessment of chemical processes, the review procedure adheres to the PRISMA 2020 statement[40] and utilises various tools from the field of science mapping analysis. Subsequent sections provide detailed explanations regarding the literature search process as well as data collection, cleaning and analysis procedures.

3.1. Data sampling, collection and cleaning

In this section, we outline the inclusion and exclusion criteria for literature selection, followed by a detailed description of the literature search process itself. First and foremost, we focused on early-stage sustainability assessment according to the definition of Argoti *et al.*[6] (including chemical route selection and process synthesis), also referred to as "process chemistry"[12,13] or TRL 1–4[14] in the literature. In this regard, early assessment differs significantly from the conceptual design phase, which necessitates more detailed information and primarily focuses on generating and optimising the process flow diagram.[6] Hence, only sustainability assessment methods applicable in the early design phase were included in the review, whereas tools designed for the conceptual design phase were excluded. If a sustainability assessment method is relevant across multiple phases of process design, it is considered for review, provided that a distinct part is applicable during the early design phase. When considering the need for a process flow diagram, Aspen Plus software can be employed to create a process flow sheet based on lab data that reflect the lab-scale process. Consequently, assessment methods that utilise a PFD generated by Aspen Plus using lab-scale data are included, while assessments based on mature PFDs are not within the scope. Furthermore, this study encompasses papers that describe the concept of a sustainability assessment method, papers that demonstrate the application of such a method and papers that address both aspects.

The primary reasons for excluding articles were their failure to meet our criteria for early sustainability assessment and the need for information that is not available during the initial stages of process development, such as process flow sheets and knowledge of unit operations. Additionally, some articles did not describe a specific sustainability assessment method, but rather an approach for "green synthesis" of chemicals in the laboratory. We also excluded articles dealing with solvent or material selection, methods for predicting chemical properties, assessments of industry sectors or chemical plants, summaries of green chemistry metrics and discussions about sustainability-related topics.

In addition to literature databases such as Web of Science and Scopus, the sample of publications for analysis was compiled from Google Scholar, publications known from earlier studies by our group and key references cited in the retrieved literature. For the literature search utilising the Web of Science and Scopus databases, the following search string was employed: ("early" OR "research and development" OR "research & development" OR "R&D") AND ("sustainability" OR "sustainable") AND ("chemical process" OR "chemical route" OR "chemical industry") AND ("framework" OR "guide" OR "metric" OR "indicator" OR "methodology" OR "assessment" OR "tool" OR "design"). The search was conducted in October 2024, focusing on peer-reviewed articles and reviews published in English from 2000 onwards. The Web of Science search yielded 338 results, while Scopus provided 170. After removal of duplicates (n = 79), the authors screened 429 records based on titles and abstracts. This led to the exclusion of 346 articles that did not pertain to early assessment methods or did not focus on the development or application of a sustainability assessment method. Consequently, 83 articles were targeted for full-text screening. Of these, 56 articles were excluded as they did not align with the scope of the research (*e.g.* articles that claimed a new sustainable synthesis method without performing sustainability assessment) or did not reflect "early-stage" sustainability assessment methods as per the defined criteria, relying instead on information available in the conceptual design phase. Ultimately, 27 articles from the Web of Science and Scopus databases were included in the review.

Apart from that, further relevant studies were identified *via* Google Scholar as well as careful evaluation of the literature reviews obtained by Web of Science and Scopus searches. Regarding the latter, we included articles cited within these reviews that significantly contributed to addressing our research questions. Moreover, we incorporated articles previously known to our research group that were instrumental in answering our research questions. In these cases, publications predating 2000 were also considered if deemed valuable. As far as the Google Scholar search was concerned, it was conducted between November 2021 and May 2022, with an update in October 2024, using the following key terms: "sustainable (chemical) process design", "sustainability assessment of chemical processes", "sustainability assessment" AND "chemical industry", "sustainability indicators" AND "chemical process", "sustainability metrics" AND "chemical process", "sustainable chemical process" AND "design tool". We focused on peer-reviewed articles and reviews as well as reports by governments or organisations published in English from 2000 onwards. In this way, we identified 57 more articles that were potentially relevant for our study (according to titles and abstracts) and subjected them to full-text screening. This process resulted in the exclusion of 31 reports and the inclusion of 26 more studies in our review.

In total, 53 records were included in the review and an overview of the literature selection process is presented in Fig. S1 in the SI, utilising the PRISMA flow diagram template for systematic reviews.[40] The 53 references included in the study were thoroughly analysed by full-text screening. Before qualitative

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and bibliometric analysis of collected data, they underwent a process of cleaning and correction. This involved merging singular and plural forms of words (*e.g.* chemical and chemicals), different punctuations (*e.g.* R&D and research & development) and synonyms (*e.g.* LCA and life cycle assessment). Details of this cleaning procedure can be found in section 2 of the SI. Notably, this cleaning procedure was applied to both the "author keywords" and "sustainability indicators" categories.

3.2. Data analysis

The research process and its outcomes, as well as their relevance to the research questions, are depicted in Fig. 1. In our study, we first performed a literature search, which resulted in the identification of 53 articles meeting our literature selection criteria. Subsequently, we conducted qualitative analysis of the full text of the papers, focusing on category creation to address research questions 1 and 2. To tackle research question 3, we employed two phases of quantitative bibliometric analysis, operating at both the document and conceptual levels. This involved analysing author keywords and sustainability indicators for trend topics and most frequently used words. Additionally, conceptual analysis was performed using information on selected qualitative categories, incorporating factorial analysis and thematic mapping.

The following section provides detailed methodological information on the qualitative content analysis of the literature retrieved on early-phase sustainability assessment as well as an overview of the bibliographic analysis tools employed.

3.2.1. Qualitative content analysis. The qualitative content analysis of the publications followed the recommendations of Mayring *et al.*,[41] who suggested content organisation through category development. The selection of subsequent categories was influenced by their relevance to the research questions and was also based on existing reviews of sustainability assessment methods found in the literature.

1. Bibliographic data: for the study, information on authors, title, publication year, DOI, and keywords were collected. As an author analysis/citation analysis study was deemed irrelevant for addressing the research questions, citations and references were not analysed.

2. Sustainability dimensionality: the study evaluated the coverage of sustainability dimensions including economic, social, health and safety, and environmental considerations.

3. Data needs: sources of data necessary to perform a certain sustainability assessment were documented, for example databases, lab data or simulations.

4. Impact assessment: the research examined various assessment methods, such as questionnaires/checklists, equation-based tools, life cycle assessments, artificial intelligence, machine learning, systematic frameworks, fuzzy optimisation and mathematical modelling, while also filtering out the data necessary for conducting sustainability assessments. A method is categorised as a framework if it involves a multi-step assessment rather than a single step, or if the authors explicitly designate it as such. Apart from that, the study explored the application of multi-criteria decision analysis, weighting, as well as statistical and multivariate analysis techniques for decision-making and emphasised whether the aspect of uncertainty was specifically addressed.

5. Assessment result: regarding the presentation of the results of a sustainability assessment method, single indicator, cumulative indicator and multi-indicator assessments were differentiated. Furthermore, it was noted whether the assessment led to a relative or absolute and quantitative or qualitative result, respectively.

6. Research field: the study carefully assessed connections to specific topics and case studies.

Organising the content of the studies into predefined categories forms the foundation for addressing research questions 1 and 2. A table format was chosen to provide a comprehensive overview of the extracted information.

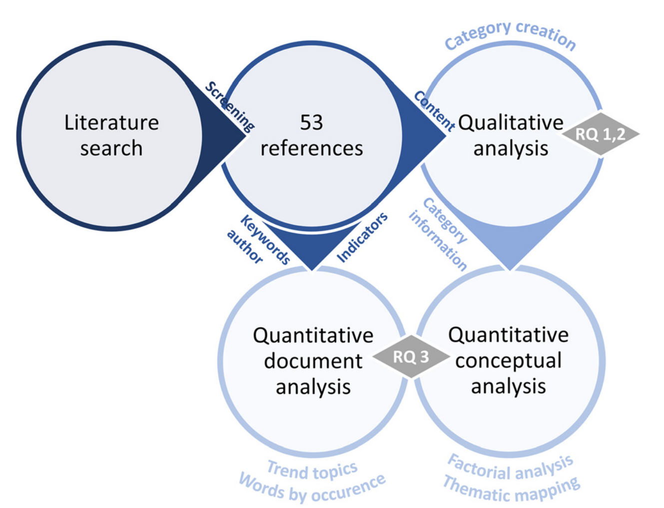

Fig. 1 Outline of the research steps.

3.2.2. Quantitative content analysis using bibliometrix. For the network and statistical analysis, the R-tool "bibliometrix"[42] was used *via* its web interface "biblioshiny", relying on the software R-studio version 2024.09.0. Bibliometric analysis software is designed to efficiently process large sample sizes. Particularly for historiographic and citation analysis, it is recommended to have a minimum sample size of 200 references or an optimal number of >1000 references,[43] as larger datasets generally allow for more robust and reliable analysis. However, valuable insights can still be derived from a small dataset of high-quality, relevant publications. Thus, the literature presents instances of handling sample sizes <100. Bibliometric analysis is occasionally applied to smaller sample sizes due to specific research focuses,[44] high-impact studies,[45] or limited availability of resources.[46,47] In conclusion, while bibliometric analysis is commonly associated with large datasets, it is also effectively utilised for smaller sample sizes in specific contexts.

The R-tool "bibliometrix" serves multiple purposes, offering various analytical capabilities.[42] On one hand, it facilitates the analysis of bibliographic coupling, co-citation and collaboration networks, allowing for an examination of connections between publications based on their citation patterns, shared

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references and author collaborations. On the other hand, features such as thematic mapping or factorial analysis enable researchers to unveil thematic structures, identify underlying patterns and visualise the interconnections between terms and concepts, thus deepening our understanding of the scholarly landscape within a specific research area. In our bibliometric analysis of reviewed literature on the topic of early-phase assessment, we use bibliometrix for the latter purpose and intentionally omit author/co-citation analysis as it does not contribute to addressing our research questions.

As a basis for bibliographic content analysis, bibliometrix offers the option of analysing publication titles, author keywords, keywords plus, abstracts, or subject categories from Web of Science. For quantitative analysis at the document level, we chose to analyse author keywords, as they were more comprehensive at representing an article's content than keywords plus.[48] If authors did not provide keywords (n = 19), we included five keywords representing the main content, which were identified through screening the article abstracts. For our conceptual analysis, we opted for a different approach, specifically analysing (i) extracted combined information from the categories author keywords, sustainability dimensionality, assessment procedure, result and research field, and (ii) economic, social, health and safety, and environmental indicators used for sustainability assessments. Thus, our aim was to ensure the inclusion of all relevant information for addressing research question 3 and to enable a comprehensive bibliometric analysis at both the document and conceptual structure levels. Further details in this respect can be found in section 3 of the SI.

3.2.2.1. Document analysis level. In our bibliometric analysis for this study at the document analysis level, we examined author keywords using the functions trend topics and words by occurrence. The most popular sustainability indicators in terms of economic, health and safety, and environmental sustainability were also assessed using the latter analysis tool. Words by occurrence presents the top 10 most frequent words, offering valuable insights into prominent terms across the literature. Meanwhile, the trend topics analysis is employed to identify and visualise the emergence and evolution of key topics or themes within a particular research field over time, offering researchers a comprehensive view of thematic trends and shifts within the literature. In our study, we employ these features to analyse trends and focal points of early-phase sustainability assessments aligning with research question 3.

3.2.2.2. Conceptional structure analysis level. In conducting bibliographic analysis at the conceptual structure level, we utilised the analytical capabilities of factorial analysis and thematic mapping for answering research question 3. As basis for our analysis, we employed (i) a combination of author keywords, sustainability dimensionality, assessment procedure, result and research fields, and (ii) economic, social, health and safety, and environmental indicators used for sustainability assessments.

Factorial analysis serves to identify subfields within bibliometric data by reducing its dimensionality and representing it in a low-dimensional space. This reduction is accomplished through methods such as multiple correspondence analysis (MCA). Following the generation of the MCA conceptual structure, the application of a k-means clustering algorithm aids in identifying clusters within this structure. Keywords are positioned close together when a substantial number of articles deal with them together, while they are situated farther apart when a small proportion of articles utilise these words in conjunction. The map's origin represents the centre of the research field (meaning common and large shared topics).[49]

The thematic map feature combines conceptual and thematic networks within a specific research field. It visualises the underlying thematic structure of the literature, providing a clear representation of the main topics and their connections. This technique relies on network analysis. By using network clustering algorithms, we used Walktrap[50] for our study, meaningful knowledge communities, referred to as "themes" and their connections can be identified and visualised. Network metrics such as the density measure a theme's internal connections, while centrality measures its connections to other themes. Based on these parameters, themes can be classified into four quadrants: emerging/declining themes, niche themes, basic themes and motor themes.[51] While this approach is typically utilised for longitudinal network analysis, we opt not to divide the dataset into time slices due to the small sample size.

4. Results

In this section, we present the results of the qualitative content analysis of the reviewed articles, as well as the quantitative analysis, which includes document analysis and conceptual analysis, aimed at addressing research questions 1–3.

4.1. Qualitative content analysis addressing research questions 1 and 2

Table 1 provides a concise overview of key categories, including author name(s), method name (if any), sustainability dimension inclusion, data requirements, assessment method, decision-making procedure, uncertainty considerations, assessment result, result characteristics and research field. For a comprehensive list, including publication title, year, DOI, keywords and a detailed inventory of used indicators, please refer to the Excel file "Supporting information_literature".

Generally, sustainability assessment tools reported in the literature concentrate on different dimensions of sustainability, encompassing the economic, environmental and social pillars either individually or in combination. When addressing the social pillar, a focus is often placed on health and safety aspects, given the complexity of assessing "soft" social implications in the early development stage. Recognising health and safety as being increasingly pivotal to sustainability, the traditional triple bottom line appears to be evolving towards a quadruple bottom line approach.[52] Hence, we differentiated between economic, social, health and safety, and environ-

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Table 1 References included in the study and qualitative content analysis according to various categories

Bibliographic data	Sustainability dimensions[a]				Data needs	Impact assessment			Assessment result		
#/Author(s)/Method name	ECON	SOC	H&S	ENV/PROC	Sources[b]	Method[c]	Decision-making[d]	Uncertainty[e]	Result[f]	Character[g]	Research field
1: Cave & Edwards (1997)[65] Environmental Hazard Index (EHI)				x	Databases, estimation	EQ			CI	QUANT, REL	Methyl methacrylate
2: Eissen & Metzger (2002)[66] Environmental assessment tool for organic synthesis (EATOS)				x	Mass of raw materials, waste	EQ			MI	REL, QUANT	4-Methoxyacetophenone
3: Gunasekera & Edwards (2003)[67] Atmospheric Hazard Index (AHI)				x	Literature, databases	EQ	Weighting		CI	REL, QUANT	Methyl methacrylate
4: Gunasekera & Edwards (2006)[68] Inherent Environmental Toxicity Index (IETH)				x	Databases, estimation	EQ			CI	QUANT, REL	Methyl methacrylate
5: Curzons *et al.* (2007)[69] Fast life cycle assessment of synthetic chemistry (FLASC)				x	Process characteristics (real or software)	LCA (ex-ante)	PCA, HCA		MI	REL, QUANT	APIs
6: X. Zhang *et al.* (2008)[70] Green degree				x	Literature, databases	EQ			CI	REL, QUANT	Solvents, process routes for methyl methacrylate, methyl methacrylate process
7: Wernet *et al.* (2009)[71] Modeling impacts of fine and basic chemical production				x	Molecular descriptors	NN		x	MI	QUANT, REL	Petrochemistry
8: Hermsen *et al.* (2013)[72] Guesstimating the energy component of the footprint				x	Raw material quantities and costs	EQ			SI	REL, QUANT	
9: Leseurre *et al.* (2014)[73] Eco-footprint				x	Process data from Chimex, MSDS, literature	EQ			MI	REL, QUANT	Meroxyl SX, pro-xylane
10: Calvo-Serrano *et al.* (2019)[74] Predict the life cycle environmental impact of chemicals				x	Molecular descriptors, thermodynamic properties, discretised σ-profiles	CS, stream-lined LCA			MI	REL, QUANT	
11: Falke & Höck (2019)[56] *Ex-ante* life cycle assessment				x	Databases, assumptions, literature, lab data	LCA			MI	REL, QUANT	Bioleaching in indium recovery
12: Gonzalez *et al.* (2019)[75] Framework toward more sustainable chemical synthesis design				x	Molecular descriptors	FW, CS (QSAR)			SI	REL, QUANT, QUAL	Organophosphates
Innovation green aspiration level (iGAL 2.0)				x	Process data	EQ			MI	REL, QUANT	APIs (umifenovir, dabigatran)

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Table 1 *(Contd.)*

Bibliographic data	Sustainability dimensions[a]				Data needs	Impact assessment			Assessment result		
#/Author(s)/Method name	ECON	SOC	H&S	ENV/PROC	Sources[b]	Method[c]	Decision-making[d]	Uncertainty[e]	Result[f]	Character[g]	Research field
13: Zuiderveen *et al.* (2021)[57] *Ex-ante* life cycle assessment of polyethylenefuranoate				x	Process data	LCA (ex-ante)			MI	REL, QUANT	Polyethylene furanoate
14: Guzman-Urbina *et al.* (2022)[76]											
15: Roschangar *et al.* (2022)[77] Fuzzy inference and emission analytics (FIEMA)				x	Database	AI/data science		x	SI	REL, QUANT	Catalyst for methanol production
16: Kleinekorte *et al.* (2023)[78] A process-specific, predictive impact assessment method for emerging chemical processes (APPROPRIATE)				x	Molecular descriptors, stoichiometry	Predictive LCA, ML		x	SI	REL, QUANT	
17: Langhorst *et al.* (2023)[79] Stoichiometry-based estimation of climate impacts				x	Stoichiometry, process data	EQ			SI	REL, QUANT	Benchmark data of 474 processes from PEP
18: Luescher & Gallou (2024)[80] Interactions of multiple metrics and environmental indicators				x	Process data, database	LCA	Weighting		MI, CI	REL, QUANT	Nanocatalyst
19: D. Zhang *et al.* (2024)[58] FineChem2				x	Molecular descriptors	NN			SI	REL, QUANT	High-volume chemicals (chemicals in daily products, food additives, plastic additives)
20: Palaniappan *et al.* (2002)[81] Overall Safety Index (OSI)			x		EHS information, process data	EQ, network			CI	REL, QUANT	Acetic acid, phenol, cumene oxidation
21: Koller *et al.* (2000)[82] Assessing safety, health, and environmental impact			x	x	Databases, estimation	EQ			MI	QUANT, REL	Pharmaceutical chemistry
22: Srinivasan & Nhan (2008)[83] Inherent benignness indicator (IBI)			x	x	MSDS, process data, factors from WAR algorithm	EQ	PCA		CI	REL, QUANT	Acetic acid, methyl methacrylate
23: Bumann *et al.* (2010)[84] Energy Index (EI)			x	x	Process data, literature, databases, estimation	EQ	Weighting		CI	REL, QUANT	Solvents
24: Hassim & Hurme (2010)[85] Inherent Occupational Health Index (IOHI)			x	x	Process data, database	EQ	Weighting		CI	REL, QUANT	Methyl methacrylate
25: Banimostafa *et al.* (2012)[86] Evaluation of EHS hazard and sustainability metrics			x	x	Literature, databases, process data	EQ	PCA, weighting		MI	REL, QUANT	4-(2-Methoxyethyl)-phenol (MEP), methyl methacrylate
26: Andraos (2013)[87] Safety Hazard Index (SHI)			x	x	Database, literature, process data	EQ	Weighting		CI, MI	REL, QUANT	Aniline, phenol, phenyl isocyanate

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Table 1 *(Contd.)*

Bibliographic data	Sustainability dimensions[a]				Data needs	Impact assessment			Assessment result		
#/Author(s)/Method name	ECON	SOC	H&S	ENV/PROC	Sources[b]	Method[c]	Decision-making[d]	Uncertainty[e]	Result[f]	Character[g]	Research field
27: Phan *et al.* (2015)[88] Green motion			x	x	MSDS, process data	EQ			CI	REL, QUANT	Vanillyl ethyl ether
28: Volanti *et al.* (2019)[89] Early-stage sustainability analysis			x	x	Database, literature, estimations, process data, simulations	LCA	Weighting		CI	REL, QUANT	Terephthalic acid
29: Plugge (2022)[90] Chemical Environmental Sustainability Index (ChemESI)			x	x	MSDS, inventory	EQ	Weighting		CI	QUANT, REL	
30: Herrgard *et al.* (2015)[91] Multi-scale framework for sustainable industrial chemicals (MuSIC)	x			x	Literature, databases	FW, LCA, CS			MI	REL, QUANT	1,3-Propanediol,3-hydroxypropionic acid
31: Moncada *et al.* (2015)[92] Early sustainability assessment for potential configurations of integrated biorefineries	x			x	Literature, databases, process data	EQ	Weighting		CI	REL, QUANT	Catalytic conversion of bio-based syngas, biochemical conversion of carbohydrates, biochemical and catalytic conversion of glycerol
32: Patel *et al.* (2015)[93] Sustainability Index Ratio (SIR)	x			x	1st stage: process data, 2nd stage: PFD (Aspen+)	FW	Weighting		CI	REL, QUANT	Production of higher alcohols from ethanol
33: van Aken *et al.* (2006)[94] EcoScale	x		x	x	MSDS, literature, process data	EQ			CI	REL, SEMI-QUANT	Aniline, benzoic acid, benzamide
34: Sugiyama *et al.* (2008)[13] Decision framework for chemical process design	x		x	x	Process data, databases	FW, LCA	Weighting		CI, MI	REL, QUANT	Methyl methacrylate
35: Sugiyama *et al.* (2008)[95] Activity modeling for integrating environmental, health and safety	x		x	x	Process data, databases	LCA, FW, activity modelling			MI	REL, QUANT	Methyl methacrylate
36: Monteiro *et al.* (2009)[96] Sustainability metrics for eco-technologies assessment	x		x	x	WAR, stoichiometry, literature, database	EQ	Weighting		CI	REL, QUANT	Dimethyl carbonate
37: Albrecht *et al.* (2010)[12] Multi-objective screening of chemical batch process alternatives	x		x	x	Process data, databases	FW	Weighting		CI	REL, QUANT	4-(2-Methoxyethyl)-phenol
38: Patel *et al.* (2012)[97]											

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Sustainability assessment of novel chemical processes	x		x	x	Basic process data, physical and chemical properties, prices, databases	EQ	Weighting	x	CI	REL, QUANT	But-1,3-diene
39: Patel *et al.* (2013)[98] Sustainability Index Ratio (SIR)	x		x	x	Process data, databases, literature	FW	Weighting	x	CI	REL, QUANT	Bio-based fuels and chemicals
40: Posada *et al.* (2013)[99] Preliminary sustainability assessment	x		x	x	Literature, process data	EQ	Weighting	x	CI	REL, QUANT	Biorefinery
41: Shadiya & High (2013)[100] Sustainability evaluator	x		x	x	Literature, simulation (Aspen+)	FW, CS	Weighting		CI	REL, QUANT	Acrylonitrile
42: Shadiya & High (2013)[101] Sustainability evaluator	x		x	x	Literature, simulation (Aspen+)	FW, CS			MI	REL, QUANT	Dimethyl ether
43: Liew *et al.* (2014)[102] Sustainability indicator	x		x	x	Chemical properties, process conditions	FO, FW			CI	REL, QUANT	Biodiesel
44: McElroy *et al.* (2015)[103] Holistic approach to metrics for the 21st century pharmaceutical industry	x		x	x	Process data, literature, database	FW (0–1–2–3 order pass)			MI	REL, QUANT, QUAL	Developed for pharma, but no case study
45: Saavalainen *et al.* (2015)[104] Sustainability assessment of chemical processes	x		x	x	Process data (lab scale), reaction routes, thermodynamic simulations, database, literature	EQ			MI	REL, QUANT	Dimethyl carbonate
46: Serna *et al.* (2016)[105] Sustainability Cumulative Index (SCI)	x		x	x	Literature, process data	EQ	Weighting, AHP, DEMATEL		CI	REL, QUANT	Ethyl acetate
47: Grimaldi *et al.* (2020)[106] Life cycle assessment and cost evaluation	x		x	x	Process data, database	LCA			MI	REL, QUANT	Rufinamide
48: Narváez Rincón *et al.* (2020)[107] Global sustainability indicator	x		x	x	Literatures, MSDS, databases, estimation	FW	Weighting, AHP, PROMETHEE		CI	REL, QUANT	Glyceryl monostearate, formulations

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Table 1 *(Contd.)*

Bibliographic data	Sustainability dimensions[a]				Data needs	Impact assessment			Assessment result		
#/Author(s)/Method name	ECON	SOC	H&S	ENV/PROC	Sources[b]	Method[c]	Decision-making[d]	Uncertainty[e]	Result[f]	Character[g]	Research field
49: Saavalainen *et al.* (2017)[108] Sustainability assessment tool (SAT)	x	x	x	x	Literature, estimations, process data, experience	QUEST			MI	REL, QUANT	Formic acid
50: Xu *et al.* (2018)[109] Sustainability assessment framework for chemical processes selection under uncertainties	x	x	x	x	Experience, literature, simulation, experiments, mathematical techniques	MATH (VECTOR), FW	Weighting, FAHP (fuzzy AHP), DEMATEL	x	CI	REL, QUAL, QUANT	Ammonia
51: Caldeira *et al.* (2022)[34] Safe and sustainable by design (SSbD)	x	x	x	x	Databases, estimations, literature, process data	FW (5 steps) incl. LCA	MCDA/ weighting can potentially be applied	x	MI	REL, (ABS), QUANT, QUAL	See (Caldeira *et al.*, 2023)[110]
52: Caldeira *et al.* (2023)[110] Safe and sustainable by design (SSbD)	x	x	x	x	Databases, estimations, literature, process data	FW	MCDA/ weighting	x	MI	REL, (ABS), QUANT, QUAL	Plasticiser, flame retardants, surfactants
53: Pizzol *et al.* (2023)[111] Screening level approach for making safe and sustainable by design decisions	x	x	x	x	Databases, literature, process data	QUEST			MI	REL, QUAL	Nano-enabled PFAS, nano-drops of essential oil

[a] ECON: economic dimension, SOC: social dimension, H&S: health & safety dimension, ENV/PROC: environmental dimension/process characteristics; x= sustainability dimension included in the assessment. [b] MSDS: material safety data sheet, WAR: waste reduction algorithm, PFD: process flow diagram, EHS: environment health safety. [c] QUEST: questionnaire/checklist, EQ: equation, LCA: life cycle assessment, AI: artificial intelligence, ML: machine learning, CS: computer simulation, NN: neural networks, FW: systematic framework, FO: fuzzy optimisation, MATH: mathematical modelling. [d] AHP: analytical hierarchy process, ANP: analytic network process, PROMETHEE: preference ranking organisation method for enrichment of evaluations, DEMATEL: decision making trial and evaluation laboratory, PCA: principal component analysis, HCA: hierarchical cluster analysis. [e] x = uncertainty included in the assessment. [f] CI: cumulative indicator, MI: multiple indicators, SI: single indicator. [g] REL: relative sustainability, ABS: absolute sustainability, QUANT: quantitative method, QUAL: qualitative method.

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mental sustainability aspects. Health and safety aspects encompass risks associated with chemical attributes (*e.g.*, flammability, explosiveness), process parameters (*e.g.*, temperature, pressure) and workers' welfare (toxicity, irritation), while aspects linked to individuals' well-being, such as equality and working conditions, are included within the social dimension. As far as process-related indicators are concerned, which are increasingly being integrated into sustainability assessments of chemical processes, we categorised them according to their primary impacts. Process indicators linked to health and safety concerns, such as temperature, pressure and heat of reaction, were placed in the health and safety category. Conversely, those associated with process efficiency and resource utilisation were designated as environmental indicators. For instance, processes that yield higher outputs tend to lower resource usage and minimise pollution per unit of production. Additionally, factors like process complexity, maturity, technical configuration and operational mode are closely tied to energy efficiency and thus exert an indirect environmental influence. For a comprehensive list detailing the contribution of process indicators to the health and safety or environmental categories, please refer to section 1.1 in the SI.

The bulk of reviewed sustainability assessment methods for early chemical process design primarily emphasise environmental aspects (n = 19). However, a considerable number of methods (n = 16) consider the three sustainability dimensions economy, health and safety, and environment. A limited number of papers concentrate on health and safety in conjunction with environmental factors (n = 9), while all four sustainability dimensions are taken into consideration in five instances. In a few rare cases, only economic and environmental aspects are taken into account (n = 3) and in an even smaller number of cases, only health and safety aspects are considered (n = 1).

As is widely recognised, early-stage assessments of chemical processes frequently encounter challenges regarding the availability and quality of data. In terms of data requirements, the reviewed assessment methods gather the necessary data from various sources including the literature (*e.g.* safety data sheets), databases, process simulations, theoretical assumptions, laboratory and early process data and molecular descriptors. Based on this information, data are often processed using equation-based methods (n = 25) or life cycle analysis-based methods (n = 12) to provide insights into sustainability. Furthermore, computer-aided methods are increasingly being applied for early-stage sustainability assessment of chemical processes, including computer simulation (n = 5), artificial intelligence (n = 1), machine learning (n = 1) and neural networks (n = 2). Furthermore, various approaches for early-stage sustainability assessments reviewed are based on a framework (n = 15) that involves multiple assessment steps. Additionally, qualitative tools such as checklists and questionnaires are employed in a few cases (n = 2), while mathematical modelling, a network approach and fuzzy optimisation are each utilised in only one of reviewed assessments.

Focusing on the decision-making process itself, for early-stage sustainability assessments a variety of tools are commonly used, such as multi-criteria decision analysis (MCDA) and statistical and multivariate analysis methods. The latter enables the analysis of data involving multiple variables to understand relationships or identify patterns, while MCDA is utilised to evaluate conflicting criteria. Among the reviewed assessments, MCDA tools like the analytic hierarchy process (AHP), the preference ranking organisation method for enrichment of evaluations (PROMETHEE) and the decision making trial and evaluation laboratory (DEMATEL) are frequently featured, while statistical and multivariate analysis, including principal component analysis (PCA) and hierarchical cluster analysis (HCA), are employed in a smaller number of cases. Furthermore, in cases where a cumulative sustainability result is targeted, weighting (n = 22) based on individual considerations, the literature, LCA methods, or survey results is applied.

In our analysis of the results of sustainability assessment methods being reviewed, we considered the incorporation of uncertainty, the types of result indicators used and whether the results were qualitative or quantitative, as well as relative or absolute. When it comes to uncertainty analysis, early-stage sustainability assessments often rely on assumptions or low-quality data, making it essential to address uncertainty for a better understanding of the assessment results. Among the reviewed literature, nine sustainability assessment tools accounted for uncertainty, employing methods such as Monte Carlo analysis (n = 3), quantification of prediction uncertainty, fuzzy logic and data quality rating (n = 2 each). In terms of result indicators, the reviewed methods yielded outcomes based on a single indicator (n = 6), multiple indicators (n = 23), or a cumulative indicator (n = 27). The reviewed tools predominantly concentrated on relative and quantitative sustainability assessment, allowing the comparison and ranking of different process alternatives based on specific sustainability scoring. However, they do not evaluate whether a process can be considered sustainable in absolute terms, such as in relation to the carrying capacity of ecosystems or planetary boundaries.[53] Only Caldeira *et al.* emphasise the ambition of the SSbD concept to transition from a relative to a more absolute assessment approach.[34] Finally, the early-phase sustainability assessment methods in the literature primarily target various industries including industrial chemicals (*e.g.*, ammonia, acetic acid), solvents (*e.g.*, ethyl acetate), biodiesel/biorefinery, active pharmaceutical ingredients and the pharmaceutical sector, as well as methyl methacrylate.

After examining the literature, several prominent trends and concepts commonly utilised in early-stage sustainability assessments emerged, such as green chemistry, life cycle thinking, the waste reduction algorithm (WAR), inherent safety and computer science. Green chemistry, introduced by Anastas and Warner,[7] emphasises the design of chemical products and processes to minimise or eliminate the use and generation of hazardous substances with the aim of achieving sustainability at the molecular level. The 12 principles of green chemistry[7] have also translated into sustainable chemistry metrics,[10] providing a standard for evaluating the sustainability of chemical processes. These metrics primarily consider mass flows within the technosphere and are indirectly linked to impact cat-

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egories in life cycle assessments.[54,55] Life cycle assessment remains a crucial tool in sustainability assessment, commonly employed in the early-stage evaluation of chemical processes. It is often utilised in *ex-ante*[56,57] or pre-LCA[58] evaluations. *Ex-ante* LCA represents a prospective approach, evaluating the potential environmental impacts of a technology or process before full development or commercialisation, while pre-LCA serves as an even earlier-stage screening tool, offering an initial sustainability estimate with minimal data. Alternatively, early process design can be upscaled utilising procedures documented in the literature,[59] followed by conducting an LCA of the upscaled process. In this scenario, it is essential to acknowledge that scaling up introduces additional uncertainties to the assessment. Additionally, some assessments are based on the waste reduction algorithm,[60,61] which incorporates environmental and economic sustainability aspects, providing a description of potential environmental impacts throughout a chemical process and involving the use of process simulation software. Owing to its simplicity, ease of use and availability of a database on the potential environmental impacts of common chemicals, the algorithm has found widespread application.[62] Moreover, the consideration of health and safety holds significant importance in the early-stage sustainability assessment of chemical processes. In particular, the concept of inherent safety (IS) involves reducing or eliminating hazards associated with materials and operations used in a process, emphasising the design of processes to avoid hazards rather than solely relying on management and control.[63] Furthermore, the incorporation of digitalisation[5] and artificial intelligence[64] in driving the sustainability of the chemical industry is gaining attention, with both concepts increasingly being applied to aid sustainability assessments of chemical processes.

When striving to design a sustainable process, the pivotal question of whether a specific design tool can truly lead to the "right" result – a sustainable industrial process – becomes of paramount importance. Many researchers view hypothetical case studies as a valid means of demonstrating a concept, sometimes comparing their results with those obtained using other tools documented in the literature. Additionally, sensitivity and uncertainty analyses are at times employed to validate the suitability of a particular tool. Unfortunately, to our current knowledge, there has been no real-world implementation of an industrial process tracked from its early design phase through to its operation. Such a study would yield valuable insights into the strengths and weaknesses of the applied sustainable design and assessment tools, while also addressing the question of whether the simple sustainability criteria often used in research and development are adequate, or if more intricate criteria are necessary to effectively guide sustainable process development.

4.2. Quantitative document analysis addressing research question 3

Among the reviewed publications, Hungerbühler K. emerges as the most prolific author, with 6 contributions, followed by Fischer U., Papadokonstantakis S. and Sugiyama H., each with 4 publications, all published between 2000 and 2010. Furthermore, Patel A. and Patel M. are credited 4 times for their collaborative work on several publications. In general, the annual scientific production shows a relatively even distribution over the period under review, with a slight peak in the mid-2010s.

4.2.1. Analysis of the most frequently used words. Analysis of the most frequently used words among author keywords revealed the following topics of high interest (the number of mentions are given in parentheses): LCA (life cycle assessment, 17), EHS (environment health safety, 10), sustainability assessment (10), process design (8), environmental impact (7), green chemistry (7), methyl methacrylate (6), multicriteria assessment (6), sustainable chemistry (6), inherent safety (5).

As anticipated, life cycle assessment-based tools are extensively utilised, also in the early-stage sustainability evaluation of chemical processes. The assessment of sustainability aligns closely with process design, placing significant emphasis on environmental, health and safety considerations, with inherent safety being particularly crucial. Environmental sustainability emerges as the most prominent dimension of sustainability, especially in the realm of green chemistry and sustainable chemistry. Numerous assessments concentrate on methyl methacrylate, a pivotal compound widely employed in the production of poly(methyl methacrylate), a transparent thermoplastic commonly recognised as acrylic glass.

In our study we also examined the most frequently occurring words among indicators used to assess economic, health, safety and environmental sustainability. Notably, the analysis did not cover social indicators due to their infrequent use, with no indicator appearing more than twice in the literature searched. In terms of economic indicators, the top three indicators used were raw material costs (7), economic constraint (5) and process costs and environmental impacts (4). Meanwhile, health and safety were assessed through explosiveness (11), acute toxicity, human toxicity potential, reactivity (7 each), as well as flammability, pressure and temperature (6 each). As for environmental indicators, global warming potential (13) had the highest frequency, followed by acidification potential (10), cumulative energy demand, eutrophication and ozone depletion (9 each).

4.2.2. Trend topics. The trend topic graph based on author keywords, depicted in Fig. 2, is a scatter diagram where time is represented on the *x*-axis and topics on the *y*-axis. Each bubble on the graph corresponds to a specific topic, with the reference year for each topic being determined using the median of the occurrence distribution over the considered time period. The size of each bubble is proportional to the word occurrences, while the grey bar denotes the first and third quartiles of the occurrence distribution.

In the analyzed literature, spanning from 1997 to 2024, several prominent trend topics are apparent from Fig. 2. Beginning with the most recent trends based on the median of the occurrence distribution, "safe and sustainable by design" has gained prominence, attributed to the endeavours of the

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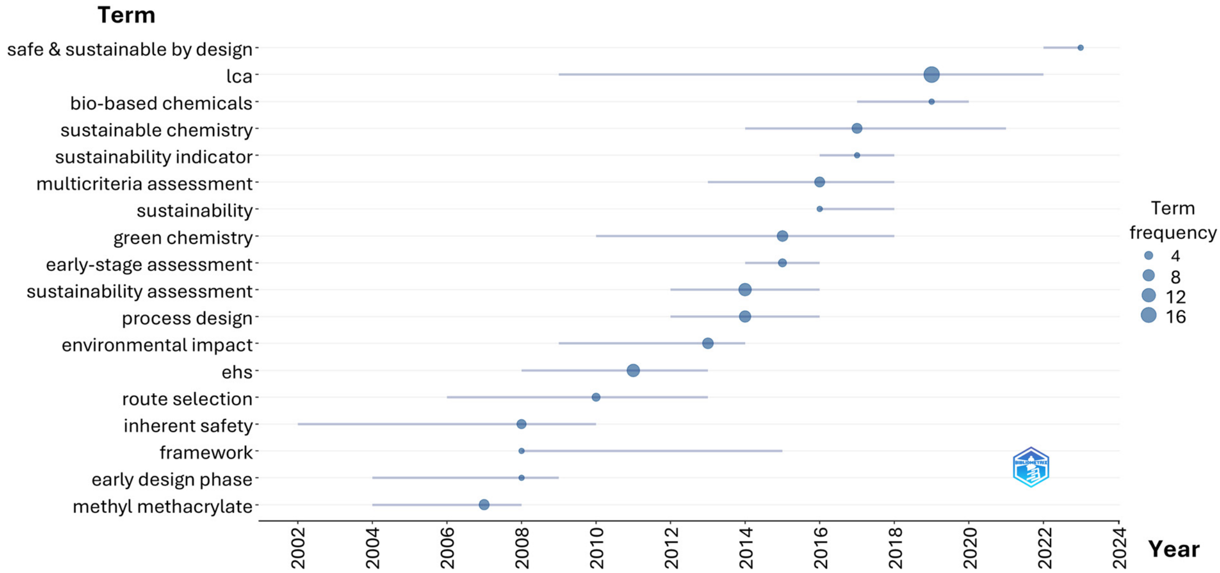

Fig. 2 Trend topic analysis based on author keywords.

Joint Research Centre of the European Commission.[33] This initiative aims to facilitate the development of safe and sustainable chemicals and materials during research and innovation.[34] Furthermore, "life cycle assessment" has consistently been a relevant topic, especially from 2019 onwards, indicating its increasing significance in sustainability evaluations. During the 2010s, "sustainable chemistry", "green chemistry" and "bio-based chemicals" attracted considerable scientific interest. According to the graph, assessments focusing on environmental impacts and multicriteria assessments are the most common types of assessment, with the latter being more prominent in the past decade. In the early 2010s, keywords like "environment, health and safety", "route selection" and "inherent safety" were frequently referenced. Additionally, "methyl methacrylate" emerged as a prominent research topic at the start of the century.

4.3. Quantitative conceptual analysis addressing research question 3

4.3.1. Factorial analysis. Factorial analysis was based on combined information extracted from the categories author keywords, sustainability dimensionality, assessment procedure, result and research field. Fig. 3 shows an illustration of the conceptual structure of research regarding early-phase sustainability assessment of chemical processes, based on factorial analysis employing MCA and *k*-means clustering. Thereby, the percentage values indicate how much variance in the data is explained by the respective axis. In our analysis, the first two dimensions accounted for 67.05% of the total variance (Dim. 1 = 40.80%, Dim. 2 = 26.25%). The results are interpreted based on the relative positions of the points and their distribution along these two dimensions. Terms that exhibit similar distribution patterns across publications are positioned closer to each other.[42] The proximity of a keyword to the origin of the coordinate system indicates its alignment with the average profile of the 53 publications. Additionally, the two dimensions segment the data in such a way that clusters positioned on opposite ends of a dimension represent opposed profiles.

Apparent from Fig. 3, 5 different clusters were identified. Cluster B, which includes the terms "ehs", "sustainable chemistry", "multicriteria assessment" and "econ.h.s.env", is the most central one. Therefore, the typical research profile consists of early-stage sustainability assessment methods that address economic, health and safety, and environmental aspects, emphasising environment, health and safety (EHS) and employing multiple criteria for the assessment. For instance, sustainability assessment tools identified in the works of Albrecht *et al.*[12] and Serna *et al.*[105] fall into this category. Apart from that, cluster A, positioned on the left side of the graph, concentrates on route selection using cumulative indicators that take into account (inherent) health, safety and environmental aspects. These methods are equation-based and can be exemplified by the methodologies presented by Srinivasan and Nhan[83] and Hassim and Hurme,[85] both of which analyse different routes for the synthesis of methyl methacrylate. Clusters A and B represent the two largest clusters depicted in the graph, while three smaller clusters are situated on the right side. Cluster C, positioned above the main cluster B, emphasises environmental aspects in line with green chemistry principles, often employing single indicator methods such as the framework toward more sustainable chemical synthesis design developed by Gonzalez *et al.*[75] On the other hand, cluster D, located opposite cluster A, integrates life cycle-based approaches, along with assessments focusing on economic and environmental aspects, frequently utilising computer simulation. In this context, the multi-disciplinary assessment approach for evaluating the technological, economic and environmental performance of bio-based chemicals

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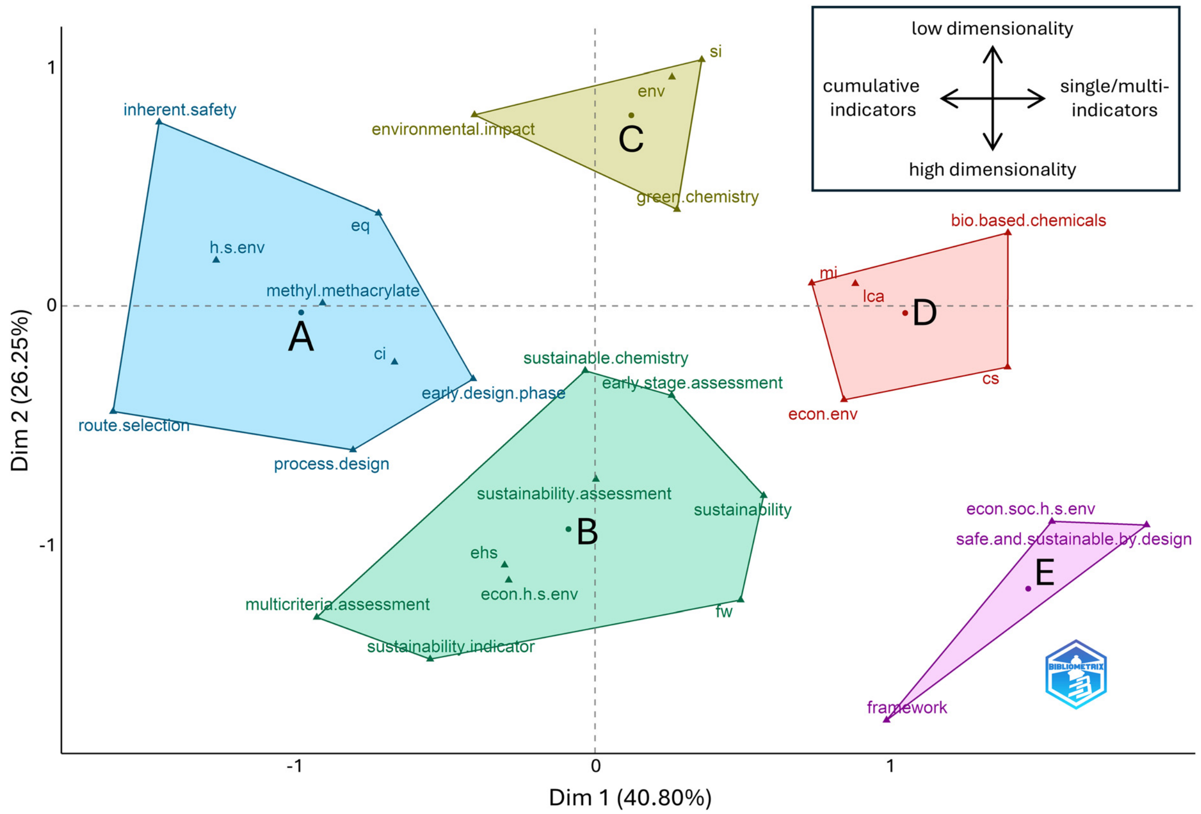

Fig. 3 Factorial analysis based on combined information extracted from the categories author keywords, sustainability dimensionality, assessment procedure, result and research fields (cluster A: cumulative indicator and equation-based methods for route selection, including health, safety and environmental aspects; cluster B: multi-criteria methods considering economic, health and safety, and environmental aspects; cluster C: single indicator methods emphasizing environmental aspects and green chemistry principles; cluster D: methods frequently using computer simulation, integrating LCA, and focusing on economic and environmental aspects; cluster E: 4-dimensional methods and safe and sustainable by design frameworks).

documented by Herrgard *et al.*[91] stands out as a representative of cluster D. The last and smallest cluster E, located on the lower right side of the graph, encompasses 4-dimensional sustainability assessment frameworks and safe and sustainable by design approaches, exemplified by the efforts of the European Joint Research Centre.[34,110] It is important to note that not all articles exclusively belong to one cluster but may share characteristics identified in different clusters.

The distribution of clusters along dimension 1 (~40% variance explained) suggests a division between cumulative indicator assessments (left) and single/multi-indicator assessments (right). The graph depicts cluster A, representing "cumulative indicator" on the left half. Cluster B is positioned towards the centre of the *x*-axis, with the term "multicriteria assessment" situated towards its left end. On the right half of the graph, cluster C encompasses "single indicator" on its right side, while cluster D is associated with "multi-indicator" assessments. Moreover, "LCA" is part of the latter, as life cycle analysis is commonly utilised as an assessment tool to analyse multiple indicators.

Meanwhile, the distribution along the *y*-axis (dimension 2) (~26% variance explained) reflects the scope of sustainability assessment, ranging from environmental and health and safety (H&S) assessments at the upper end to comprehensive, multi-dimensional assessments that incorporate economic, social (often in terms of H&S) and environmental factors at the lower end. Clusters A and C use two-dimensional and one-dimensional sustainability assessment tools, respectively, focusing on "H&S + environmental" and "environmental" indicators. In contrast, cluster B integrates three dimensions, "economy + H&S + environment" while cluster E encompasses all four dimensions of sustainability, encompassing "economic + social + H&S + environmental" indicators.

4.3.2. Thematic mapping. Thematic mapping was employed to explore the sustainability indicators utilised in the assessments included in the study, covering economic, environmental, social, and health and safety aspects. This method is based on network analysis, using metrics like density to assess a theme's internal connections and centrality to gauge its connections to other themes. Themes are then categorised into four quadrants based on these parameters: emerging/declining themes, niche themes, basic themes and motor themes. As depicted in Fig. 4, three motor themes emerged, primarily centred on environmental factors (global

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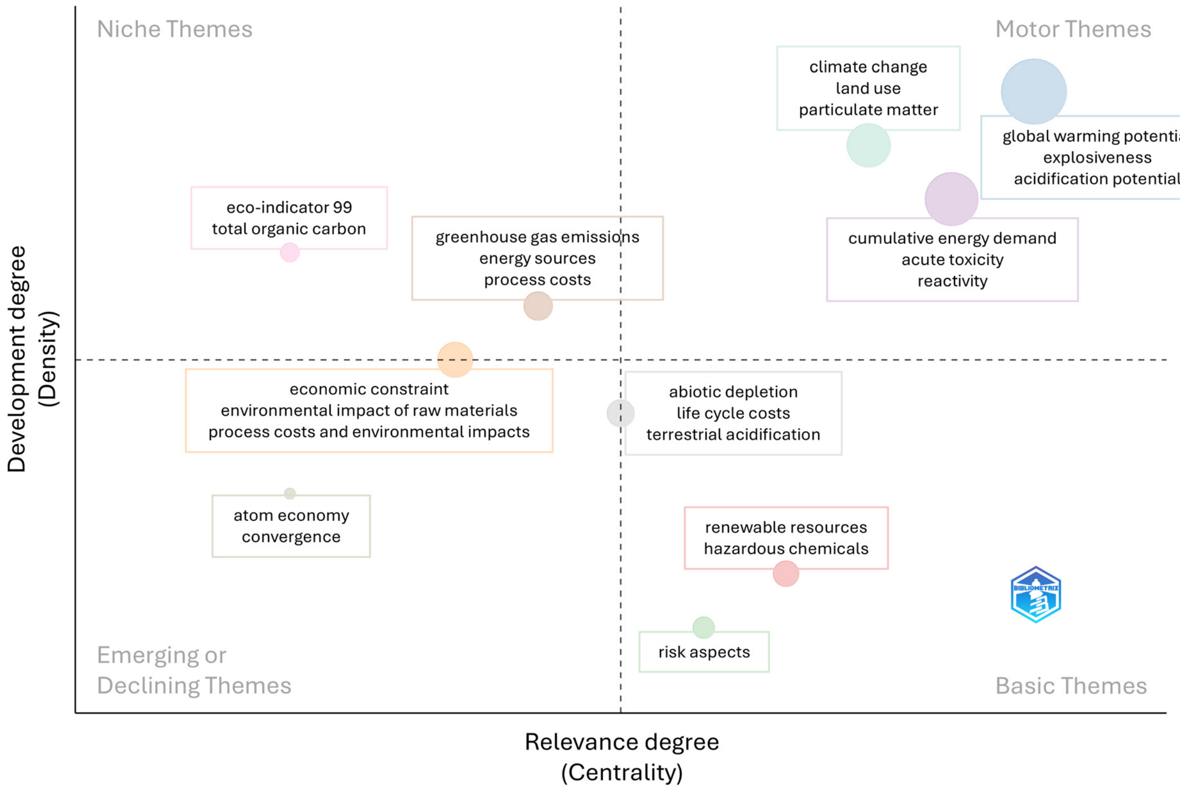

Fig. 4 Thematic mapping of economic, environmental, and health and safety sustainability indicators used in the assessments reviewed.

warming potential, cumulative energy demands, climate change) with some focus on safety issues (explosiveness, acute toxicity). These exhibit the largest bubble size among all clusters, indicating that a greater number of articles have delved into these specific aspects compared to the other clusters. The aspects of renewability, chemical hazards and risk were designated as basic themes, while atom economy and convergence were determined as emerging or declining themes. Convergence is a relatively new and emerging topic, aiming to streamline the synthetic process by minimising the number of steps, reducing waste and improving overall efficiency.[80] The concept of atom economy, a fundamental principle in green chemistry, has been integral to the development and evaluation of sustainable chemical processes. However, its significance may be diminishing over time. Apart from that, indicators such as eco-indicator 99, total organic carbon, process costs and energy sources were positioned in the niche quadrant due to their sporadic use in the reviewed sustainability assessment methods. Furthermore, two transitional themes are centred around the origin of the graph, encompassing economic aspects (economic constraint, process costs and environmental impacts, life cycle costs) and environmental factors (terrestrial acidification, abiotic depletion).

From a green chemistry perspective, Fig. 4 reveals connections between various aspects related to motor, basic, or emerging/declining themes and the 12 principles of green chemistry.[7] This linkage underscores the significance of green chemistry in the context of early-phase sustainability assessments of chemical processes. The indicator convergence aligns with principle 1 (waste prevention), while atom economy corresponds to principle 2 of the same name. Hazardous chemicals encompass principles 3–5 (less hazardous chemical synthesis, designing safer chemicals, safer solvents and auxiliaries), cumulative energy demand relates to principle 6 (design for energy efficiency) and renewable resources are associated with principle 7 (use of renewable feedstocks). Principle 11 (real-time pollution prevention) is addressed by the indicator particulate matter and principle 12 (safer chemistry for accident prevention) is mirrored by indicators such as reactivity, explosiveness and risk aspects. The direct link between several indicators and the topic of green chemistry underscores its critical role in conducting sustainability assessments of chemical processes during the early design phase.

5. Discussion

In the following, findings from qualitative and quantitative analysis are summarised and related to the three research questions.

5.1. Research question 1

Over the past few years, there has been growing focus on early-stage sustainable chemical process design, leading to a sub-

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stantial body of literature on the subject, as summarised in Table 1. With regard to the first research question – (1) which sustainability assessment methods are suitable for early-phase chemical process design? – the following specific examples are highlighted to provide an understanding of available tools addressing diverse sustainability dimensions.

Starting with four-dimensional sustainability assessment methods considering economic, health and safety, social, and environmental aspects, the sustainability assessment tool[108] by Saavalainen *et al.* is a comprehensive Excel-based checklist designed for early process design. This tool, aligning with green chemistry principles and European chemicals regulations, assesses 209 multiple-choice questions, each scored based on its impact severity. It covers 7 categories, addressing waste prevention, materials efficiency, raw material selection, benign by design products, fewer ancillaries, energy efficiency of the process, as well as risk and hazard management. Demonstrated through a comparison of formic acid production routes, the tool effectively guides researchers in early process development, depending upon data quality. Additionally, the Joint Research Centre of the European Commission has introduced a framework for safe and sustainable by design criteria for chemicals and materials.[34] This framework aims to support the design of safe and sustainable chemicals and materials, encompassing research, innovation and existing chemicals. This approach comprises five steps focusing on hazard assessment, human health and safety, environmental aspects, and social and economic sustainability. Data availability and quality are crucial throughout, with the potential for support from artificial intelligence and digitalisation. In case studies for sustainability assessment of plasticisers, flame retardants and surfactants in textiles,[110] challenges emerged related to data availability, quality and uncertainty. These experiences emphasised the importance of early-stage chemical/material assessment, specific expertise for each step, and effective communication and data exchange between suppliers.

Several assessment methods address economic, health and safety, and environmental sustainability. Patel *et al.* introduced a rapid preliminary evaluation methodology for chemical processes at the laboratory stage, incorporating the principles of green chemistry, techno-economic analysis and life cycle assessment.[97] This multi-criteria method encompasses economic constraint, environmental impacts, process costs, and environmental, health and safety indices and was tested in a case study for the production of but-1,3-diene. Also, Serna *et al.* introduced a multi-criteria analysis methodology utilising normalised indicators, which were consolidated into a Sustainable Cumulative Index (SCI) across three sustainability dimensions.[105] This index considers the weights and relationships between the various indicators, which were quantified through input from experts and senior students of chemical engineering. Apart from that, Liew *et al.* presented a sustainability assessment for biodiesel production through fuzzy optimisation, emphasising inherent safety, health, environment and economic performance.[102] The aspect of inherent safety and health is addressed through the utilisation of well-established metrics such as the Prototype Index of Inherent Safety (PIIS), the Inherent Occupational Health Index (IOHI) and the Inherent Environmental Toxicity Hazard (IETH), while the economic performance is assessed based on operating costs and revenue. Subsequently, fuzzy optimisation is applied to compare various reaction pathways with respect to multiple objectives. Instead, the sustainability evaluator by Shadiya and High is an Excel-based tool integrating mass and energy flows for early process design assessment, covering economic, environmental and social aspects.[100,101] Its effectiveness was evidenced through the evaluation of two dimethyl ether production processes, with the environmental assessment results aligning with the outcomes of the Environmental Protection Agency's waste reduction algorithm. Monteiro *et al.* conducted a comprehensive comparison of chemical routes for dimethyl carbonate production, considering toxicity, environmental impact and profit potential.[96] They aggregated the individual metrics into a total score and recommended further in-depth comparison of the best performing routes, such as through life cycle assessment, as more information became available. Further frameworks, including Sugiyama's decision framework for chemical process design, encompass different stages of environmental, health and safety (EHS) assessment using a stage-and-gate approach and multi-objective evaluation.[13] Each stage includes different indicators covering life cycle impacts, economic performance and EHS aspects, and in the study, routes for the synthesis of methyl methacrylate were evaluated.

In addition to tools that encompass environmental, economic and social aspects of sustainability, there are also various concepts that concentrate on only two of the three dimensions. Several tools and indices with a focus on environmental and health and safety considerations have been developed. For instance, Andraos introduced the Safety/Hazard Index (SHI), which encompasses 12 safety-hazard potentials such as flammability, skin dose and corrosiveness, each contributing to risks related to environmental impact and the health and safety of workers.[87] When combined with efficiency parameters and the benign index, this facilitates the assessment of the overall "greenness" indicator of a synthesis plan. To serve a similar purpose, the Inherent Benignness Indicator (IBI) has been developed, utilising principal component analysis to compare the diverse environmental, health and safety aspects of the various alternatives.[83]

Tools that focus on a single sustainability dimension are also briefly discussed. These tools can be categorised into those addressing classical environmental aspects and those concentrating on inherent hazards. In the former category, the improved innovation green aspiration level (iGAL 2.0) is designed to reduce pharmaceutical manufacturing waste,[76] while the green degree method[70] encompasses 9 environmental impact categories. Meanwhile, tools developed within the chemical industry include the web-based Fast Life Cycle Assessment of Synthetic Chemistry (FLASC™), serving to assess the relative sustainability of pharmaceutical production processes within GSK[69] and an Eco-footprint tool employed at

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Chimex,[73] which considers 10 indicators to assess their process sustainability. Turning to the second group of tools focusing on inherent hazards, the Atmospheric Hazard Index,[67] the Environmental Hazard Index[65] and the Inherent Environmental Toxicity Hazard[68] have been reported in the literature.

5.2. Research question 2

Regarding the second research question – (2) which categories can be used for comparing sustainability assessment methods for early-stage chemical process design and how do they differ? – the qualitative content analysis of the retrieved literature revealed significant variations. These sustainability assessment methods differ across several categories, including the incorporation of sustainability dimensions (economy, society, health and safety, environment), data requirements, assessment methodologies, decision-making processes, consideration of uncertainty and the outcome types in terms of indicators. Some methods are specifically tailored to certain research fields, while others offer general adaptability.

In terms of sustainability dimensions, environmental and health and safety aspects are predominantly assessed, with only a few cases including economic factors and rare consideration of social aspects beyond health and safety. Due to data limitations in early-phase process development, the assessed methods rely on preliminary lab or theoretical data, assumptions, the literature, or databases. The growing importance of artificial intelligence and machine learning in sustainability assessment and chemical process design has led to the utilisation of computer simulations to generate and analyse sustainability data. Additionally, the assessments commonly involve frameworks, mathematical equations and life cycle assessment. Multi-criteria decision analysis and statistical and multivariate analysis techniques are frequently employed during decision-making and data analysis, respectively. The results of the reviewed sustainability assessment methods often manifest as single indicators, multi-indicator types, or cumulative indicators, with the latter usually necessitating the application of weighting to aggregate diverse data into a composite measure. While a composite measure facilitates the comparison of different process routes, the selection of weighting factors is often a subjective decision, influencing the final assessment outcome significantly. Thus, the decision of whether to employ weighting and how to establish the weights represents a critical aspect in the development of a sustainability assessment method and can spark debate among practitioners.[112] Furthermore, the incorporation of uncertainty into sustainability assessments is observed in only about one-fifth of publications, despite its crucial role in risk mitigation, robust decision-making and stakeholder confidence. This calls for wider implementation of uncertainty analysis in the field of sustainability assessment for chemical processes. By integrating uncertainty into sustainability assessments during early process design, engineers and decision-makers can make more informed choices, leading to the development of more sustainable and resilient solutions.

While a multitude of methods for sustainability assessment of early-stage chemical processes exist, they often encounter common challenges. The quality of available data significantly impacts the significance of assessment results.[34] Therefore, it is advisable to evaluate data quality, use known best estimates and incorporate uncertainty analysis to address data-related issues.[113] At times, combining elements from different sustainability assessment methods may be necessary to best address the research question.

In summary, the diversity of methods for sustainability assessment in the early design phase necessitates the selection of the appropriate method based on the specific research question, desired scope, data availability, time frame, workload and specific knowledge. The maturity and nature of the chemical process under consideration also influence the choice of the most suitable assessment method. As the field of early-phase sustainability assessment for chemical processes is constantly evolving, it is expected that future advancements will address the challenges and limitations associated with early-stage assessments.

5.3. Research question 3

In addressing the third research question – what are trends and topics in the field of early-phase sustainability assessment and which sustainability indicators are frequently considered? – notable findings have emerged.

Analysis of the most frequently used author keywords and trend topic analysis has revealed that life cycle analysis, environment health safety (often in combination with inherent safety) and green chemistry are of considerable interest and are frequently included in the reviewed methodologies within the field of early-phase sustainability assessment of chemical processes. Apart from that, the multi-dimensional nature of sustainability and the diverse array of sustainability indicators used have led to multicriteria assessment being a key aspect in this domain.

Thematic mapping further revealed that multicriteria assessment, leading to either a multi-indicator or cumulative indicator assessment result and encompassing one (environmental) or three dimensions (economic, health and safety, and environmental) of sustainability, formed the foundational basis of research in this field. Conversely, holistic assessment methods that incorporate all sustainability dimensions, including social aspects, are less common due to the challenge of quantifying "soft" aspects such as gender equality, well-being, or fair salary, particularly in the early development phase, where data availability is restricted and there is a lack of consensus on relevant criteria for social sustainability.[114] Additionally, thematic mapping highlighted computer simulation as an emerging theme, consistent with qualitative analysis hypotheses.

Factorial analysis, based on multiple correspondence analysis and *k*-means clustering, is another statistical method used to identify clusters of related research topics in the field. Analysis of the distribution of clusters along the *x*-axis and the *y*-axis suggested a division of clusters based on result indi-

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cators (single indicator, multiple indicators, cumulative indicator) as well as the coverage of sustainability dimensions. In total, 5 different clusters were identified. The central cluster, which corresponds to the average research profile, comprises three-dimensional assessment methods (economy, health and safety, environment), in accordance with the basic theme identified by thematic mapping. Notably, distinct clusters were identified around topics such as inherent safety, green chemistry and life cycle assessments, aligning with earlier assumptions based on trend topic analysis and thematic mapping. A smaller cluster, which involves 4-dimensional or safe and sustainable by design assessment, is positioned slightly apart in the lower left corner of the diagram. In summary, these findings align with the initial assumptions based on the most frequently used words, trend topic analysis and thematic mapping.

When considering the indicators used for early-stage sustainability assessment of chemical processes, it is observed that costs in different forms are the most prominent economic indicator, while health and safety aspects focus on dangers arising from the intrinsic reactivity of chemicals, their toxicity potential and processing conditions. The environmental dimension, still receiving the greatest attention, is primarily assessed by global warming potential, energy demands, and the effects of air and water emissions, categories often analyzed in life cycle assessment frameworks. Notably, route and process-related aspects such as atom economy, yield, or process mass intensity, derived from the 12 principles of green chemistry, are increasingly assessed, contributing to health and safety or environmental considerations. A relatively new process indicator, "convergence", has appeared, assessing the efficiency of multistep synthesis by gauging the number of key construction steps in relation to the number of starting materials, as evidenced in recent publications.[80]

5.4. Synthesis

As a synthesis of the review, our objectives are to (i) visually represent the sustainability assessment methods studied and (ii) propose a systematic decision-making process for selecting the most fitting sustainability assessment tool for a specific research question.

To illustrate the array of sustainability assessment methods, we adopted a target-based model, similar to the structure known in archery, with a dual-level organisation. Firstly, the target is segmented into quarters (1–4), each representing one-, two-, three-, or four-dimensional methods for assessing sustainability. In this respect, one-dimensional methods are further categorised into tools that focus on environmental or health and safety aspects, while two-dimensional methods encompass either environmental and health and safety or environmental and economic considerations. Secondly, the target comprises concentric rings (A–C), where the proximity to the centre correlates with the time and data complexity of the respective sustainability assessment method. As we move towards the centre of the target, time and data efforts of sustainability assessment methods increase and so do the significance of the results and the likelihood to "hit the target" and design a sustainable process. The outermost ring encompasses heuristic assessment methods, which are simple procedures relying on a minimum set of data (such as substance properties or basic process data), allowing for quick assessments of sustainability aspects (*e.g.* screening methods). Moving towards the centre, the middle ring incorporates more time-consuming and complex multicriteria methods based on profound process data, enabling a more comprehensive sustainability evaluation. These methods often employ statistical or multivariate analysis tools such as MCDA or AHP for the decision-making process. The innermost ring includes assessments that are most data- and time-intensive, showing characteristics of life cycle assessment, depending on elaborate process or computer simulations, featuring complex mathematical models or including scenario and uncertainty analysis. These tools are positioned closest to the centre, which symbolises the goal of developing a sustainable chemical process. The division of sustainability assessment methods into the three concentric rings is based on the application of the method rather than its development, with the significance of the result also being considered. The specific placement within a segment is arbitrary and lacks any meaning. It is important to note that there are no distinct boundaries between the segments and the placement of tools is based on the authors' perception and could be a subject of discussion.

An illustration of the sustainability assessment target and the positions of the reviewed sustainability assessment tools can be found in Fig. 5. As can be seen from the figure and as

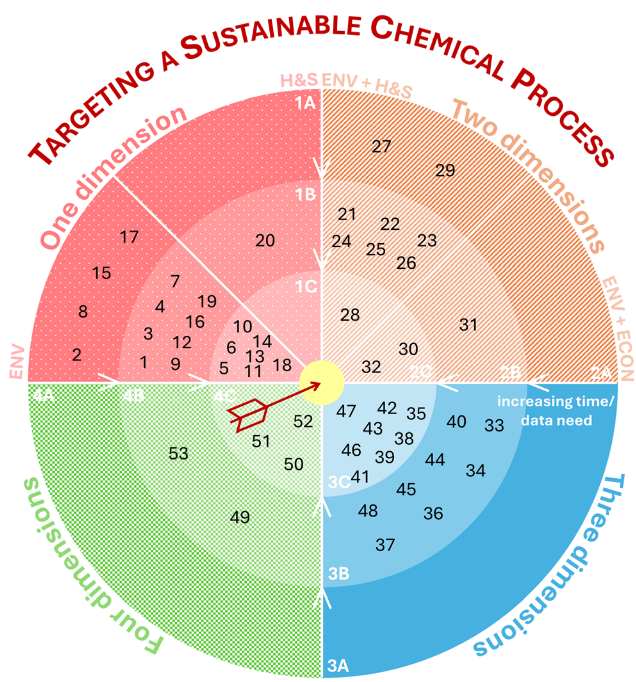

Fig. 5 Sustainability assessment target (numbering of references based on Table 1; segments 1–4: number of sustainability dimensions included; rings A–C: increasing complexity of assessment method).

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one would expect, the incorporation of additional sustainability dimensions into an assessment tool generally leads to methods that are more complex and require increased time and data resources.

Apart from that, we want to offer a systematic guide for selecting an appropriate sustainability assessment method for practitioners. Before being able to select an appropriate method, one must know what process data are available or can be retrieved from other sources, what time and effort should be spent, and what knowledge is available (*e.g.* LCA expertise, simulation *etc.*). Then, it has to be decided what sustainability aspects should be covered by the assessment. Is a comprehensive, four-dimensional sustainability assessment targeted or should the focus lie on specific aspects? Depending on context-specific priorities driven by stakeholder interests or the need for decision-making simplification, the utilisation of low-dimensional sustainability assessment methods may be justified, even though incorporating more sustainability dimensions improves the prospect of developing a sustainable chemical process. In certain cases, a combination of methods may be the most appropriate approach to address the issues of interest, as exemplified by our group's endeavour to evaluate the sustainability of an early-stage electrochemical process for synthesising noroxymorphone.[115] Additionally, one could also combine a heuristic screening method for rapid pre-selection with a more complex assessment tool to conduct in-depth analysis of promising pathways.

When choosing a suitable method for carrying out a sustainability assessment, practitioners should essentially consider the following questions, as outlined in the decision tree in Fig. 6:

1. What dimensions of sustainability shall be considered in the assessment, such as economic, environmental, social, and health and safety factors?

- *Follow path* 1, 2, 3 *or* 4 -

2. Should the evaluation be quick and with limited data and time efforts (for screening purposes)?

- *If yes: check methods* 1A–4A, *depending on the path; if no: continue on path* 1, 2, 3 *or* 4 -

3. What is the desired level of detail/complexity of the assessment (medium: multicriteria methods; high: LCA-based, simulation-based, or complex mathematical tools)?

- *If medium: check methods* 1B–4B, *depending on the path; if high: check methods* 1C–4C, *depending on the path* -

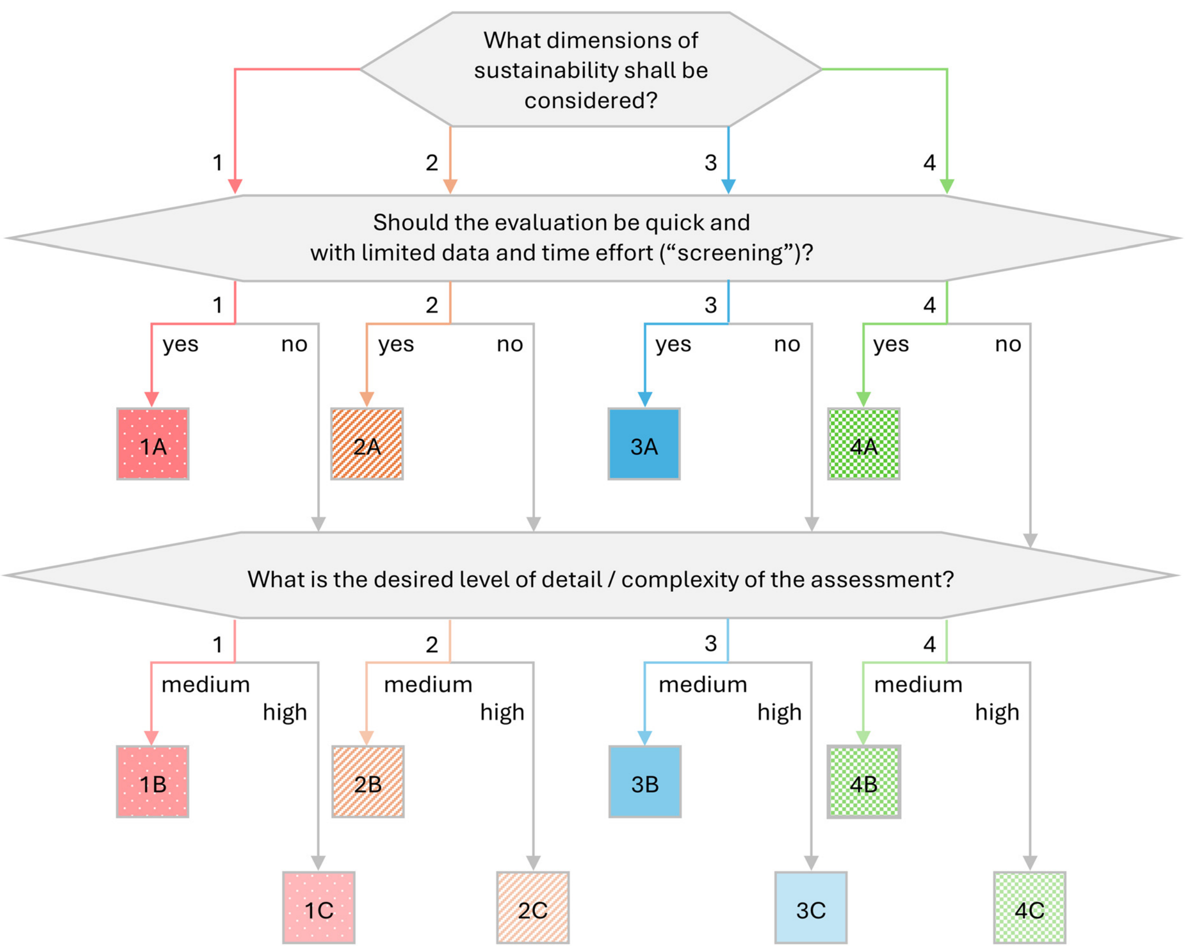

Fig. 6 Decision tree for selecting a sustainability assessment method.

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The decision tree directs the practitioner towards a specific quadrant and concentric circle of the target, where references satisfying the chosen criteria for sustainability dimensions, as well as time/data efforts, can be found. Within this segment, the selection of a particular method may be influenced by factors such as the incorporation of uncertainty, the nature of the indicator result, existing expertise or the field of research. Ultimately, the choice of the most suitable method depends on the practitioner's judgment and experience. With this systematic selection strategy, we aim to enable researchers to make an informed decision on the selection of a suitable method for sustainability assessment.

6. Conclusion

The importance of considering sustainability from the early stages of process design cannot be overstated. This study aims to present an extensive review of sustainability assessment methods applicable in the initial design phase of chemical processes, encompassing the process synthesis phase or TRL 1–4. Our comprehensive literature review identified 53 relevant publications meeting our selection criteria, which were analyzed using a mixed-method approach.

The qualitative analysis involved categorising the articles' content into areas such as bibliographic data, data requirements, sustainability dimensions, indicators, assessment methods, decision-making procedure, result characteristics and research field. The reviewed methods vary significantly in their use of sustainability indicators and their consideration of economic, social, health and safety, and environmental sustainability. To illustrate the diversity of applicable methods, we presented one-, two-, three- and four-dimensional assessment tools. These methods often incorporate elements of life cycle assessment, utilise mathematical equations, or form part of a broader multi-step framework. Notably, computer-aided methods are increasingly leveraging computer simulation, artificial intelligence, machine learning and neural networks. Moreover, the evaluated methods vary in their decision-making processes, incorporating elements of multicriteria decision making, weighting, statistical analysis and addressing uncertainty through techniques such as Monte Carlo analysis, quantification of prediction uncertainty, fuzzy logic and data quality ratings. The assessment results can be based on a single indicator, multiple indicators, or a cumulative indicator, requiring practitioners to select an appropriate method for their specific research question. It is evident that these tools predominantly evaluate the relative sustainability of a chemical process, identifying the most sustainable option among a set of possible reactions, rather than providing absolute sustainability assessments. Notably, the Safe and Sustainable by Design concept of the EU shows efforts towards absolute sustainability assessment and suggests including elements of the use of the chemical (such as the type and quantity used), therefore going beyond mere relative comparisons of chemicals.[34] Furthermore, our study highlights that many sustainability assessment methods are based on well-established concepts such as green chemistry, life cycle thinking and inherent safety.

For the second level of analysis, we employed quantitative methods utilising the bibliometric analysis tool "bibliometrix". This involved document analysis, which examined the most frequently used words and trending topics, as well as conceptual analysis, including factorial analysis and thematic mapping. At the document level, we analyzed author keywords to reveal the most frequently considered aspects in the research field, including LCA, EHS, environmental impact and green chemistry. Trend topic analysis showcased interest in key research topics over time, such as the recent emphasis on safe and sustainable by design, the continuous impact of LCA or the past efforts related to sustainability assessments of methyl methacrylate. Furthermore, we examined economic, health and safety, and environmental indicators to identify the most popular indicators used in the reviewed frameworks. In terms of conceptual analysis, we studied selected categories from the qualitative analysis, such as author keywords, sustainability dimensionality, assessment procedure, results, research field and used sustainability indicators. Factorial analysis, employing multidimensional scaling and *k*-means clustering, identified five distinct clusters of research, with their relative positions correlating with the type of assessment result (single, multi-, or cumulative indicator) and the sustainability dimensionality assessed. The central research cluster, corresponding to the average research profile, comprises early-stage sustainability assessment methods, including aspects of economic, health and safety, and environmental sustainability. Apart from that, thematic mapping of sustainability indicators unveiled basic, motor, niche and emerging/declining themes, offering valuable insights into the research field's structure and indicator usage.

Finally, we visualised the dimensional scope as well as time and data requirements of the reviewed literature methods in a figure in the form of a sustainability target. This visualisation enables a quick perception of the distribution of available methods for the purpose of chemical process design. Accompanied by a decision tree, the figure is designed to assist practitioners in identifying an appropriate assessment tool tailored to their specific needs.

6.1. Future research

The exploration of early-stage sustainability assessment in the literature has been extensive. Our study uncovered current topics and trends in this field, shedding light on areas for potential future research. Notably, social sustainability assessment tends to focus on tangible and quantifiable health and safety aspects, highlighting the need to integrate more "soft" social aspects into these evaluations. Additionally, certain relevant topics, like endocrine disrupting chemicals and persistent organic pollutants, have been mentioned in the literature but have not received sufficient attention in the past. An endocrine-disrupting chemical is an exogenous chemical or mixture of chemicals that can interfere with any aspect of

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hormone action.[116] Besides having serious (sometimes irreversible) effects on the body, especially in phases of development (fetal, childhood, puberty), it is especially concerning that endocrine disruption takes place at extremely low concentrations.[117] Increasing research on the topic of endocrine disruption has indicated that it has become a serious public health issue and there has been little progress in implementing regulatory processes.[117] Another class of chemicals of special concern are persistent organic pollutants (POPs). In most cases, POPs are highly lipid soluble molecules, which tend to bioaccumulate in living organisms, are toxic and remain within the ecosphere for a long period of time due to their stability.[118] Although measures to eliminate or reduce the release of known POPs have been taken, such as the Stockholm Convention phasing out various polychlorinated compounds among others, new chemicals are released to the market at a speed exceeding the capacity to conduct chemical safety assessments,[119] increasing the risk to release potentially harmful and persistent compounds into the environment.

Furthermore, the assessment of sustainability has predominantly been conducted in absolute terms, with the SSbD concept by Caldeira *et al.*[34] representing one of the few initiatives striving to advance more absolute sustainability assessment. Nevertheless, given the imperative to revolutionise the chemical industry – a major consumer of resources and energy and a substantial contributor to global carbon emissions[120] – it becomes necessary to question whether merely selecting the "least unsustainable" process alternative is adequate, particularly without a comprehensive evaluation of process sustainability in absolute terms. Consequently, future endeavours in this domain are indispensable to attain a genuinely sustainable chemical industry.

Another significant topic that has attracted considerable attention, albeit outside the realm of early-stage assessment of chemical processes, is circularity. While there have been notable efforts in promoting the circular use of chemicals, these initiatives have not yet been fully integrated into the sustainability assessment of chemical processes. For instance, Wang and Hellweg[121] outlined steps to incorporate the concept of circularity into practice, introducing a stage for "sustainable circularity" assessment. Similarly, Keijer *et al.*[122] presented the twelve principles for circular chemistry, aiming to provide a comprehensive systems approach. Although frameworks for acknowledging circularity in chemicals exist, the integration of circular chemistry concepts into early-stage sustainability assessment represents an area for future research.

Based on the literature review, social considerations predominantly focus on health and safety aspects and the significance of inherent safety indices in reducing risks associated with chemical plant operations is emphasised. Various case studies[123–125] indeed demonstrate the effectiveness of inherent safety indices in promoting a safer chemical process and preventing accidents at production sites. Nonetheless, it is crucial to recognise that the occurrence of accidents depends not only on inherent hazards but also on the implementation of risk management measures.[126] Thus, it is imperative to prioritise risk management efforts, even when inherent hazards are lower, to preclude chemical plant accidents.[83]

6.2. Limitations

Despite efforts to minimise potential limitations in the current study by using both quantitative and qualitative methods, certain constraints may persist in the study design and result interpretation. The definition of the search string, including the selection of keywords and Boolean operators, as well as the choice of search database, significantly impacts the obtained results during the literature search. Additionally, the exclusion of conference papers, books, industry reports, non-English literature and material published before 2000 limits the scope of the study. Moreover, the bibliometric analysis is based on a relatively small sample of papers due to the focus on early-phase sustainability assessments, setting the groundwork for future research in this area. The outcome of the analysis is influenced by various settings, such as the minimum cluster frequency and the number of words in the thematic map analysis, or the number of terms and clusters in the factorial analysis. It is important to note that while bibliometric analysis provides objective metrics, the interpretation of networks, trends and clusters involves subjective judgment.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

The data supporting this article have been included as part of the SI.

Supplementary information is available. Information on data extraction, data cleaning and data analysis (PDF); comprehensive list of reviewed literature including author names, year, publication title, DOI, author keywords, sustainability dimension inclusion with a detailed inventory of used indicators, data requirements, assessment method, decision-making procedure, uncertainty consideration, assessment result, result characteristics and research field (XLSX). See DOI: **https://doi.org/10.1039/d5gc02565f**.

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